PROTOCOL FOR THE COMPREHENSIVE ASSESSMENT OF NEURODEGENERATION AND DEMENTIA (COMPASS-ND) STUDY

CCNA-2015

The Canadian Consortium for Neurodegeneration in Aging

Protocol Version *[9.6] [15-May-2017]*

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PROTOCOL APPROVAL PAGE

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_____ _____

Name Date

_____

Title, Affiliation

INVESTIGATOR AGREEMENT

The Canadian Consortium for Neurodegeneration in Aging

I have read the protocol and agree that it contains all necessary details for carrying out this study. I undertake to conduct this trial within the time designated.

I understand that all patient information in connection with this trial is considered confidential information.

The information includes the clinical protocol, the Case Report Form, technical methodology and basic scientific data.

By my signature below, I hereby attest that I have read, understood and agree to abide by all conditions, instructions and restrictions contained in the above protocol.

Investigator:

Name	Signature	Date

Name and Address of Investigational Site:

TABLE OF CONTENTS

CCNV CCNA

TIME AND EVENTS SCHEDULE

Visit	1	2	3	4	5	6	7	8	9	…	k
Study Procedures											
Informed Consent	X										
Inclusion/Exclusion	X										
Hearing & Vision Acuity	X						X				
CDR*	X										
Logical Memory 1 & 2*	X										
CERAD word list recall*	X										
MoCA	X					X	X	X	X	X	X
Lawton-Brody IADL scale*	X										
Benson Figure Copy & Recall@	X										
Mini-Mental Status Exam©	X										
Disease-Specific Inclusion & Exclusion Criteria	X										
Clinical PPA Features / Clinical bvFTD Features µ	X										
General Sociodemographic Information¥	X										
General Health Questionnaires¥	X	X					X				
Vital Signs		X					X				
Blood, saliva, & urine collection		X					X				
Oral Swab		X					X				
Fecal sample collection (optional)€		X					X				
Medical/Surgical History		X					X				
Concomitant Medications		X					X				
Cognitive/Neurological Symptoms		X					X				
Physical/Neurological Exam		X					X				
Hachinski Ischemic Scale		X					X				
Disease Specific Questionnaires¥		X					X				
Neuropsychological assessment,			X				X				
MRI£				X			X				
Lumbar Puncture (optional)					X		X				
Annual Telephone Follow-up						X		X	X	X	X
2 year follow-up							X				
Brain Donation Consent (optional)	X					X	X	X	X	X	X

*: Administered to SCI, MCI, V-MCI, AD, & Mixed Dementia groups only.
@: Administered to LBD, PDD, PD-MCI, and FTD spectrum groups only.
©: Administered to PD participants only
µ: Administered to FTD spectrum participants only
¥: Part of these questionnaires are completed by the participant & informant at home.
£: Can be scheduled for anytime in the 3 month period, but must be before the lumbar puncture if consented to.
€: Sample to be collected by participant at home.

PROTOCOL SYNOPSIS

Title

The Comprehensive Assessment of Neurodegeneration and Dementia study

Sponsor

The Canadian Consortium on Neurodegeneration in Aging

Objectives

PRIMARY OBJECTIVE

The primary objective is to create a pan-Canadian set of cohorts of subjects with various cognitive conditions that will, for the first time, integrate a wide range of experimental, clinical, imaging, and genetic expertise to specifically address the causes, identification, management, treatment, and prevention of these conditions in the aging population.

SECONDARY OBJECTIVE

To create a pan-Canadian set of cohorts of patients with various cognitive conditions wherein the biospecimens, imaging, genetics, and brain donations will support the research agendas of 20 associated national research teams.

Study Design

This is a 5-year observational study. Sixteen-hundred (1600) subjects, between the ages of 50 and 90,years old, with SCI, MCI, V-MCI, AD, Mixed dementia, LBD, PDD, PD-MCI and FTD, will be enrolled into this study from up to 30 centres across Canada. All subjects involved in the study will undergo rigorous evaluations at baseline, including clinical assessment, neuropsychological assessment, genomics and neuroimaging. Biosamples from blood, saliva, urine, fecal matter, buccal cells and cerebrospinal fluid will be collected, stored, and analyzed. Basic follow-up determining if there has been any change in their diagnosis will be carried out annually and longitudinal re-evaluation will be carried out after two years.

Study Population

Subjects must meet the inclusion/exclusion criteria for their condition and then also meet the inclusion/exclusion criteria for each platform testing. If patients do not meet the criteria for a specific platform they may still participate in the study as long as a minimal amount of data (i.e., diagnosis, demographics and MRI) is collected on them. Sex distribution of the cohort will be monitored to insure sufficient numbers to test for sex related differences in key outcome studies.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	
AD	Alzheimer's Disease
ADL	Activities of Daily Living
ADNI	The Alzheimer's Disease Neuroimaging Initiative
ALP	Alkaline phosphatase
ALT	Alanine Transaminase
ANOVA	Analysis of Variance
AST	Aspartate Transaminase
BAIVI	Brain Atrophy Ischemic Vasculopathy Index
BIS	Behavioral Inhibition Scale
bvFTD	Behavioral variant of frontotemporal degeneration
BVMT	Brief Visuospatial Memory Test
C5R	The Consortium of Canadian Centres for Clinical Cognitive Research
CBC	Complete Blood Count
CBS/CBD	Cortical basal syndrome/autopsy confirmed cortical basal degeneration
CDIP	Canadian Dementia Imaging Protocol
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CIHR	Canadian Institutes of Health Research
CIMA-Q	Consortium pour l'identification précoce du Maladie d'Alzheimer du Québec
COWAT	Controlled Oral Word Association Test
CRF	Case Report Form
CSF	cerebrospinal fluid
CVD	Cardiovascular Disease
DCF	Data Clarification Form
DKEFS	Delis-Kaplan Executive Function System
DNA	Deoxyribonucleic acid
DTI	Diffusion Tensor Imaging
eCRF	Electronic case report form
EOS	End of Study
eQTL	Expression Quantitative Trait Loci
FA	Fractional Anisotrophy
FLAIR	Fluid Attenuation inversion recovery
fMRI	Functional MRI
FSL	FMRIB Software Library
FTD	Frontotemporal dementia
FTLD	Frontotemporal Lobar Degeneration
GATK	Genome Analysis Toolkit
GAD-7	Generalized Anxiety Disorder 7-item scale
GCP	Good Clinical Practice
GDS-30	Geriatric Depression Scale
GWAS	Genome-Wide Association Studies
HEENT	Head, eyes, ears, nose and throat
iADL	Instrumental Activities of Daily Living
ICH	International Conference on Harmonization
ICMJE	International Committee of Medication Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRI	Interpersonal Reactivity Index
K-M	Kaplan-Meier
LBD	Lewy Body Dementia

LONI	Laboratory of NeuroImaging
MANOVA	Multivariate Analysis of Variance
MCI	Mild Cognitive Impairment
MDS-UPDRS	Unified Parkinson's Disease rating score
MITNEC	Medical Imaging Trial Network of Canada
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NDD	Neurodegenerative Disease
NIA-AA	National Institute on Aging-Alzheimer's Association
NIHSS	National Institutes of Health Stroke Scale
NPI-Q	Neuropsychiatric Inventory Questionnaire
OBI	Ontario Brain Institute
ONDRI	Ontario Neurodegenerative Research Initiative
PD	Parkinson's Disease
PD/T2	Proton Density
PDD	Parkinson's with dementia
PD-MCI	Mild Cognitive Impairment in Parkinson's Disease
PD-NCI	Parkinson's Disease with no cognitive impairment
PDQ-39	Parkinson's Disease Questionnaire
PET	Positron emission tomography
PNFA	Progressive Non-fluent Aphasia
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy
PURE-MIND	The Prospective Urban Rural Epidemiologic
QA	Quality Assurance
QC	Quality Control
QLS	quasi-elastic light scattering
QoL	Quality of Life
qPCR	Quantitative Polymerase chain reaction
RNA	Ribonucleic Acid
RS-MS	Revised Self-Monitoring Scale
S & E	Schwab & England
SCI	Subjective Cognitive Impairment
SD	Semantic Dementia
SNPs	Single nucleotide polymorphism
T (Imaging)	Tesla
TIA	Transient ischemic attack
TSH	Thyroid-Stimulating Hormone
V-MCI	Vascular Mild Cognitive Impairment
VEGF	Vascular Endothelia Growth Factor
Vfi	Verbal fluency Index
VOSP	Visual Object Space Perception
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WES	Whole exome sequencing
WHO	World Health Organization
WMD	White matter disease

1. INTRODUCTION

1.1. BACKGROUND

Four years ago, a demographic milestone was reached across North America – the baby boomers began to become senior citizens. The proportion of the Canadian population over age 65 will climb from 11.6% in 1991 to 16% in 2016, and 23% in 2041. As this demographic evolution occurs, the concerns and problems of elderly people will take centre stage in Canada. Various reports, most notably "Rising Tide: The Impact of Dementia in Canada" have delineated the scope of the dementia problem. Currently 500,000 Canadians have Alzheimer Disease (AD), and this will rise to 1,100,000 within a generation. The annual cost to the country is now 15 billion dollars. This will rise to 153 billion dollars within a generation[1]. A call to action has come internationally from the World Health Organization (WHO)[2]. This report (March 2012) stresses that each country should determine a priority research agenda with research evidence underpinning policy and clinical actions. Multidisciplinary research is essential and an appropriate balance must be struck between basic research on disease mechanisms and applied research dealing with pharmacologic and non-pharmacologic approaches to the prevention, treatment, and/ or care of those with dementia. The WHO report stresses that significantly more research is needed to better understand the causes of dementia and how and when lifestyle factors influence the risk of developing it. As a response, the Canadian Institutes for Health Research (CIHR) in Canada has organized an "International Collaborative Research Strategy for Alzheimer's Disease" as one of the CIHR's Roadmap Signature Initiatives[3]. Its focus is AD and related neurodegenerative disorders (NDD). This initiative has established the Canadian Consortium on Neurodegeneration and Aging (CCNA) which will be the major vehicle to coordinate and strengthen Canadian research on AD and NDD. It is intended to foster innovative and collaborative research across Canada.

NDD refers to a class of disorders characterized by the progressive deterioration of thinking ability in areas such as memory, function, and behaviour as the brain becomes damaged[1]. This study will unite the tremendous resources of clinician researchers, basic scientists, social scientists, and allied professionals from across Canada to explore the causes and improve the identification, management, treatment and prevention of NDD that lead to impairments in memory, cognition, and function.

AD is the most common form of neurodegenerative disease and contributes to approximately two-thirds of cases in older adults. It is a progressive degenerative and fatal brain disease[1]. Vascular dementia (VaD) accounts for 20% of dementia cases, second only to AD[4]. While vascular cognitive impairment is not infrequently the result of a stroke, it is more often not preceded by a discrete cerebrovascular event[5]. Mixed dementia – cognitive impairment where multiple brain pathologies are present – represents the most prevalent type of cognitive impairment[6]. FTD (frontotemporal dementia) accounts for 20% of pre-senile dementia cases. Symptoms can begin to appear on average around 45-65 years of age[7]. Symptoms of FTD progress at a rapid, steady rate. Patients suffering from the disease can survive between 2-10 years[8]. Dementia with Lewy Bodies (DLB) accounts for 10-15% of cases of NDD.

There is an urgency to be able to identify those who will develop NDD before function is compromised, so that treatment may be enacted to maintain independence. It is well established that Mild Cognitive Impairment (MCI) represents a significant risk factor for dementia[9], but it remains a subject for debate what proportion of patients with MCI will eventually develop dementia[10,11]. In recent years there has been increased interest in those who have a complaint about their cognition, but no objective impairment. This population has been referred as having subjective cognitive impairment (SCI), and there is evidence that they are at increased risk of developing dementia[12,13]

Therapeutic approaches that are directed at single biological mechanisms or targets may be inadequate give the complexity of these multifaceted neurodegenerative disorders[14]. Successful treatment may require a cocktail approach as has been applied in cancer. These may vary depending on the stage of the disorder being treated, the genetic predispositions discovered to be contributing to an individual's disease (i.e. the need to consider the role of "personalized medicine" with respect to genetic determinants, sex and gendered lives) and the possible role of mixed pathologies.

This study aims to lead to an understanding of the bases, commonalities, and distinguishing characteristics of these often devastating conditions. Through a single unprecedented collaboration studying SCI, VCI, AD/Mild Cognitive Impairment (MCI), Mixed Dementia, FTD, LBD, we aim to develop and evaluate proactive treatment strategies designed to meaningfully modify the course of each.

By employing a standardized patient approach, we can meaningfully conduct cross-comparisons amongst these conditions. Six assessment platforms have been set up to study the diseases over 5 years. They are as follows:

a) Clinical - Demographics, history, and physical exam

b) Clinical - Neuropsychology

c) Neuroimaging

d) Biosamples

e) Genomics

f) Brain donation and Neuropathology

1.2 JUSTIFICATIONS OF PLATFORMS

Clinical (Demographics, history, and physical exam)

As with all medical conditions, a person's life experience and past and current overall health status can contribute greatly to understanding how neurodegenerative diseases emerge and express themselves within an individual. An extensive clinical work-up will be administered including medical & social history, physical exam and past & current

medications, as well as gait assessment, and questions related to cognitive reserve and reproductive history.

Clinical (Neuropsychology)

Cognitive changes are core features of many neurodegenerative diseases. Specific patterns of cognitive strengths and weaknesses, quantified by neuropsychological testing, have been shown to help distinguish AD, FTD, Lewy Body Dementia (LBD), and other NDD from normal aging and each other. However, the full extent of these differences is still being researched as well as their earliest neuropsychological manifestations. We will be administering a series of tests assessing multiple domains of cognitive function with the goal of furthering our understanding of these diseases and how they affect cognition. Neuropsychological testing has minimal risks limited to fatigue and/or frustration associated with participating in cognitively demanding testing.

Neuroimaging

Over the past decade, magnetic resonance imaging (MRI) and more recently positron emission tomography (PET) has taken a greater role in the management of patients with dementia[15]. For example, after diagnosis imaging can be used to increase the certainty that AD pathology underlies dementia. Prior to diagnosis, imaging can be used to establish the etiology of disease and may help predict progression to dementia. Finally, in the pre-symptomatic phase, markers of amyloid accumulation and neurodegeneration can be used to establish pathophysiological changes in the brain[16]. The benefit of imaging will be in the form of the generation of new knowledge related to differential anatomical changes among the study cohorts.

Biosamples

Even though, neurodegenerative diseases primarily impact the brain, they also have effects on the rest of the body and these effects may be measured in blood[17], CSF[18], and saliva[19]. Buccal swabs can give an indication of telomere length[20]. Fecal samples can also be collected to study the microbiome[21]. The importance of this is that it can help us to better understand the mechanisms and effects of neurodegeneration, as well as provide potential diagnostic markers, which may aid in earlier diagnosis of these diseases in the future.

Genomics and Epigenetics

In the past 50 years, there has been considerable progress in delineating the etiologies of hereditary neurodegenerative disorders, including familial forms of AD, FTD, and LBD[22]. The rare familial forms are single-gene disorders that result from rare mutations in a well-defined panel of genes for each disease; these can be detected using DNA sequencing methods. In addition, it is now appreciated that a substantial proportion of patients who present with these diseases clinically have a genetic susceptibility component that is the aggregate of many common variants of small effect (single nucleotide polymorphisms [SNPs]), rare variants of large effect, as well as structural or copy number variants. The results of genome-wide association studies have allowed for genotyping of known SNPs to create a genetic risk score as the foundation of genetic susceptibility. A substantial

proportion of the genetic susceptibility to these disorders remains unaccounted for, but may include epigenetic and mitochondrial effects.

Brain donation and neuropathology

In many NDD, a definitive diagnosis can only be made through brain tissue analysis, generally acquired at autopsy. Despite advances in diagnostic technologies, such as the advent of amyloid imaging, tissue pathology is still the "gold standard" for NDD diagnosis. It also represents an important tool to examine epigenetic and proteomic aspects of NDD[23,24]. As part of this consortium, we will be creating a voluntary National Brain Donation Program tied to a National Brain Banking Network (NBBN) in order to optimize the collection of brain samples and to standardize the handling and analysis of brain tissue across the 10 existing brain banks in the country. The benefit of this will be the creation of a national resource, which heretofore has not been available within Canada and will allow correlations between pathology and longitudinal clinical, neuropsychological and imaging data.

1.3 RATIONALE FOR THE STUDY

To date, a collaborative approach to research that spans a wide breadth of presumably related NDD has rarely been undertaken. Not only will our research plan span a wide range of conditions, it will help with the development of standardized assessment protocols, which will allow for comparison to be made across disease states. These comparisons will allow us to identify common and unique factors across these diseases. Furthermore, creation of core assessment platforms that include multiple modalities will give us a more comprehensive evaluation of brain health in each of these disease states that is not currently available. Using these multiple modalities will allow us to identify clinical, imaging, genetic and other biological markers associated with the different neurodegenerative and vascular pathologies in the pathogenesis of adult onset dementia.

Current therapeutic approaches in neurodegenerative diseases tend to be directed towards single biological mechanisms, which may be inadequate given the complexity of these multifaceted diseases. 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 disease that may ultimately be relevant towards the identification of subjects in pre-symptomatic stages, and (2) personalized "cocktails" of therapeutic approaches that may be more effective than current approaches. Hence, this well-structured and integrated longitudinal exploratory study has the potential to deliver significant impacts on health care in the rapidly growing area of neurodegenerative disease.

This project will provide exceedingly rich research platforms that will allow us to advance our current understanding of the clinical, experiential, biological and genetic correlates of disabling outcomes in adult-onset neurodegenerative disease that have not been possible with the current funding mechanisms available. These data will also lead to development of innovative investigative tools (e.g. a mixed disease neurodegenerative gene chip) and the evaluation of both novel clinical tools (e.g. metabolomic profiles derived from salivary

samples) and therapeutic approaches. Therefore data from this project will help to focus future basic and translational research efforts.

1.4 DESCRIPTION OF PLATFORMS

Clinical

The clinical assessment will provide information on demographics, past and current medical and psychiatric conditions, past and current medications, reproductive history, childhood adversity, past and current sleep quality and patterns, past and current pain status, nutrition, lifestyle factors including physical and social activity and other domains of interest as well. In addition, the clinical items were chosen to overlap as much as possible with several large-scale provincial initiatives (Consortium pour l'identification precoce de la maladie d'Alzheimer - Quebec[25]; Ontario Neurodegenerative Disease Research Initiative[26]).

Neuropsychology

The neuropsychology platform will provide a characterization of cognitive profiles for discriminating dementia types and tracking changes in cognitive processes and systems associated with dementia progression. Domains assessed will be broad-based, including attention, learning and memory, speech production, language, executive function, and visuo-spatial function. In designing the battery of tests, we built upon the recommendations of the VCI harmonization standards[27] given the stated goal of critically evaluating the contributions of vascular disease to each of the targeted disease states. The Movement Disorder Society Task Force Guidelines were also used to design the battery of clinical tests for Parkinson's Disease patient cohort. In addition, the test battery was chosen to overlap as much as possible with several large-scale provincial initiatives. These included the Consortium pour l'identification precoce de la maladie d'Alzheimer - Quebec[25]; Ontario Neurodegenerative Disease Research Initiative[26]) and several provincial disease-specific studies (Frontotemporal dementia in British Columbia[28] and Parkinson's disease in Alberta[29]).

Neuroimaging

The neuroimaging platform will use MRI to characterize the neuro-anatomical, microstructural, and functional profiles of the dementia types and monitor changes in these phenotypes as dementia progresses. In the development of the COMPASS-ND protocol, our imaging group was able to meet with imaging colleagues across the country, to establish a "Canadian Dementia Imaging Protocol, CDIP " that will be used not only in CCNA, but in multiple other Canadian studies where brain imaging is involved. By achieving this cooperation, scientists will maximize the knowledge gained from these different studies, and be able to compare the brain images obtained similarly across by different research groups.

Specific neuro-anatomical measurements will include hippocampal volume, brain ventricle volume, and whole brain volume/cortical thickness, and may be extended to other

measurements as required for each cohort. White matter hyperintensities observed in MRI FLAIR images will provide a measure of the burden of vascular disease and the number and location of microbleeds will be directly assessed with gradient echo MRI. The integrity of white matter tracts will be assessed by diffusion tensor imaging. Specifically, we will measure fractional anisotropy and mean diffusivity that are derived directly from the diffusivity of water molecules within the tissue. We will also examine the integrity of specific fibre tracts using tractography. Finally, we will measure the functional connectivity of the default mode network using resting state functional MRI. All neuroimaging measures have been shown to be affected in one or more dementia cohorts. Therefore careful measurement using standardized methodology in the current study will allow unprecedented comparison and contrast between the various dementias studied.

Biosamples

The biosamples platform will collect blood, urine, and saliva in all participants. We will also be asking participants if they would be willing to undergo a lumbar puncture for collection of CSF samples. We expect that 25% of the cohort will consent to undergo a lumbar puncture in order to provide CSF samples (the anticipated proportion is a conservative estimate based on our review of similar observational studies that included the option of a lumbar puncture)[30]. We will also do buccal swabs on 200 participants from across the diagnostic groups. The samples will be collected, handled, stored and shipped according to rigorously established standard operating procedures. A set of core established biomarkers will be assessed for all participants including general measures of health, measures of sex-related hormones, inflammation, lipid metabolism, and oxidative stress. Further experimental measures will be assessed on sub-samples of participants based on the needs of the researchers.

Genomics

In patients, the genomics component will use: 1) sequencing (both next-generation based candidate gene resequencing and whole exome sequencing) to define the presence of mutations in genes causing familial forms of neurodegenerative diseases; and 2) common and rare variant assays, predominantly the NeuroX chip (Illumina)[31] to evaluate the common genetic susceptibility component in our patients. This will allow all CCNA program participants to be characterized as extensively genetically as they will be clinically and phenotypically. Uniquely, we will be able for the first time to test for rare monogenic and complex polygenic susceptibility across the full range of patients with neurodegenerative disorders. Familial cases with high opportunity for discovery of novel genes and novel variants will undergo whole-exome sequencing.

Brain donation and Neuropathology

Assessment of brain tissue post-mortem will provide definitive diagnoses for the various types of NDD that we will enroll into the consortium as well as providing a wealth of information that can be used to correlate with clinical, neuropsychological and imaging findings. In addition, access to brain tissue samples will allow for epigenetic and proteomic analyses of NDD. Following workshops, a voluntary national brain donation protocol will be set up to catalyze and organize brain donation of CCNA cohort subjects. A standardized

neuropathology protocol will also be established. All brains will be stored in 1 of 6 designated national CCNA brain bank centres.

2. OBJECTIVES/HYPOTHESES

2.1 PRIMARY HYPOTHESIS

Degenerative cognitive impairment can be caused by a heterogeneous group of disorders in interaction with a heterogeneous set of influences, including life experiences, sex differences, and other factors, that can be explained, characterized and predicted using an integrated multimodality approach.

2.2 PRIMARY OBJECTIVE

The primary objective is to use a pan-Canadian research consortium that will, for the first time, integrate a wide range of experimental, clinical, cognitive, imaging and epidemiological expertise to specifically address the occurrence, management, treatment, and prevention of acquired cognitive impairment in the aging population.

Using current diagnostic criteria (see Appendices A-E), our goal is to establish subject research cohorts that are well characterised in terms of their demographics, pre-morbid history, cognitive function, genetic profile, neural structure and pathology, and important biomarkers and biological indices. These data will then be made available to the research teams, allowing them access to a more extensive dataset than is typically possible.

2.3 GENERAL STUDY OBJECTIVES

1. To collect data on medical & social history, physical exam and past & current medications, as well as gait assessment and sensory function (audition, vision), and questions related to cognitive reserve and reproductive history.
2. To collect neuropsychological data assessing episodic, associative and prospective memory, attention, language, visuoperceptual abilities, processing speed and executive function.
3. To carry out collection of biosamples of blood, saliva, and urine in all participants, and CSF collection in at least ¼ of the cohort.
4. To collect MRI data according to CDIP protocol (described on page 38)
5. To identify psychosocial issues to inform the development of programmes to support patients and families.

2.4 DISEASE SPECIFIC OBJECTIVES

SCI

1. To determine if clinically meaningful subgroups of SCI (e.g., at high risk for progression to MCI and/or dementia) can be created by an integrated, multi-modality approach.
2. To determine if biomarker abnormalities can be delineated at the SCI stage.

V- MCI

1. To define clinical, neuroimaging, neuropsychological and biological fluid biomarker profiles in patients with V-MCI and evidence of a clinically unrecognized, "silent" potential vascular contribution to MCI based on neuroimaging evidence of silent brain infarcts or extensive ischemic white matter disease.

2. To determine factors, beyond age and stroke severity, that predict cognitive dysfunction in vascular populations using a multi-modal approach – e.g. MRI parameters, genetic burden, life experiences (e.g., education, SES, gender).

3. To determine if cognitive decline can be predicted by an integrated, multi-modality approach.

4. To identify protective factors which allow patients to be less cognitively impacted

5. To identify novel targets for intervention that may improve the functional status and cognition of patients after TIA.

MCI

1. To determine if clinically meaningful subgroups of MCI can be created by an integrated, multi-modality approach.

AD

1. To determine if clinically meaningful subgroups of AD can be created by an integrated, multi-modality approach.

LBD/PDD/PD-MCI/PD-NCI

1. To determine the prevalence of non-motor symptoms across the spectrum of these disorders.

2. To identify vascular risk profiles in Lewy-body related disorders and identify if patients are obtaining treatment for these.

3. To determine whether LBD patients with a greater "genetic load" (as determined by the presence of genetic risk factors for LBD, PD, other neurodegenerative diseases, vascular diseases, neuroinflammation) have cognitive and other clinical phenotypic differences from those lacking these factors (i.e. "reverse phenotyping"). These studies will serve as a basis for important future basic mechanistic studies on the links between these mutations/polymorphisms and LBD pathologies.

4. To carry out an evaluation of the specific MRI imaging profile and MRI/ symptom correlation of patients with LBD.

5. To determine the impact of non-motor symptoms and vascular comorbidity on key medical and health outcomes such as falls, hospitalization, nursing home placement and death.

FTD

1. To develop a longitudinal cohort of patients with FTD to obtain integrated clinical, genetic, blood, CSF, and neuroimaging (MRI and PET) data to study the natural history and biomarker characteristics of FTD and its subtypes as the disease progress.

2. To carry out collection of biosamples of blood and saliva in patients with FTD for genetic/genomic/proteomic/biomarkers studies.

3. To establish a nationwide clinic registry of FTD to expedite recruitment for future clinical studies. This registry would also allow the first national survey of FTD and its prevalence. At present, there isn't funding to undertake this. It will be pursued once funding is available.

3. STUDY DESIGN

This is an observational cohort study. The recruitment of this cohort will be carried out over 3 years. Assuming sufficient funding is available, there will be longitudinal follow-up 2 years after the initial assessment. Sixteen-hundred (1600) subjects, with SCI (n=300), V-MCI (200), MCI (400), AD/Mixed dementia (n=300), LBD/PDD/PD-MCI (n=200), FTD/PPA/CBD/PSP (n=200) will be predominantly enrolled into this study from up to 35 centres across Canada – Memory Clinics affiliated with the Consortium of Canadian Centres for Clinical Cognitive Research (C5R), select Canadian Stroke Clinics, and select Canadian Movement Disorders Clinics. Patients will be 55-85 years of age and recruited based on the normally occurring sex distribution of the condition.

Subjects involved in the study will undergo comprehensive evaluations at baseline, including clinical and neuropsychological assessment, biospecimen collection genomics and MRI neuroimaging. Participants may still continue to be a part of the study if they decline to undertake some procedures. The minimum level of participation required for study inclusion is the MRI scan and clinical assessment.

4. STUDY POPULATION

1600 subjects with SCI (n=300), MCI (400), V-MCI (200), AD/Mixed dementia (n=300), LBD/PDD/PD-MCI (n=200), FTD/PPA/CBD (n=200) are to be enrolled. The sex distribution of participants will be monitored to ensure that sufficient numbers of each sex are being recruited to allow evaluation for potential differences between them on key study outcomes.

The specific inclusion and exclusion criteria for enrolling subjects in the study are described below.

4.1 General Inclusion Criteria (All Conditions)

Subjects must meet each of the following criteria for enrolment into the study:

1. Written informed consent must be obtained and documented (from the patient or, where jurisdictions allow it, from their legally appointed agent).
2. Sufficient proficiency in English or French to undergo clinical and neuropsychological assessment.
3. Willing to be audio-recorded for certain assessments and to have the audio-recordings available without identifying information for analysis for 25 years.
4. Geographic accessibility to the study site.
5. Must have a study partner who can participate as required in the protocol (provide corroborative information). Study partner must have regular contact with the participant (at least one interaction per week).

4.2 CONDITION SPECIFIC INCLUSION CRITERIA

For patients with:

SCI

1. 60-90 years of age
2. Subject must meet SCI criteria (see Appendix A).

MCI

1. 60-90 years of age
2. Subject must meet NIA-AA core clinical criteria for amnestic or multiple domain Mild Cognitive Impairment (see Appendix B)
3. Select causes of impaired cognition ruled out by standardized work up for dementia including brain imaging (e.g., significant cerebrovascular disease, mass lesion) and blood work (e.g. vitamin B12 deficiency, hypothyroidism, chronic kidney disease)

Vascular MCI

1. Age 60-90.
2. Subject meets criteria for amnestic or multiple domain MCI as defined in Appendix B
3. No history of previous symptomatic stroke (asymptomatic MRI or CT evidence of silent brain infarction is not an exclusion)
4. Clinical or research CT or MRI showing either: a) 2 or more supratentorial silent brain infarcts, OR b) extensive white matter disease defined as score >=2 on the ARWMC scale for MRI or CT (see Appendix C for details)

AD

1. 60-90 years of age
2. Subject meets the NIA-AA core clinical criteria for Alzheimer's disease (see Appendix D)
3. Non-AD causes of dementia ruled out by standardized work up for dementia including brain imaging and blood work

Mixed Dementia

1. 60-90 years of age
2. Subject meets the NIA-AA core clinical criteria for Mixed Etiology dementia (see Appendix E)

LBD

1. 50-90 years of age
2. Subject meets LBD criteria (see Appendix F)

Parkinson's Disease Dementia (PDD)

1. 50-90 years of age
2. Subject meets the MDS core clinical criteria for Parkinson's Disease Dementia (see Appendix G)

Mild Cognitive Impairment in Parkinson's Disease

1. 50-90 years of age
2. Subject meets the MDS core clinical criteria for Mild Cognitive Impairment in Parkinson's Disease (see Appendix H)

FTD

1. 50-90 years of age
2. Subject meets the FTD subtype criteria for PPA or possible or probable bvFTD or corticobasal syndrome, or PSP (see Appendix I)

4.3 PLATFORM SPECIFIC INCLUSION CRITERIA

Subjects must meet specific criteria to participate in the platform. Subjects may still participate in study even if excluded from a specific platform (other than the clinical assessment and neuroimaging).

4.3.1 NEUROPSYCHOLOGY

Subject has sufficient vision and hearing to participate in testing based on screening measures.

a. Pure-tone hearing thresholds will be tested in each ear at 25 dB HL at 1000, 2000 and 4000 Hz. Participants whose hearing does not meet these minimum thresholds in at least one ear with correction will be provided with an assistive listening device (e.g., a Pockettalker®) during clinical interview and neuropsychological testing.

b. Visual acuity (both eyes) will be assessed via a question on ability to read standard newsprint with or without the aid of corrective eyewear. If the response is negative they will be excluded from neuropsychological testing.

4.3.2 NEUROIMAGING

All subjects will be eligible.

4.3.3 GENOMICS

Must be willing to provide blood.

4.4 GENERAL EXCLUSION CRITERIA (ALL CONDITIONS)

Subjects who exhibit any of the following conditions are to be excluded from the study:

1. The presence of other significant known chronic brain disease such as: moderate to severe chronic static leukoencephalopathy (including previous traumatic injury), multiple sclerosis, a serious developmental handicap, malignant tumors, Parkinson's disease (other than for the Parkinson's/ LBD cohort), and other rarer brain illnesses
2. Ongoing alcohol or drug abuse that in the opinion of the investigator may interfere with the subject's ability to comply with the study procedures.
3. Subject does not have a study partner who can provide corroborative information.
4. Individuals where English or French is not sufficiently proficient for clinical assessment and neuropsychological testing.
5. Total score on the MoCA<13
6. Symptomatic stroke within the previous year
7. Unable to undergo MRI scan due to medical contraindications or inability to tolerate the procedure.

4.5 CONDITION SPECIFIC EXCLUSION CRITERIA

For patients with:

<u>SCI</u>

1. Age younger than 60

2. Major surgery within last 2 months

3. History of intracranial surgery

4. Serious comorbid condition that, in the opinion of the study investigator, is likely to result in death within a year.

<u>MCI</u>

1. Age younger than 60

<u>Vascular MCI</u>

1. Subjects with history of symptomatic stroke (CT or MRI evidence of silent brain infarcts is allowed).

2. History of planned carotid revascularization (if enrolled with TIA).

<u>AD/Mixed Dementia</u>

None.

LBD/PD MCI/PDD

None

FTD

1. Subjects with probable Alzheimer's disease (and only possible FTD) or history of multiple head traumas, lifelong schizophrenia, or chronic depression

4.6 PLATFORM SPECIFIC EXCLUSION CRITERIA

Subjects must meet specific criteria to participate in the platform. Subjects may still participate in the study even if they are excluded from certain specific platforms (all participants must undergo a clinical assessment and neuroimaging).

4.6.1 NEUROPSYCHOLOGY

All enrolled subjects will be eligible.

4.6.2 NEUROIMAGING

All enrolled subjects will be eligible.

4.6.3 GENOMICS

N/A

4.6.4 BIOSPECIMENS

If a subject is on anticoagulants, they are excluded from undergoing lumbar puncture.

5. STUDY PROCEDURES AT EACH VISIT

All study evaluations and procedures are provided in the Time and Events schedule. The total expected duration of subject participation is approximately 5 years. Beside each visit in brackets is the estimated time for the visit and beside each procedure in brackets is the proposed administrator of the procedure and who it will be administered to.

5.1 (VISIT 1) SCREENING & DEMOGRAPHICS (ESTIMATED TIME: 2 - 2.5HOURS)

The following study procedures will be performed:

- Written informed consent prior to study procedures (study investigator or delegate of investigator; participant and study partner)
- Assess inclusion/exclusion criteria (study coordinator or nurse; participant and study partner)
- Hearing and Vision assessment (study coordinator or nurse; participant)
- Logical Memory 1 & 2 from Wechsler memory scale[32] (for SCI, MCI, V-MCI, AD, Mixed) (psychometrician; participant, audio-recorded)

- Clinical Dementia Rating scale[33] (for SCI, MCI, V-MCI) (study coordinator or nurse; study partner and participant)
- CERAD word list Recall[34] (for SCI, MCI, V-MCI, AD, Mixed) (psychometrician; participant; audio-recorded)
- MoCA[35] (all groups. SCI must have a score ≥ 25; all participants must have a score ≥13) (investigator or nurse; participant, audio recorded)
- Lawton Brody IADL scale[36](for SCI, MCI, & Vascular MCI)) (investigator or nurse; study partner)
- Benson Figure Recall[37] (for FTD, PD) (psychometrician; participant)
- Clinical PPA and bvFTD features from NACC Uniform Data Set FTLD Module[38] (FTD) (physician or nurse; study partner)
- Geriatric Depression scale & Generalized Anxiety Disorder 7 item Scale

  Some sociodemographic and physical activity information will be collected in between LM 1 & 2 for SCI, MCI, V-MCI, AD, and Mixed Dementia participants and the Generalized Anxiety scale will be administered between CERAD 1 & 2. The sociodemographic information will be collected prior to the Benson Figure Copy & Recall test and physical activity information will be collected between the Benson Figure Copy & recall in the PD spectrum and FTD spectrum groups (coordinator or nurse; participant or study partner)
- Audio recorded conversation between participant and study partner (optional)
- Take home packet provided

  Day 1 will be the date the consent is signed and all follow-up visits will be scheduled based on this. There will be a 12-week window from time of consent to complete all screening and baseline procedures.

5.2 SELF-ADMINISTERED PROCEDURES AND QUESTIONNAIRES TO BE COMPLETED BETWEEN VISITS 1 AND 2

- Fecal sample collection: the participant will be provided with a fecal swab collection and preservation kit. They will be asked to use the swab to collect a sample of feces from toilet paper they have used after a bowel movement. They will then store swab in the preservation tube and return it at their next visit.

- Hobbies and leisure activities (participant or study partner if the local investigator or staff determines that the participant is unable to complete the questionnaire)

- Tobacco and alcohol consumption (participant or study partner if the local investigator or staff determines that the participant is unable to complete the questionnaire)

- Activities of Daily Living (study partner)

- Quality of Life (participant)
- End of Life Care (participant or study partner if the local investigator or staff determines that the participant is unable to complete the questionnaire)
- Social network, support, & activities (coordinator; participant or study partner if the local investigator or staff determines that the participant is unable to complete the questionnaire)
- Adverse childhood experiences questionnaire (optional) (take home) (participant or study partner if the local investigator or staff determines that the participant is unable to complete the questionnaire)
- MDS-UPDRS, parts IB – II (LBD, PDD, PD-MCI, PD-NCI & FTD spectrum only) (study partner)
- PDQ-39 (LBD, PDD, PD-MCI, PD-NCI & FTD spectrum only) (study partner)
- Behavioral Inhibition Scale (FTD spectrum only) (study partner)
- Interpersonal Reactivity Index (FTD spectrum only) (study partner)
- Revised Self-Monitoring Scale (FTD spectrum only) (study partner)
- Neuropsychiatric Inventory - Questionnaire (study partner)
- Apathy Inventory (FTD spectrum only) (study partner)

5.3 VISIT 2: CLINICAL AND PHYSICAL ASSESSMENT (ESTIMATED TIME: 2.5 -3.5 HOURS)

At visit 2 the following information will be gathered and study procedures performed:

- Physical Measurements (nurse; participant)
- Fasting blood collection (nurse; participant)
- Saliva collection (nurse; participant)
- Urine collection (nurse; participant)
- Buccal Swab
- Health perception, fatigue, falls history & balance assessment (nurse; participant)
- Walking speed (4 and 6m)(nurse or coordinator; participant)
- Grip strength(nurse or coordinator; participant)
- Vision assessment (nurse or coordinator; participant)

- Hearing assessment(nurse or coordinator; participant)
- Olfaction assessment(nurse or coordinator; participant)
- Nutrition (nurse or coordinator; participant)
- Oral Health (nurse or coordinator; participant)
- Sleep (coordinator; participant or study partner)
- Cognitive fluctuations (coordinator; study partner)
- Caregiver burden assessment (coordinator; study partner [and participant if in a caregiving role])
- Current and past medications (coordinator or nurse; participant or study partner)
- Medical, mental health, and surgical history (coordinator or nurse; participant or study partner)
- Family history (coordinator or nurse; participant or study partner)
- Initial Disease Symptoms (coordinator or nurse; participant or study partner)
- Disease course (coordinator or nurse; participant or study partner)
- Signs and Symptoms (physician; participant)
- Physical examination (physician; participant)
- Neurological examination (physician; participant)
- Hachinski Ischemic Scale[39] (physician; participant)
- Clinical Diagnosis (physician)

5.4 VISIT 3: NEUROPSYCHOLOGICAL ASSESSMENT (ESTIMATED TIME: 3 HOURS)

At visit 3, the following information will be gathered and study procedures performed:

- Neuropsychology: IQ estimate, Verbal Memory tests (RAVLT, Digit symbol recall, Envelope test), Attention, Working Memory, processing speed tests, Visuoperceptual and construction tests (psychometrician; participant) Visual Memory tests (BVMT, Face-Name Matching), Language tests, Complex attention, executive, theory of mind tests, Neuropsychiatric scales (psychometrician; participant). This session will be audio recorded.

5.5 VISIT 4: MRI SCAN (ESTIMATED TIME: 1 HOUR)

At visit 4, the following information will be gathered and study procedures performed:

Magnetic Resonance imaging scan (imaging technician & study coordinator; participant). This visit may be scheduled any time after Visit 1. It may be done prior to the clinical and neuropsychological assessments but must be done prior to the LP.

5.6 VISIT 5: LUMBAR PUNCTURE (ESTIMATED TIME: 1 HOUR)

At visit 5, the following information will be gathered and study procedures performed:

Lumbar puncture (if consented to) (physician; participant)

5.7 FOLLOW-UP

All cohort subjects and/or informants will be contacted via telephone on an annual basis to insure continued willingness to participate and to request permission to consult their treating physician in order to determine if there has been any diagnostic change. Assuming sufficient funding is available, 2 years after the initial visit, the participants will be invited back to clinic to undergo the same procedures as in visits 2-5. If brain donation has been consented to, upon the subject's death their brain will be collected according to established protocols. If at any time during the follow-up, the participant no longer has the capacity to consent to continuing in the study (e.g. they have become severely demented), the consent of a substitute decision maker (SDM) will be sought if one has been designated. If there is not a designated SDM, consent will be considered withdrawn and participation terminated.

5.8 ADD ON STUDIES

There are studies planned by researchers in the CCNA that will recruit participants who are enrolled in the COMPASS-ND study. There may also be studies that will recruit study partners of participants in the COMPASS-ND study. Participation in these add-on studies isn't required to be enrolled in the COMPASS-ND study, although participation in the COMPASS-ND study may be a prerequisite to be recruited for some of the add-on studies. The data collected within COMPASS-ND may represent the baseline or pre-treatment data for the interventional trial and will be shared with the interventional trial research teams without identifying information attached. The protocols for these studies will be presented for review separately, but will be described in summary here along with the COMPASS-ND data that will be shared with each one.

- "SYNERGIC TRIAL" (SYNchronizing Exercises, Remedies in GaIt and Cognition); A Randomized Controlled Double Blind Trial
  The proposed SYNERGIC TRIAL is uniquely designed to evaluate the effect of aerobic and progressive resistance training exercises, isolated or combined with cognitive training and vitamin D supplementation, in older adults with MCI. Based on recent literature, after twenty to twenty four weeks (four to six months) of supervised multimodal exercise (aerobic and progressive resistance training)

alone and/or in combination with cognitive training (CT) and/or vitamin D. Primary outcome will be global cognitive function, as assessed by primary outcome Alzheimer's Disease Assessment Scale-Cognitive subscale plus (ADAS-Cog-Plus).

- Data shared from COMPASS-ND baseline assessment: All clinical, neuropsychological, MRI, and biospecimen data collected from the participant.

- Multifaceted cognitive stimulation to enhance cognitive reserve in older adults with subjective cognitive decline.

  The aim of the project is to develop and test a multi-faceted intervention program meant to increase cognitive and brain reserve by providing cognitive stimulation through participation in cognitive training sessions and engaging leisure activities. This will be done with a double-blind, randomized, controlled trial in participants with subjective cognitive decline (SCD). Exploring Novel Group Activities for Geriatric Enrichment (ENGAGE), is a 4-month long, innovative, multifaceted program which combines formal education on brain health, formal teaching of cognitive strategies to improve attention and memory skills, leisure activities known to impact cognition and potentially boost cognitive reserve: music lessons, second language (Spanish) lessons, and carefully selected videogames. Ninety participants with subjective cognitive decline (SCD) but no objective impairment based on cognitive tests will be recruited in Montreal and randomly assigned to either the cognitive program (ENGAGE SPANISH or ENGAGE MUSIC) or the active control program (ENGAGE DISCOVERY). Participants in the ENGAGE DISCOVERY program will undergo the same amount of activities as proposed in the ENGAGE SPANISH/MUSIC programs, but those activities will be designed not to be cognitively challenging. The interventions – ENGAGE SPANISH/MUSIC or ENGAGE DISCOVERY – will be provided over a 4-month period, twice a week for the first 2 months, and then only once a week for the last two months. The training will be delivered to small groups of 5 to 8 participants, at the Centre de Recherche du l'Institut Universitaire de Geriatrie de Montréal. The sessions will be about 2.5 hours long and will be complemented by assignments to be completed at home between the class sessions (1 to 2 hours per week). Behavioral measures (objective and subjective measures of cognition and efficiency in everyday life functioning) as well as neuroimaging measures (fMRI scan during a memory task) will be collected at 3 time points: before the intervention (PRE), immediately after the intervention (POST-1), and 18 months after the intervention (POST-2).

  - Data shared from COMPASS-ND baseline assessment: All clinical, neuropsychological, MRI, and biospecimen data collected on the participant.

- Nutrition, Exercise and Lifestyle Intervention

This study investigates how a combination of exercise and nutritional changes effects brain health. We will ask 66 participants aged 55 to 80 with memory concerns who have 2 of the following conditions: high blood pressure, high cholesterol,

type 2 diabetes, or are overweight to participate in this study. These 60 individuals will be randomized into one of two arms: 1) a 6-month combined aerobic and resistance exercise intervention with additional Brain Health Food Guide (BHFG) counseling (EX+BHFG) and 2) a 6-month aerobic exercise intervention with standard of care materials on healthy lifestyle (EX+noBHFG).

- Data shared from COMPASS-ND baseline assessment: All clinical, neuropsychological, MRI, and biospecimen data collected on the participant.

Participants recruited into one of these add-on studies will have to provide separate consent for the add-on component.

5.9 Study Procedure Descriptions

Informed Consent

The participant and their study partner will meet with the study physician and/or their delegated representative to go over the consent form which will include information concerning the study purpose and procedures, what would be asked of the participant and study partner, the potential benefits and risks of participation, the confidentiality of the information being collected, and the rights of the participant to withdraw consent to study participation at any point without penalty. If they agree to participate in the study, they will be asked to sign the consent form. As part of the consent process for this study, participants will be asked if they would be willing to be re-contacted for other CCNA studies they may be eligible for. Their willingness to permit this would have no impact on other aspects of the consent process. If the participant lacks capacity to consent and has a legally designated agent who could consent for them, this person can consent for the participant as long as the participant indicates a willingness to participate.

Inclusion/Exclusion Criteria

Both general and disease specific inclusion/exclusion criteria will be assessed and captured in the CRF.

Hearing and Vision Assessment

Vision assessment will consist of the participant being asked if he/she is able to read standard newsprint with his/her standard corrective lenses. If the response is no, the participant will be excluded from certain elements of the study requiring reading or visual processing of stimuli. Hearing will be assessed with a pure-tone audiometer and assess hearing in each ear at 25 dB HL at 1000, 2000 and 4000 Hz. If participant is unable to detect a signal at any point, an assistive listening device will be used at all subsequent clinical and neuropsychology visits.

Subjective Memory Assessment (administered to SCI cohort)

Three questions will be asked to assess the level of subjective memory awareness and concern: “Do you feel like your memory or thinking is becoming worse?”, “Does this concern you?”, and “Do you feel like your memory or thinking is worse than that of other people the same age as you?” These questions are adapted from the work of Jessen et al.[13]

LOGICAL MEMORY I & II (FOR SCI, MCI, V-MCI, AD, MIXED)

The participant will be instructed to listen to a story and repeat it back after it has been read. They will then be asked to recall the story approximately 30 minutes later. Administration will be audio-recorded for quality assurance of procedure.

MONTREAL COGNITIVE ASSESSMENT (MOCA)

The MoCA is a 10-minute test that provides a global assessment of cognition, covering domains of memory, language, attention, visuospatial, and executive functioning. It will be administered and captured in the CRF. Administration will be audio-recorded for quality assurance of procedure.

FUNCTIONAL CAPACITY QUESTION

Do the participant's cognitive deficits interfere with independence in everyday activities such as paying bills or managing medications? Response is recorded as Yes/No.

LAWTON-BRODY IADL SCALE (FOR SCI, MCI & VASCULAR MCI ONLY)

This 10-15 minute scale captures functional ability on 8 instrumental activities of daily living (telephone use, shopping, food preparation, housekeeping, laundry, transportation, medication management, and ability to handle finances). Each activity has a series of levels of capability described, ranging from full capability to no capability. A total score out of 23 is derived from the levels of capability for each activity with a higher score representing better functional capacity.

CERAD WORD LIST RECALL (FOR SCI, MCI, V-MCI, AD, MIXED)

This test consists of ten words to be remembered which are repeated over three study-test trials, a ten minute retention interval, a delayed recall test, and finally a twenty-word recognition test (ten studied and ten unstudied words). Administration will be audio-recorded for quality assurance of procedure.

CLINICAL DEMENTIA RATING SCALE (FOR SCI, MCI & VASCULAR MCI ONLY)

This scale collects information in a standard way from both the study partner and from the subject relative to memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. From the information collected, a severity rating is derived for each domain, as well as a global dementia severity rating. The rating is a five-point scale in which CDR-0 connotes no cognitive impairment, and then the remaining four points are for various stages of dementia: CDR-0.5 = questionable dementia; CDR-1 = mild dementia; CDR-2 = moderate dementia; CDR-3 = severe dementia.

BENSON COMPLEX FIGURE COPY & RECALL (FTD & PD ONLY)

The purpose of the test is to assess visuoconstructional and visual memory functions. The participant is first presented the figure and instructed to copy it. After they have completed

the copy, they are told to remember the figure. After 10-15 minutes they are given a blank sheet and asked to draw the figure from memory.

CLINICAL PPA AND BVFTD FEATURES QUESTIONNAIRE FROM NACC UNIFORM DATA SET FTLD MODULE (FTD ONLY)

Gateway questions are asked about the presence of PPA or bvFTD and if the answers indicates the presence of one or the other, then the rest of the related questionnaire section is filled out. For the PPA section, there are 10 follow-up questions. For the bvFTD section, there are 8 follow-up questions.

SOCIODEMOGRAPHIC DATA

Sociodemographic data (sex, age, handedness, languages, marital/partner status, living circumstances, reproductive history, education, employment history and volunteerism, household income, and driving history) will be captured in the CRF.

PHYSICAL ACTIVITY

Present levels of physical activity will be assessed with the Physical Activity Scale for the Elderly[40]. Levels of activity throughout the life span will be assessed with The California Teachers Study Long Term Recreational Physical Activity Survey[41,42].

GERIATRIC DEPRESSION SCALE[43]

Depressive symptoms will be assessed with the Geriatric Depression scale. This is a 15-item scale of Yes/No questions where each point represents a depressive answer. A score over 10 suggests depression and a score over 15 suggests major depression.

GENERALIZED ANXIETY DISORDER 7-ITEM SCALE[44] (GAD-7)

Anxiety symptoms will be assessed with the GAD-7. The proband is asked how frequently they felt the way described in a given item over the last two weeks (choices are “Not at all sure”, “Several days”, “over half the days” & “Nearly every day”). If any of the items are indicated to have been experienced several days or more, there is a follow-up question on how much difficulty this created in being able to work, take care of things at home, or get along with other people. The score is based on the frequency of each experienced item with “Not at all sure” =0 points, “Several days”=1 point, “Over half the days”=2 points, and “Nearly every day”=3 points. A score greater or equal to 10 suggests generalized anxiety.

AUDIO-RECORDED CONVERSATION BETWEEN PARTICIPANT AND STUDY PARTNER (OPTIONAL)

At, the end of this visit, if the participant and their study partner have both consented to it, they will be audio-recorded while they converse about a topic or topics of their choosing. To avoid accidental recording of other people not involved in the study, this will occur in a private room with the door closed. If a third party not involved with the study is inadvertently recorded, that section or sections of the taped conversation will be erased. The taped conversation will be analysed for communication strategies that contribute to

the resolution or the worsening of misunderstandings in communication. In addition to having a conversation taped, the study partner will be asked to complete the Perception of Conversation Index – Dementia of the Alzheimer's Type (PIC-DAT)[45]. This procedure is only being performed in English speaking participants as the PIC-DAT has only been validated in that population.

FECAL SAMPLE COLLECTION

The participant will be given package containing a swab and a capped tube with sample stabilising liquid inside. They will be asked to use the cotton swab to collect a sample of feces from toilet paper they have used after a bowel movement. They will then put the swab in the tube, re-affix the cap and return it at their next visit.

HOBBIES AND LEISURE ACTIVITIES (TAKE-HOME)

Hobbies and Leisure activities will be captured by a questionnaire developed by Rami et al.[46] and adapted for French and English by CIMA-Q[25].

SMOKING AND ALCOHOL CONSUMPTION (TAKE-HOME)

Smoking and alcohol consumption will be captured with a series of questions developed for the ONDRI clinical survey[26].

ACTIVITIES OF DAILY LIVING (TAKE-HOME)

Function in basic and instrumental activities of daily living will be captured with the Modified OARS activities of daily living scale[47].

QUALITY OF LIFE (TAKE-HOME)

Perceived quality of life will be captured through the QoL-AD scale[48].

END OF LIFE CARE (TAKE-HOME)

End of life care preparedness will be captured by three Yes/No questions about whether wishes on end of life care have been discussed and whether a power of attorney and/or advance directive have been completed (and enacted)..

SOCIAL ENGAGEMENT (TAKE-HOME)

Social engagement will be captured by assessing the social participation, support, and activities of participants. Lifetime & present social network will be assessed by six items adapted from the CIMA-Q study[25]. Social support is assessed by the MOS Social Support Survey[49] supplemented with items from Rami et al.[46] and an item addressing loneliness[50]. Social activities will be assessed using items adapted from the CLSA[51].

ADVERSE CHILDHOOD EXPERIENCES (OPTIONAL TAKE-HOME)

Adverse experiences of childhood will be captured through the Adverse Childhood Experiences scale[52].

MDS-UPDRS (LEWY-BODY DISEASE, PARKINSON'S DISEASE, & FTD SPECTRUM PATIENTS ONLY)

To capture the extent and severity of Parkinson's disease symptomatology, the Movement Disorders Society Unified Parkinson's Disease Rating Scale[53] will be administered and captured in the CRF. Parts IA, III, & IV will be done during the clinical visit with the physician; parts IB & II will be done at home by the participant.

PARKINSON'S DISEASE QUALITY OF LIFE QUESTIONNAIRE (LBD, PD SPECTRUM ONLY) (TAKE HOME)

This is a 39-item questionnaire assessing the impact of Parkinson's symptoms on quality of life. (participant)

BEHAVIORAL INHIBITION SCALE (FTD SPECTRUM ONLY)(TAKE HOME)

Part of the NACC Uniform Data Set (UDS)-FTLD Module Version 3.0[38], the BIS[54] is a 7 item scale that captures the degree of behavioral inhibition exhibited by the participant. (Primary informant)

INTERPERSONAL REACTIVITY INDEX (FTD SPECTRUM ONLY)(TAKE HOME)

Part of the NACC Uniform Data Set (UDS)-FTLD Module Version 3.0[38], the IRI is a 14 item scale designed to capture the level of empathy and perspective-taking of the participant. (Primary informant)

REVISED SELF-MONITORING SCALE (FTD SPECTRUM ONLY)(TAKE HOME)

Part of the NACC Uniform Data Set (UDS)-FTLD Module Version 3.0[38], the RS-MC[55] is a 13 item scale designed to capture the level of the participant's attention to the impact of his or her behaviour on others. (Primary informant)

NEUROPSYCHIATRIC INVENTORY –QUESTIONNAIRE[56] (TAKE-HOME)

General neuropsychiatric symptomatology of the participant will be captured with this instrument. (Primary informant)

APATHY INVENTORY[57](TAKE-HOME)

This scale assesses the perceived level of interest in activities and interactions with others. (Primary informant)

SCHWAB & ENGLAND ACTIVITIES OF DAILY LIVING SCALE[58] (LBD, PD SPECTRUM ONLY)

This is an instrument to assess participant's perception of general functional capacity on a scale from 100% capacity to 0% capacity.

CAREGIVER BURDEN ASSESSMENT(TAKE-HOME)

Caregiving perception of both the study informant and the participant (if in a caregiving role) will be captured by the Caregiving Burden Scale[59].

PHYSICAL MEASUREMENTS

Measurements will be taken of height, weight, circumference of waist, hip, neck and calf, resting blood pressure in the supine, sitting, and standing positions, and orthostatic change will assessed 1 and 3 minutes after standing.

HEALTH PERCEPTION, FATIGUE, FALLS AND BALANCE

Questions on personal perception of health status and level of fatigue will be administered to contribute to assessment of frailty[60]. Perception of falls and balance will be assessed via the Activities specific Balance Confidence scale[61,62].

FASTING BLOOD COLLECTION

BD Vacutainer tubes (BD Diagnostics, Franklin Lakes, NJ) will be used to collect approximately 60 mL of blood by standard venipuncture. The participant will have been directed to fast no less than 12 hours beforehand. If the participant has eaten within 12 hours, it will be noted along with the time of the last meal.

SALIVA COLLECTION

OG-500 kits (DNA Genotek, Kanata, Ontario) will be used to collect approximately 4mL of saliva by passive drool. The collection protocol will be as follows:

Pre-collection Steps:

1. Ask participant if they've had anything to eat or drink in the last 30 minutes (when making appointment to collect saliva, specify that the participant should refrain from eating and drinking for 30 minutes prior to the appointment)
2. If they accidentally did eat or drink, ask them to rinse out mouth with water (clean cup/disposable Dixie cup), wait 30 minutes
3. If they haven't had anything to eat or drink, ask participant to wash out mouth with water (clean cup/disposable dixie cup), wait 2 minutes
4. Put on gloves so that tester skin cells don't cross-contaminate specimen
5. Ask participant to use hand sanitizer (voluntary) prior to handling kit

Collection:

1. Hand participant Oragene collection tube and explain what needs to be done: Point out the fill line and explain amount of liquid saliva needed, timeframe (~20 minutes), can touch lips to outer rim, but avoid filling the tube completely (make sure there is room at top of tube for the liquid in the lid, as the tube can overflow quite easily)
2. Spit until amount of liquid saliva (not including bubbles) reaches the fill line
3. Once saliva reaches the fill line, have the participant return the tube to the tester to close the lid by firmly pushing the lid down until a loud click is heard; the liquid in the lid will then be released into the tube containing the saliva
4. Unscrew the funnel from the tube (put into disposable bag) and screw the small cap tightly onto the tube, all the while ensuring the tube is kept upright, then proceed to invert the tube for 5 seconds to ensure the liquids mix adequately
5. Place remaining items in disposable bag for autoclaving (gloves, packaging, etc.)

URINE COLLECTION

A urine collection container will be provided for each participant to obtain a random urine sample.

BUCCAL SWAB

Samples will be collected by rubbing a Norgen swab across the inner cheek for 30 seconds. The swab will then be put into a tube containing sample stabilizing fluid and stored at ambient temperature..

WALKING SPEED

Participants will perform walks along a 6 metre path. Institutions with available pressure sensitive mats (GAITRite® system) will perform all walk assessments attempted with the mat.

Participants will perform three main tasks: 1) preferred walking speed, 2) dual-task walking and 3) fast walking. If participants use assistive aids (cane, walker) then the tester will determine the participant's capacity to walk safely without the use of the aid. If participants are willing, they will then perform one test walk without the use of the aid. To ensure the safety of participants, they will be accompanied during the performance of gait tasks when the risk of falling is judged by the local investigator or staff to be significant.

The first walking block will measure self-selected or preferred walking. Participants are instructed to "walk at a comfortable and secure pace" and it will be assessed over four[63] and six[64] meters. Participants will be asked to walk twice over a marked, six-metre course at their usual walking pace. The time in seconds to get to four meters and six meters will be captured. Each performance will be recorded as the number of metres walked per second over four and six metres.

The second block of trials will be dual-task walking. There will be an initial determination at least an hour prior to the walking tasks of the ability of the participant to perform the

cognitive tasks as outlined. If unable to perform a task, the specific testing will not be done. The first dual task will be walking while counting backward by serial 1's from 100 (100-99-98…). The second dual task will be walking while naming animals (fluency test). The third dual task will be serial 7s in which participants will be asked to walk while subtracting 7's from 100 (100-93-86…). During this trial participants are encouraged to keep walking even if they cannot do the subtractions. The evaluator must not on the form how many numbers were subtracted or if the participant did no subtractions. Participants are encouraged to continue walking during all trials.

The third and final block will include a single walk where the participant is asked to walk as quickly as possible as a 'capacity' reference for preferred walk velocity.

In all walks, participants will start 1 meters before the start of the 6 meter walk and continue 1 meter past the end of the 6 meter walk to ensure steady state walking.

Participants with slow walking speed (i.e., less than 0.6m/s) or participants with lower limb disability will be allowed to complete one walk if they are not able to perform the 3 trails.

GRIP STRENGTH

Grip strength will be assessed using a Jamar dynamometer. The participant will be asked to squeeze the hand-grip as hard as they can. They will have three trials on each hand, each of which will be recorded in the CRF.

VISION ASSESSMENT

Subjective experience of visual ability will be assessed by a question on perceived visual ability and an inventory of visual aids used. Visual contrast sensitivity will be assessed with the Mars Contrast Sensitivity Test[65]. Visual acuity will be assessed with the MNREAD Visual acuity chart[66].

HEARING ASSESSMENT

Subjective experience of hearing ability will be assessed by a question on perceived auditory ability and an inventory of audition aids used. Auditory acuity will be assessed with the Digits in Noise test[67]. Perceived impact of hearing loss will be assessed with the Hearing Handicap Inventory for the Elderly – Screening version[68].

OLFACTION ASSESSMENT

Olfaction acuity will be assessed with the Brief Smell Identification Test[69].

NUTRITION

Nutritional risk will be measured using the abbreviated version of the SCREEN II[70]. In addition, we will collect information on frequency of fast-food consumption, coffee and

tea consumption, and on food security. Nutrition will be measured using the Short Diet Questionnaire (SDQ)[71].

ORAL HEALTH

Oral health will be measured in the COMPASS-ND using a questionnaire based on the Ontario Health Study and studies by Locker et al.[72-74] The oral health instrument has six items measuring general oral health, chewing problems, and oral care and takes approximately two minutes to administer.

SLEEP

Sleep quality will be assessed with the Pittsburgh Sleep Quality Index[75]. In addition, we will ask questions about REM sleep behaviour (acting out dreams) and restless leg syndrome, both of which are related to neurodegeneration[76,77]

COGNITIVE FLUCTUATIONS

Level of fluctuation in cognition will be assessed with the Mayo Clinic Fluctuations Scale[78]

FREEZING OF GAIT QUESTIONNAIRE[79] (LBD, PD SPECTRUM ONLY)

A six-item scale assessing gait freezing.

CURRENT AND PAST MEDICATIONS

All prescribed and over the counter medications as well as any natural therapies received by the subject following screening must be recorded in the CRF. As well prior medications will also be recorded in the CRF.

MEDICAL, MENTAL HEALTH, AND SURGICAL HISTORY

Relevant medical, mental health and surgical history will be captured in the CRF.

FAMILY HISTORY

Relevant medical history of first-degree relatives will be captured in the CRF.

INITIAL DISEASE SYMPTOMS

Initial symptoms will be captured in the CRF.

DISEASE COURSE

Course of the disease will be captured in the CRF.

SIGNS AND SYMPTOMS

Presenting neurological, cognitive, and functional symptoms will be captured in the CRF.

PARKINSON'S DISEASE QUALITY OF LIFE QUESTIONNAIRE (LBD & PDD SPECTRUM ONLY)

This is a 39-item questionnaire assessing the impact of Parkinson's symptoms on quality of life.

PHYSICAL EXAMINATION

A complete physical examination (general appearance, HEENT [head, eyes, ears, nose and throat], lung/chest, heart, abdomen, skin, lymph nodes, musculoskeletal, neurological, extremities, other) will be performed.

NEUROLOGICAL EXAMINATION

A complete neurological exam, assessing level of consciousness, cranial nerves, motor strength, cerebellar function, sensory function, deep tendon reflexes, plantar reflexes, and gait will be performed.

HACHINSKI ISCHEMIC SCALE

The 13 item HIS[39] will be captured in the CRF.

CLINICAL DIAGNOSIS

Based on the information gathered, the presenting diagnosis will be confirmed or re-evaluated.

NEUROPSYCHOLOGY

To minimize time-of-day effects, neuropsychological assessment will always be conducted in the morning, with the final task being completed by 12:00 noon.

The battery requires between 2 and 3 hours to administer. Testing session will be audio-recorded for quality assurance of procedures.

Tests that have been administered clinically in the past 12 months will not be repeated (unless there is a discrepancy between test versions). Consent forms for each site will include a statement asking participants to allow for their clinical results from tests overlapping with the CCNA battery to be entered into the CCNA case report form. If a patient was assessed using a different version of the same test used in the CCNA neuropsychological battery, the test will be repeated using the version consistent with the study.

Test Battery#				
Domain	**Test**	**Description**	**Battery**	**Time (min)**
Premorbid IQ	WAIS-III Vocabulary subtest	Expressive Vocabulary	Core	10
Attention, working memory, processing speed	WAIS-III Digit Span forward and backward	Attention span and working memory	Core	5-10
	WAIS-III Digit Symbol-Coding	Processing speed	Core	5
Complex attention, executive, theory of mind	DKEFS Phonemic Fluency	Phonemic (letter) fluency	Core	5
	Reitan Trail making test	Switching attention	Core	5-10
	DKEFS Color Word Interference	Inhibition and switching	Core	7-12
	Hayling Sentence Completion Test	Inhibition (verbal)	Core	10
	NACC Social Norms Questionnaire	Knowledge of Appropriate Social Mores	Core	5
	Victoria Longitudinal Study on Aging Simple and Choice Reaction Time Measure	Reaction Time	Core	10
Visuoperceptual and construction	Object Decision Test - Birmingham Object Recognition Battery (BORB)	Object perception	Core	5
	Judgment of Line Orientation (split half)	Visual perception	Core	10
	Brief Visuospatial Memory Test Copy	Visuoconstruction	Core	3
Speech and language	DKEFS Semantic Fluency	Semantic (category) fluency	Core	3
	Cookie Theft Picture Description	Spoken Language	Core	5
	NACC Word Reading Test	Reading of regular and irregular words	Core	2-3
	NACC Semantic Word-Picture Matching Test	Word Recognition and Comprehension	Core	5
	NACC Semantic Associates Test	Knowledge of Meaning of objects	Core	5

	NACC Northwestern Anagram Test	Grammatical knowledge	Core	10
	NACC Sentence Repetition Test	Oral Repetition	Core	1
	NACC Noun and Verb Naming Subtests	Naming of objects and actions	Core	6
	NACC Sentence Reading Test	Sentence Reading	Core	1
Memory	Rey Auditory Verbal Learning Test	Word-list learning	Core	5-8
	Brief Visuospatial Memory Test	Figure learning	Core	10-15
	Face-Name Matching	Associative Recall	Core	10-15
	Digit Symbol - Incidental Recall	Incidental Associative Recall	Core	5
	Envelope Test	Prospective Memory	Core	5
Behaviour in testing situation*	NACC Social Behavior Observer Checklist	Completed by psychometrician	FTD only	

*Tests listed in this section will be completed by informants and/or be completed outside of the neuropsychological testing session (e.g., at home). As such, they will not require on-site administration time.

These tests will be audio-recorded.

Test Descriptions

WAIS-III Vocabulary subtest[80]

This subtest measures expressive vocabulary and requires participants to verbally define an increasingly difficult series of words that are presented visually and aurally. This subtest assesses overlearned verbal knowledge (crystallized intelligence).

WAIS-III - Digit Span[80]

This test includes two tasks, Digits Forward and Digits Backward, which are administered separately. On both tasks, the examiner reads a series of number sequences of increasing length. On Digits Forward, the participant is asked to repeat the digits in the same order as presented; on Digits Backward, the participant repeats the digits in the reverse order. On both tasks there are two trials for each sequence length, and the task is discontinued after the subject fails both trials of a given sequence length.

WAIS-III Digit Symbol Coding task and Incidental Recall[80]

This timed task asks participants to pair specific numbers with geometric figures according to a defined key. Immediately after the 120 second response period, the defined key is removed from view and participants are given another sheet containing just the symbols. Participants are then required to recall the symbols which corresponded with each number.

Delis-Kaplan Executive Function System (DKEFS) - Phonemic Fluency[81]

For this task, the participant is asked to generate words that begin with a particular letter as quickly as possible, within a 60 second time window. Three trials are given, each with a different letter. Participants are not to include names of people, places or numbers. This task measures the participant's ability to produce words in an effortful, phonemic format.

Reitan Trail Making Test[82]

This timed task assesses the participants' ability to rapidly scan and sequence: (1) a series of dots containing numbers (Part A); and (2) a series of dots containing numbers and letters in an alternating series (Part B). Errors are corrected prior to the participant moving onto the next dot. The time it takes to complete the task is the recorded response, up to a maximum of three minutes for Part A and up to a maximum of five minutes for Part B.

DKEFS - Color Word Interference[81]

This timed task requires participants to (1) name a series of colors, (2) read a series of words and then (3) name the color of the ink of dissonant color words (i.e., must say "green" when the word red is written in green ink). The latter task is a measure of response inhibition as participants must inhibit an overlearned verbal response of reading the particular word (red) in favor of generating a conflicting response of naming the different ink color (green). For the fourth trial, participants must alternate between naming the ink color of dissonant color words and simply reading the word and ignoring the ink color. The time it takes to complete the task is the recorded response, The maximum time for reading for each of the color and word trials is 90 seconds and the maximum time for the response inhibition and inhibition switching trials is three minutes.

Sentence Completion Task[83]

This is a computerized task that is a modification of the original Burgess & Shallice (1996) task[84]. Participants hear a series of 30 sentences, presented one at a time, in which the last word missing. They are asked to either give a word that fits at the end of the sentence or to give a word that is unrelated to the sentence. For the related words condition, responses are scored as either correct or incorrect. For the unrelated words condition, responses are scored as either totally unrelated, partially related or related. Response time is also recorded.

National Alzheimer's Coordinating Center - Social Norms Questionnaire[38]

The participant is given a list of twenty-two behaviors and asked whether or not the behavior is socially acceptable and appropriate in mainstream culture. Participants are asked to consider these behaviors in the context of interactions with a stranger or acquaintance, not a family member or close friend.

Victoria Longitudinal Study on Aging Reaction Time Measure[85]

This computerized task consists of both simple and choice reaction time measures, assessed by having participants make a key press to stimuli presented on the screen.

Birmingham Object Recognition Battery (BORB)- Object Decision Task[86]

Participants are shown a series of pictures and asked to identify whether the object could be real or unreal.

Judgment of Line Orientation[86]

This task requires participants to match the orientation of two lines to a selection of lines. A 15 item split half version will be administered to participants to assess spatial ability.

Brief Visuospatial Memory Test-Revised[87]

On this task, participants are presented with a 2 x 3 array of six line drawings for ten seconds. After the display is taken away, participants are asked draw each figure accurately and in its correct location on the page. There are three learning trials, a 25 minute delayed recall trial, a delayed recognition memory trial and a copy trial.

Clock Drawing Task[88]

Participants are asked to draw a clock, putting in all of the numbers and setting the hands to ten past eleven. This is a measure of visuoconstructional abilities, planning and organization and abstract thinking.

BDAE Cookie Theft Picture Description task[89]

Participants are presented with a line drawing of a scene where multiple things are happening and asked to give a verbal description of the scene. This is a measure of spoken language ability and the assessment is recorded.

National Alzheimer's Coordinating Center (NACC) Fronto-Temporal Lobe Dementia Module (NACC FTLD Module)- Selected subtests[38]

Word Reading Test Participants are asked to read 15 regular and 15 irregular words from a stimulus card. If the patient does not read the word perfectly, his/her response is transcribed verbatim and the type of error is recorded (i.e., semantic error, super-ordinate error, subordinate error, within-category errors, thematically related word). This assessment is audio-recorded.

Semantic Word-Picture Matching Test Participants are presented with an array of four pictures and asked to point to the picture that matches the word that is read by the examiner. The score is the total correct out of the twenty words that are read by the examiner.

Semantic Associates Test Participants are presented with two pairs of pictures and asked to point to the pair that have a relationship with each other. There are a total of sixteen items, eight animals and eight tools.

Northwestern Anagram Test Participants are presented with a series of pictures demonstrating an action and randomly arranged individual magnetic words on a dry-erase board. Participants are told that they must arrange all of the words to make a sentence describing the picture, beginning with "Who is". There are a total of ten items, with five items representing "Subject Who Questions" and five items representing "Object Who Questions".

Sentence Repetition Test Participants hear recordings of sentences of increasing complexity and are asked to repeat them. There are five sentences, and the score consists of the number of completely accurate sentences. In cases where sentences were not accurately repeated, the number of words omitted from the sentences, the number of semantically related or unrelated incorrect read words and the number of phonologically related words or nonword errors are recorded. This assessment is audio-recorded.

Sentence Reading Test Participants are asked to read the same five sentences, and the scoring system is the same. This reading subtest is always to be given after the repetition subtest and not given in direct succession. This assessment is audio-recorded.

Noun and Verb Naming Subtests Participants are asked to name sixteen pictures of nouns and sixteen pictures of verbs. Responses are recorded verbatim, but only scored for accuracy. Inaccurate responses are not prompted by either semantic or phonemic cues.

Social Behavior Observer Checklist Completed by the examiner at the end of the testing session, this assesses participant behaviour during the testing session within 15 domains.

DKEFS Semantic Fluency[81]

This task asks participants to verbally generate as many words as they can according to specific categories (animals and boys names) with a 60 second time period. This test is a measure of semantic knowledge.

Rey Auditory Verbal Learning Test[90]

Participants are asked to recall fifteen orally presented nouns after each of five trials. A second list of fifteen nouns is then presented and participants are asked to recall words from this second list. Participants are then asked to recall words from the initial list, without the benefit of additional repetition from the examiner. Recall and recognition for this initial list are further assessed after a 20 minute delay.

Face Name Matching

On this experimental memory test, adapted from a task developed by Dr. Simona Brambati based on her previous work[91], a series of faces paired with names are presented for

encoding and memory for names associated with each face is tested both immediately and after a 20 minute delay.

Envelope Test

This task is based on the work of Huppert, Johnson and Nickson (2000)[92] and assesses prospective memory. Participants are told that at a future time, they will be asked to write a name and address on an envelope, and that they are also to write their initials on the back. There is a ten minute delay, after which participants are given the name, address and phone number and asked to write this on the envelope. Whether or not the participant spontaneously recalls the additional instruction to write their initials on the back is recorded. If they do not spontaneously recall the additional instructions, they are prompted for the additional action.

LUMBAR PUNCTURE (ADAPTED FROM PROCEDURE USED IN THE PREVENT-AD TRIAL[93])

Patients must be lying on the lateral decubitus, at the edge of a, procedure bed, flexed, with the back horizontal and perpendicular to the bed throughout its entire length. It is important to ensure the patient is as flexed as possible, but shoulders should be perpendicular to bed, and knees and ankles should be symmetrically placed. Chorhexidine or iodine aqueous solution skin application must start in the site of puncture and continue in a concentric motion towards the iliac crest. A sterile swab should be used to wipe off the antiseptic solution from the LP site. Sterile drapes should be placed to keep sterile conditions. CSF should be collected from the vertebral interspace L3-L4 as indicated by a line joining the tips of the iliac crests or L4-L5. The goal is to anesthetize the equivalent of a volume equivalent of a radius of 2 cm including the skin and soft tissue adjacent to the intervertebral space L3-L4. Lidocaine 1% should be infiltrated subcutaneously and immediate tissues with a short (yellow) 25G needle. Following the infiltration, subcutaneous lidocaine should be dispersed by gently applying pressure with gauze above the infiltration site. Subsequently, local subcutaneous lidocaine administration should be repeated with a long (blue) 25G needle. Check the introducer and the 24G sprotte spinal needle to make sure that there are no defects. Insert the needle introducer on skin towards L3-L4 intervertebral space and subsequently the spinal needle through the introducer. At a depth of about 4-7 cm more firm resistance may be encountered as the ligamentum flavum is reached. Beyond this one should feel a slight ‘give’ as the needle punctures the dura. The stylet should be removed and clear CSF should drip out of the needle. If no fluid appears the stylet should be reinserted, the needle partially withdrawn and then advanced with a slightly different angle. CSF opening pressure should be conducted and recorded. It is good practice to take 4 tubes and to fill them each by at least 1 ml. Up to 40-50 mL CSF can be safely removed during a lumbar puncture, assuming the absence of contraindications. All tubes and .5 ml polypropylene containers will be labeled with correct bar code for the subject. The tubes should be numbered 1 to 4 according to the order they were filled. After the CSF collection, the stylet must be reinserted before the spinal needle can be removed. Finally, the spinal needle introducer should be removed. It is good practice to swab the LP site with saline soaked gauze. CSF samples will be aliquoted into .5 ml polypropylene containers and then stored in a -80 fridge until they can be transported via cryoshipper to the Canadian Biosample Repository in Edmonton for more permanent storage.

NEUROIMAGING

2/3 of magnetic resonance imaging will be performed on 3 Tesla systems and 1/3 on 1.5 Tesla systems. The following image sets will be acquired at 3T:

1. 3D T1-weighted MRI (Standardized across platforms)
2. PD/T2-weighted MRI (Standardized across platforms)
3. FLAIR (Standardized across platforms)
4. Gradient Echo (Standardized across platforms)
5. Resting state fMRI (Standardized across platforms)
6. Diffusion Tensor Imaging (DTI) (Standardized across platforms)

The following image sets will be acquired at 1.5T:

1. 3D T1-weighted MRI (Standardized across platforms)
2. PD/T2-weighted MRI (Standardized across platforms)
3. FLAIR (Standardized across platforms)
4. Gradient Echo (Standardized across platforms)

The total test time for the MRI scan will be approximately 1 hour.

BIOSAMPLES

A total of 62 mls of blood will be collected via venipuncture in 10 tubes. A total of 4 mls of saliva will be collected by passive drool in 1 tube. A total of 20 mls of CSF will be collected via lumbar puncture. The samples will be aliquoted into 500-µL V bottom, screw-top tubes (Matrix Tubes, Thermo Fisher Scientific, Carlsbad, CA) and stored in a -80 fridge until they can be transported via cryoshipper to the Canadian Biosample Repository in Edmonton Alberta under the supervision of Dr. Bruce Ritchie for more permanent storage. Core biomarkers will be assessed at 3 labs in Canada: blood and urine biomarkers will be assessed at the Clinical Chemistry lab of the Jewish General Hospital in Montreal, Quebec under the supervision of Dr. Elizabeth MacNamara; CSF core biomarkers will be assessed at the Douglas Mental Health University Institute in Montreal under the supervision of Dr. Judes Poirier; saliva biomarker will be assessed at the University of Alberta under the supervision of Dr. Roger Dixon.

GENOMICS

Blood Samples will be sent to the Clinical Genomics Centre in the Mount Sinai Hospital, 600 University Ave, Toronto, ON M5G 1X5, Canada and will be processed under the guidance of Dr. Kathy Siminovitch.

Biological samples will be handled using Health Canada Level 2 bio containment standards and DNA extractions will occur in a containment hood. All DNA must be of high quality, as indicated by: UV spectrophotometer 260/280 >1.6; 260/230 >1.7 ratios; no degradation on gel; minimum 5 µg for exome sequencing, 250 ng for the NeuroX array, 60 ng for re-sequencing panel plus extra aliquots for Sanger and qPCR validation studies, including

0.5-1.0 µg for assessment of C9orf72 expansion for specific probands. Aliquots of plasma and extracted RNA will be stored for future use.

A custom-designed CCNA Neurodegeneration Re-sequencing Panel based on IlluminaNextera Custom Enrichment chemistry will be used for all 1600 subjects (familial and sporadic) and will be sequenced on the IlluminaMiSeq platform at RRI. We will use 2 x 150 bp chemistry and will multiplex 12 samples per MiSeq run to achieve a minimum of 100x coverage. Targets represent candidate gene coding regions and 5' and 3' UTR regions and will total approximately 700 kilobases of sequence. Re-sequencing data will be aligned, annotated and variant calls will be generated at the three analysis sites. Standardized workflows on both MiSeq Reporter v2.2 and CLC Bio Genomics Workbench v6 will be used for parallel analysis. Both raw and processed data will be posted to the LORIS server.

All samples will be genotyped at the UHN Clinical Genomics Centre (CGC)/University of Toronto using the Illumina NeuroX chip suitable for genetic association analysis for all neurodegenerative diseases. This chip will provide a cost-effective common, cross-disease platform for the discovery of: a) all known mutations (~1,000) in genes known to cause neurodegenerative diseases; b) ~10,000 key tagging SNPs for all genome-wide significant loci published in human GWAS for PD, FTLD, ALS, AD and stroke together with the top ~1,000 SNPs just below genome-wide significance; c) ~240,000 coding sequence variants with a frequency of >1% in the human genome; d) ~5,000 novel coding variants currently detected by whole exome sequencing of familial cases affected by different neurodegenerative disorders; and e) ~1,000 eQTL markers. All data will be archived in LORIS within 72 hours of passing Quality Control.

If analysis with the NeuroX microarray and the Neurodegeneration candidate gene re-sequencing panel is inconclusive, there may be a benefit to extend the genomic analysis using a more comprehensive method called whole exome sequencing (WES). This might require inclusion of family members. The clinical coordinator along with the clinical lead and the appropriate genetic lead scientist will discuss the best strategy to select and contact additional family members to allow for the most informative and effective use of WES.

WES will be performed on 100 subjects including family members using best practices for exome enrichment and subsequent sequence and in silico analyses. Sequencing of the captured exome libraries is carried out on the IlluminaHiSeq 2500 platform using Illumina's 100bp paired-end reads. Raw sequencing data will be analyzed using the bioinformatics pipelines for variant identification and association analyses. Briefly, these pipelines include primary analysis (i.e., generation of sequence reads and quality scores using Illumina's CASAVA tool), secondary analysis (i.e., alignment and QA using software such as BWA), and tertiary analysis (i.e., variant calling and annotation using the Broad Institute's GATK or similar). The curated sequence (including unaligned regions) will be stored for data mining (BAM files) and variants sequentially filtered to remove those found in public databases and technology-related false-positives. All variants will be validated by Sanger sequencing and qPCR variant screening in replication cohorts at current sites used by members of the genomics team, as these instruments are commonly

available, with primers designed pertinent to researchers' discoveries and evolving directions of research.

PATHOLOGY

All participants entered into the study are eligible for the voluntary brain donation program. Clinicians are encouraged to discuss with participants and their families the possibility of brain donation. This is optional for patients. If they indicate a willingness to make a donation, the participant's designated agent or next of kin will be asked to provide consent for an autopsy limited to the central nervous system at the time of the participant's death.

Procedure

At the time of patient's death, Brain will be removed and transported to one of 6 hospitals (Queen Elizabeth II Health Sciences Centre, Halifax, NS; Douglas Mental Health University Institute, Montreal; Sunnybrook Health Sciences Centre, Toronto; University Health Network, Toronto; Foothills Medical Centre, Calgary; Vancouver General Hospital, Vancouver). The brain will be divided midsagittally, one half fixed, and the other sliced fresh. Blocks from CERAD areas[94], or other areas specific for the disease under consideration, will be placed on a cassette, labelled, embedded in OCT and snap frozen. Corresponding areas will be obtained from the fixed hemisphere.

5.10 DATA STORAGE

All data collected in this study will be stored in the Longitudinal Online Research Information System (LORIS)[95] which is based in the McGill Centre for Integrative Neuroscience in Montréal, Québec.

5.11 PILOT TESTING

Study procedures (individually and in the aggregate), participant flow, and the burden on participants will be carefully evaluated in pilot testing at more than one site before the protocol is implemented.

5.12 PROCEDURE TRAINING

A series of manual of procedures has been developed describing how to administer each procedure undertaken in this study. There have also been videos developed to model the proper administration of the tests in the neuropsychology visit, the cognitive tests in the screening visit, the sensory assessments, and the gait assessment. For the neuropsychological tests and screening visit cognitive tests, research staff are required to rate the responses of the research volunteer in the videos and submit their responses for review by the neuropsychology data monitor. Research staff are also required to obtain an acceptable criterion on a series of multiple choice questions pertaining to each test to demonstrate knowledge of testing administration and scoring procedures. If the research staff administering the neuropsychological tests is not a certified neuropsychologist, they must do a dry run through the test battery (both screening and neuropsychology visit measures) with another individual and be observed by a certified neuropsychologist prior

to testing any actual participants to ensure test administration occurs according to standardized procedures. In addition, a certified neuropsychologist will observe the first two participant assessments to demonstrate proficiency with administering the tests. If there is not a certified neuropsychologist on site to do this observation, research staff will be observed by the CCNA Neuropsychology coordinator via an encrypted video streaming service. In addition, the entire neuropsychology visit and the cognitive tests in the screening visit will be audiorecorded for all participants to facilitate data monitoring. The research staff's scoring will be monitored until such a time as the data monitor feels that the research staff has reached an acceptable criterion with minimal errors. Following this time, every second participant will be monitored by that research staff.

6. ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

6.1 DEFINITIONS

6.1.1 ADVERSE EVENT (AE)

An adverse event (AE) is any untoward medical occurrence in a subject that may present itself during the conduct of a research study and which may or may not have a causal relationship with the study procedures. An AE can therefore be any unfavourable or unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with a study procedure. An AE may be a new illness, worsening of a sign or symptom of a condition, or an effect from a study procedure.

6.1.2 SERIOUS ADVERSE EVENT (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death

- Is life-threatening, i.e., the subject was at immediate risk of death at the time of the event; it does not include any event which hypothetically might have caused death if it had occurred in a more severe form.

- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalizations and/or surgical procedures that are scheduled to occur during the study period, for an illness or disease that existed before subject enrolment in the trial, will not be considered AEs provided the pre-existing condition did not deteriorate (e.g., surgery performed earlier than the planned date).

- Results in persistent or significant disability/incapacity

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate. In other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the

subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

6.2 CLASSIFICATION

6.2.1 SEVERITY

Adverse events will be classified as mild, moderate or severe in severity as follows:

- Mild: Discomfort noticed but no disruption of normal daily activity.

- Moderate: Discomfort sufficient to reduce or affect normal daily activity.

- Severe: Incapacitating with inability to work or perform normal daily activity.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

6.2.2 ATTRIBUTION

The relationship of the AE to study procedure will be assessed by the investigator to be not related, unlikely, possible, probable or definite, as follows:

- Not related: No relationship between the AE and the study procedure, judged clearly and incontrovertibly due to extraneous causes such as concomitant medication(s) or the subject’s clinical state.

- Unlikely: The AE is more likely due to an alternative explanation such as concomitant medication(s), concomitant disease(s) and/or the time relationship suggests that a causal relationship is unlikely.

- Possible: The AE might be due to a study procedure. An alternative explanation such as concomitant medication(s), concomitant disease(s) is inconclusive. The time relationship is reasonable therefore the causal relationship cannot be excluded.

- Probable: The AE might be due to a study procedure. An alternative explanation such as concomitant medication(s), concomitant disease(s) is less likely. The time relationship is suggestive, i.e. it is confirmed by de-challenge.

- Definite: The AE cannot be reasonably explained by an alternative explanation such as concomitant medication(s), concomitant disease(s). The time relationship is very suggestive, i.e. it is confirmed by de-challenge and re-challenge.

For the purposes of safety analyses, all SAEs classified with a relationship to a study procedure of possible, probable or definite will be considered study-related events.

6.3 PROCEDURES FOR AE AND SAE REPORTING

All AEs experienced by the subject between the signing of the Informed Consent and discontinuation of the study will be reported. All AEs must be recorded in the CRF. For both serious and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

All SAEs will be recorded in the CRF starting from the time of the signing of the Informed Consent up to and including the end of study.

All SAEs, regardless of the relationship to study procedures, must be reported within one working day of site personnel being notified of the occurrence of the event.

SAE forms will be provided to each study site. The initial SAE report should include at a minimum: subject number, a narrative description of the event, and an assessment by the investigator of the intensity of the event and relationship of the event to study drug. The initial SAE report received from the site should be complete as soon as possible. A complete follow-up SAE report must be submitted when the information, not available at the time of the initial report, becomes available. The sponsor (or designee) may request SAE follow-up information.

Any SAE that occurs at any time after completion of the study, which the investigator considers to be related to study procedures, must be recorded in the CRF.

6.3.1 MONITORING OF ADVERSE EVENTS AND PERIOD OF OBSERVATION

All AEs should be monitored to determine the outcome or until the investigator considers it medically justifiable to terminate follow-up.

All SAEs should be monitored until resolved or until the SAE is clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

7. STATISTICAL METHODS

Following are the methods that will be used within each of the outlines areas.

<u>Neuropsychology</u>

Interim (baseline) analyses will include descriptive statistics, frequencies, score distributions, inter-test correlations, MANOVA (domain x diagnostic groups), logistic regression (to discriminate between groups), test sensitivity and specificity. Longitudinal

analyses will include MANOVA (domains x diagnostic groups x time)). Correlational analyses with neuroimaging and genotyping data will be completed.

Neuroimaging

Analyses 1 & 2 will be carried out for all scans. Analyses 3, 4, & 5 will be carried out in 3T scans only.

1. **Core Tissue Classification and Volumetrics.** Structural MRI will be performed using acquisition protocols that have already been standardized across vendor platforms in the PURE-MIND and MITNEC studies and are compatible with the current ADNI protocols, the VCI Harmonization criteria, and guidelines for detecting Amyloid Related Imaging Abnormalities (ARIA). The core protocol, consisting of 3D T1-weighted imaging, dual-echo PD/T2, and FLAIR sequences, allows tissue compartment classification, including a sophisticated subtype analysis of SH, classified as lacunes, and as lesions in the periventricular or deep nuclei/ white matter (not connected to the ventricles). This pipeline has been developed over the last decade and combines automatic and user-assisted manual steps. PD/T2 images are co-registered to the T1-weighted images to perform landmark-based parcellation ('SABRE"), which provides customized 26 regional volumes, not dependent on template matching, an important feature in the dementias such as FTD where focal atrophy can lead to failed template matching and case exclusion.
2. **Automated Hippocampal Segmentation.** A general computerized tool developed by CCNA researchers and provided through True Positive Medical Devices Inc.[96] will provide volumetry reports. These reports will contain age- and sex-matched measures of brain structures. The analysis will provide quantitative volumetric estimates of intracranial capacity, total parenchyma, total grey and white matter, cortical and deep grey matter, as well as cerebral spinal fluid. In addition, it will provide grey and white matter volumes for each brain lobe (frontal, parietal, temporal, occipital) as well as the cerebellum. Furthermore, state-of-the-art algorithms will provide highly precise volumes of deep grey matter structures (thalamus, caudate, putamen, globus pallidus) and medial temporal lobe cortices (hippocampus, parahippocampal gyrus, entorhinal cortex, perirhinal cortex, amygdala).
3. **Diffusion Tensor Imaging.** Preprocessing will initially be based on standard approaches using FMRIB Software Library (FSL) that have proven effective in measuring significantly preserved white matter integrity in elderly bilinguals versus monolinguals (mean age = 70.5 yrs, SD = 3 yrs) based on significant differences in fractional anisotropy (FA) and radial diffusivity. Standardised endpoint biomarkers will be defined and provided in consultation with the DTI neuroimaging researchers.
4. **Resting state fMRI.** Preprocessed resting state data sets will be provided within CCNA for each subject utilising automated pipelines: 1) with a standard fixed set of pipeline steps including adaptive physiological noise correction to eliminate the need to obtain external physiological noise measures from all subjects, and 2) an individually optimized set of pipeline steps for each subject. Standardised endpoint

biomarkers will be defined and provided (e.g., network metrics) in consultation with the resting state neuroimaging researchers.

5. **Brain Atrophy Ischemic Vasculopathy Index (BAIVI).** Using the structural imaging core protocol, the clinical neuroradiology team will help develop and validate clinical rating scales of hippocampal and global atrophy, regional microbleed counts, lacunes and white matter lesions.

Genomics

Standard bioinformatic tools will be used for data processing and analysis, including MiSeq Reporter v2.2, PLINK, PLINK/SEQ, Applied BiosystemsTaqManGenotyper and SeqScape, CLCBio Genomics Workbench v6, ANNOVAR based annotation scripts and Ingenuity Pathway Analysis.

Neuropathology

A standardized neuropathology protocol to be used on all CCNA subject brains will be developed by a group of Canadian neuropathologists and neurologists in association with Platform #6 under direction of Dr. Sultan Darvesh of Dalhousie University.

7.1 Interim Analysis

No interim analyses are planned

7.2 Handling of missing, unused or spurious data

All data will be included in data listings and/or summary tables. No imputation of values of missing efficacy or safety data will be performed.

8. ETHICAL CONSIDERATIONS

The current study will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH-GCP) and the applicable regulatory requirements.

8.1 Incidental findings

All data collected will be reviewed by a qualified reviewer for medically significant findings within 90 days of its collection. Any medically significant findings will be communicated in writing to the CCNA National Operations Manager (NOM) in Montreal. The NOM will link the participant code to his or her identity and the finding will be passed on to the study site physician of the participant in question within 24 hours. The study site physician will be responsible for determining the significance of the finding, arranging appropriate follow-up and informing the NOM and the primary care physician (if provided) in writing of the follow-up within 5 days of receiving notice of the finding. . The finding

and its follow-up will be documented and monitored until it has been resolved or as long as the participant remains in the study.

8.2 Institutional Review Board

All relevant documents for this study will be submitted to an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for review. A signed and dated letter documenting IRB/IEC approval must be obtained prior to entering subjects at the site. The IRB/IEC must be notified of all subsequent protocol amendments.

8.3 Informed Consent

Prior to any study procedures, it is the responsibility of the investigator to fully inform the subject or legally acceptable representative, of all pertinent aspects of the study. Each subject or a legally authorized representative must give written consent prior to the subject's participation in the study. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirement(s).

8.4 Confidentiality of Subject Records

The LORIS system[95] will house the data from participating institutions. LORIS is a web-based database solution for neuroimaging and other research data that is physically located at McGill University in Montreal. It will store data that has been processed to remove any direct identifiers of an individual study participant. Study subjects will be assigned a unique coded study identification number that will be used to store their data.

The investigator will grant monitor(s) and auditor(s) from CCNA and regulatory health authorities access to the subject's original medical records for verification of the data gathered and to audit the data collection process. The subject's confidentiality will be maintained. Information about study subjects will be made publicly available to the extent permitted by the applicable laws and regulations. In CCNA publications, only group data will be reported.

In cases where participant identification is required (e.g. when an incidental finding is uncovered on coded data), the recruiting site study investigator for the participant will be informed and be given access to only the minimum identifying information required to link the participant to the incidental finding and move it towards a resolution.

8.5 Participant Burden

The potential burden on participants will be carefully evaluated by pilot testing where input from investigators, potential participants and care partners will be sought. The protocol will not be implemented until this evaluation is done and all stakeholders agree that the burden on study participants is reasonable. The pilot testing will also allow us to provide specific information on the likely burden placed on participants for inclusion in the consent.

9. ADMINISTRATIVE REQUIREMENTS

9.1 PROTOCOL AMENDMENTS

The Sponsor may modify the protocol at any time during the life of the protocol. Protocol amendments will require IRB/IEC approval prior to implementation except when changes to the protocol are required to eliminate immediate hazards to the study subjects. The Sponsor and IRB/IEC must be notified immediately after such changes have occurred.

9.2 PREMATURE TERMINATION OF THE TRIAL

If the investigator or Sponsor discovers sufficient reasonable cause for the premature termination of the study, the terminating party will provide written notification documenting the reason for study termination. The appropriate regulatory agencies and IRB/IEC must be notified.

9.3 COMPLETION OF CASE REPORT FORMS

Standardised subject demographic and clinical-research meta-data

Non-imaging data (ie. Demographic, clinical) will be entered directly (or transcribed) into the LORIS system. LORIS CDEs will be incorporated into case report forms (CRFs).

Neuroimaging

Image Upload: Raw neuroimaging data and experimental meta-data (e.g. QA/QC scans, physiological signals, etc) will be de-identified and defaced and uploaded to LORIS for secure archive and sharing.

Open Access Database: Neuroimaging data sets that pass QA/QC will be automatically run through standardized, image processing pipelines at True Positive, and the results will be linked with their corresponding raw data and metadata. These standardized processing results will be provided to researchers without precluding download of raw or intermediate processed data for use of alternative (pre)processing strategies under rules to be determined by the executive and steering committee. Datasets generated by preprocessing and analysis tools at individual sites (i.e., image processing and analysis pipelines) will also be uploaded to the LORIS system, as determined by the Executive and Steering committees, using standard formats (e.g., NIfTI) where available, and linked with their corresponding raw data and metadata.

At the option of the Neuroimaging platform leaders/researchers, non-standardised preprocessing and analyses may be conducted within LORIS' secure, high-performance computing environment. This would allow neuroimaging personnel to connect to dedicated high-end servers, virtual machines, and storage over a secure virtual private network (VPN) connection to run a selected set of individual analysis tools (e.g., FSL, AFNI, Freesurfer) or manage standardized, automated pipelines using the LONI workflow management engine.

Genomics

Genomic analysis raw data and associated sample and experiment metadata will be de-identified and uploaded to the LORIS molecular database subsystem for secure archival and sharing. Data types will include resequencing (IlluminaMiSeq; approx. 600 samples; 3 GB/sample), exome sequencing (IlluminaHiSeq; approx. 100 samples; 50 GB/sample), genotyping (IlluminaiScan/HiScanexome arrays; approx. 700 samples; 5 MB/sample), as well as Sanger sequencing and qPCR/TaqMan assay outputs.

Documentation to be provided from the dedicated assay platform teams will be quality assurance reports from the assays and instruments and bioinformatics workflows including tuning parameters for the analyzed data. For analysis software tools deployed or developed centrally at LORIS there will be similar documentation available.

The investigator and site study personnel will be trained on CRF completion. The investigator is responsible for all entries in the CRF for completeness, accuracy and clarity. The investigator or designee should complete the CRF as soon as possible after the information is collected. The investigator is responsible to endorse all the information recorded in the CRF and will provide formal approval of the final submitted data.

9.4 Access to source data/documents

The investigator will permit study related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

9.4.1 Data Quality Assurance

Study data will be entered in the CRF by trained study personnel. Data validation edit checks will be defined and implemented. Inconsistent and questionable data detected during data entry or data validation process will be queried. Data clarification forms (DCFs) will be generated and any discrepancies will be resolved.

Standardised subject demographic and clinical-research meta-data

As quality control for transcribed data, double entry will be performed on a randomly chosen subset of 10% of the data from each clinical site over the course of the project. Feedback on detected errors will be immediately provided to each site for ongoing QC and data improvement.

Neuroimaging

Standardized QC: We will leverage our experience with semi-automated, web-based visual image evaluation, and quantitative QC tools (http://www.birncommunity.org/tools-catalog/) at the Montreal Neurological Institute and the Centre de recherche de l'Institut universitaire en santé mentale de Québec within Dr. Collins' and Dr. Duchesne's neuroimaging groups, respectively. (Dr. Collins & Duchesne to fill in)

9.4.2 Retention of Study Documents

The investigator must retain all study records for 25 years after the notification of the IRB/EC regarding the end of the study or according to applicable regulatory requirements.

If the investigator retires, relocates or withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

9.5 Publication and Data Access Policy

In order to access the data generated in this study, researchers must agree to abide by the CCNA Publication and Data Access policy, a document prepared by the CCNA Publicaton and Data Access Committee (PDAC) and which can be downloaded at www.ccna-ccnv.ca. The PDAC is made up of members of CCNA and is chaired by a member of the CCNA Research Executive Committee. PDAC members list is available upon request. Access to and analyses of CCNA acquired data by CCNA investigators will be granted automatically upon request of access to the PDAC. For non-CCNA investigators, CCNA data will be embargoed for one (1) year after the entire cohort has been completed, uploaded into LORIS, quality-controlled and cleaned, and subsequently locked. After the embargo period, non-CCNA investigators may be granted access to CCNA acquired data upon submission to the PDAC of background materials and of a project outline supporting their data access request. They will only be granted access to data related to the project outlined. CCNA partners will have the same access to CCNA acquired data as non-CCNA members, although they may ask CCNA investigators to pursue projects on their behalf.

Prior to submission for publication or for presentation of any data or results obtained in this study, notification of the PDAC is required. Draft manuscripts, abstracts and presentations should be submitted to the PDAC for review and approval. The Participating Institutions will retain the ownership of the data obtained in this study. Authorship of publications resulting from this study should accurately reflect the academic contribution of individuals to the design and implementation of the trial, analysis of the data and preparation of the manuscript. No researcher shall include identifiable personal health information in any publication or presentation. All publications that arise from the use of data contributed by the participating institution will give acknowledgement, attribution, or co-authorship as appropriate in accordance with the International Committee of Medication Journal Editors (ICMJE) standards and any rules established by the data access committee.

9.6 Biological Sample Access Policy

Biological samples will be stored at the Canadian Biosample Repository in Edmonton. Approximately half of the samples will be used for planned analyses which will occur at the Jewish General Hospital Clinical Laboratory in Montréal, Québec (on blood and urine), the laboratory of Judes Poirier at the Douglas Mental Health University Institute in Montréal, Québec (CSF), and the laboratory of Roger Dixon at the University of Alberta in Edmonton, Alberta. The rest will be available for investigators who wish to perform further analyses on the whole cohort or a subset. Access to these samples will be regulated by the Biological Sample Access Committee which is made up of members of CCNA (members list available on request). Requests for access will be assessed for feasibility, scientific rigour, and alignment with the consent of the participants. In order to be granted access to samples, investigators must agree that the data they generate from the samples will be included in the larger CCNA database on LORIS within 2 years of sample batch receipt. Samples will be shared within Canada only for a period of 3 years after the last

sample has been collected. After that 3 year period, they will be available to international researchers, if not already depleted. The full Biological Sample Access policy document is under development and will be made available upon its finalization.

9.7 CONFIDENTIALITY

All confidential information, verbal and written, provided to the investigator by the Sponsor will be kept in strict confidence, and restricted to the study personnel involved in conducting the study, except if the information is required by the IRB/IEC or similar committees.

9.8 FINANCING

Financing will be addressed in a separate agreement with study centres.

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Appendix A: Criteria for Subjective Cognitive Impairment (from Jessen et al., 2014)[97]

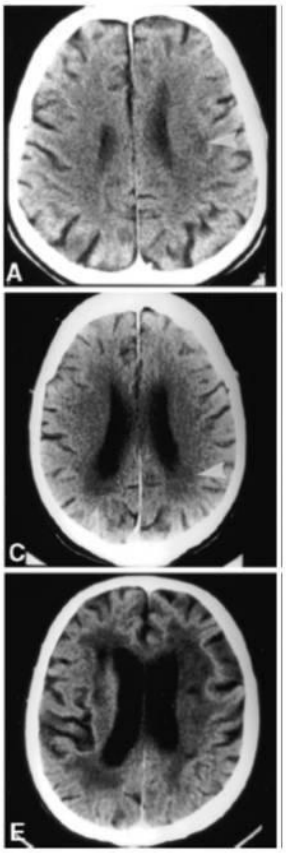
Core Diagnostic Criteria	Operationalized as
Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.	Answer "yes" to both of the following questions: "Do you feel like your memory or thinking is becoming worse?" and "Does this concern you?"
Normal age-, sex-, and education-adjusted performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal AD.	Global CDR=0; Logical Memory 2 above ADNI education-adjusted cutoffs*; CERAD word list recall score >5; MoCA total score $\geq$25.

Appendix B – NIA-AA Clinical Criteria for the Diagnosis of MCI due to AD (from Albert et al., 2011)[98]

Core diagnostic criteria	Operationalized as
Concern regarding a change in cognition	Report from patient and/or informant of such
Impairment in one or more cognitive domains	1 or more of the following: - Logical memory below ADNI cutoffs* - CERAD word list recall <6. - MoCA score 13-24 inclusive - Global CDR>0
Preservation of independence in functional abilities	Score > 14/23 on the Lawton-Brody IADL scale
Not demented	Global CDR $\leq$ 0.5

Appendix C: Criteria for Subcortical Ischemic Vascular Mild Cognitive Impairment (based on published criteria from Gorelick et al., 2011 and Sachdev et al, 2014)[4,99]

Core Diagnostic Criteria	Operationalized as
Presence of mild cognitive impairment (as defined in Appendix A)	Meets Diagnostic Criteria of Appendix B
Absence of prior symptomatic stroke (silent brain infarcts are allowed).	No reported history of symptomatic stroke
Presence of "diffuse, subcortical cerebrovascular disease"	1. Presence of 2 or more silent brain infarcts in supratentorial locations (i.e., excluding cerebellum or brainstem), OR 2. Extensive white matter disease, defined as Age-Related White Matter Change (ARWMC) scale score of 2 or higher (indicating "beginning confluence of lesions" or greater) in any brain region. (See image below)



Grade 1

Grade 2

Grade 3

TABLE 1. The ARWMC Rating Scale for MRI and CT

White matter lesions	
0	No lesions (including symmetrical, well-defined caps or bands)
1	Focal lesions
2	Beginning confluence of lesions
3	Diffuse involvement of the entire region, with or without involvement of U fibers

Grade the MRI or CT slice with the most severe signal abnormalities. Patients with score ≥2 meet eligibility criteria for the Vascular MCI cohort.

APPENDIX D – NIA-AA DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DISEASE (AD) (from McKhann et al., 2011)[100]

Core diagnostic criteria	**Operationalized as**
Gradual progressive change in memory and/or other cognitive function over more than 6 months.	Report from patient and/or informant of such
Objective evidence of significant decline in at least 2 of the following cognitive /behavioural domains: - Episodic memory - Reasoning, problem solving - Visuospatial abilities - Language - Personality/behavior	2 or more of the following: - Logical memory below ADNI cutoffs* - CERAD word list recall <7. - MoCA score 13-24 inclusive (with at least one point lost in a non-memory task). - Positive response to the question: Has the participant had any changes in personality or behaviour Yes/No
Impairment of functional abilities	Positive response to the question: The cognitive deficits interfere with independence in everyday activities such as paying bills or managing medications Yes/No
Non-AD causes of dementia ruled out	No report or sign of any of the following: sudden onset, focal neurological features, early extrapyramidal signs, metabolic abnormalities, cerebrovascular disease, or MRI T2 or FLAIR signal abnormalities, or evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Appendix E: Criteria for Mixed Dementia (from McKhann et al., 2011)[100]

Core Diagnostic Criteria	Operationalized as
Gradual progressive change in memory and/or other cognitive function over more than 6 months.	Report from patient and/or informant of such.
Objective evidence of significant decline in at least 2 of the following cognitive/behavioural domains: - Episodic memory - Reasoning, problem solving - Visuospatial abilities - Language - Personality/behaviour	2 or more of the following: - Logical memory below ADNI cutoffs* - CERAD word list recall <7. - MoCA score 13-24 inclusive (with at least one point lost in a non-memory task). - Positive response to the question: Has the participant had any changes in personality or behaviour in the last year Yes/No
Impairment of functional abilities	Positive response to the question: The cognitive deficits interfere with independence in everyday activities such as paying bills or managing medications Yes/No
Non-AD causes of dementia may be present	Report or sign of one or more of the following: sudden onset, focal neurological features, early extrapyramidal signs, metabolic abnormalities, cerebrovascular disease, or MRI T2 or FLAIR signal abnormalities, or evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition

APPENDIX F - REVISED CRITERIA FOR THE CLINICAL DIAGNOSIS OF DEMENTIA WITH LEWY BODIES (from McKeith et al., 2005)[101]

Core diagnostic criteria	Operationalized as
Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.	Report from patient and/or informant of such over the course of at least one year
Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.	MoCA score 13-24 inclusive on testing within the last year.
Has two or more of the following core features by themselves, or one or more if at least one suggestive feature (criteria below) is present: – Fluctuating cognition with pronounced variations in attention and alertness. – Recurrent visual hallucinations that are typically well formed and detailed. – Spontaneous features of parkinsonism.	Positive responses to 2 or more of the following check box items: - Does the participant have fluctuating cognition with pronounced variations in attention and alertness Yes/No - Does participant have recurrent visual hallucinations? Yes/No - Does the participant have spontaneous features of parkinsonism Yes/No
Has one or both of the following suggestive features: – REM sleep behavior disorder. – Severe neuroleptic sensitivity.	Positive responses to 1 or more of the following check box items: - Does the participant move in their sleep or act out their dreams? Yes/No - Does the participant have severe neuroleptic sensitivity? Yes/No/Unknown

APPENDIX G: Criteria for Diagnosis of probable Parkinson's Disease Dementia (from Emre et al., 2007; Dubois et al., 2007 & Postuma et al., 2015)[102-104]

Core diagnostic criteria	Operationalized as
Both must be present: Meets the International Parkinson and Movement Disorder Society clinical diagnostic criteria for Parkinson's disease. Has a dementia syndrome based on MDS Task Force proposed criteria: insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, and defined as: - Impairment in more than one cognitive domain. - Representing a decline from premorbid level. - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms.	"Yes" response to 8 items of the diagnostic rating sheet for probable PD-D recommended by the MDS task force: 1. Parkinson's disease? 2. Parkinson's disease developed before dementia? 3. MoCA≤20? 4. Dementia has Impact on ADLs? 5. Impaired cognition? (For Yes, at least of 2 of 4 tests below are abnormal) Mark which Tests are abnormal (taken from MoCA): Sevens backwards; Lexical fluency or clock drawing; Figure copy; delayed word recall less than 3 of 5. 6. Absence of Major Depression? 7. Absence of delirium? 8. Absence of other abnormalities that obscure diagnosis?

Appendix H: Criteria for Mild Cognitive Impairment in Parkinson's Disease (from Litvan et al., 2012)[105]

Core Diagnostic Criteria	Operationalized as
Diagnosis of Parkinson's disease as based on the IPMDS Criteria	"Yes" response to check box item on diagnosis of Parkinson's Disease
Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician	Report from patient and/or informant of such
Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities	MoCA 13-24 inclusive

Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present	Negative response to the question: The cognitive deficits interfere with independence in everyday activities such as paying bills or managing medications Yes/No

APPENDIX I - Diagnostic criteria for FTD subgroups

Progressive Supranuclear Palsy (PSP) Diagnostic Criteria (from Litvan et al., 1996)[106]

Core diagnostic criteria	**Operationalized as**
Possible PSP - Vertical supranuclear palsy OR - Both slowing of vertical saccades & postural instability with falls < 1yr after disease onset Probable PSP - Vertical supranuclear palsy & postural instability with falls < 1yr after disease onset	a)"Definitely present" box checked on Clinical PSP features question on presence of supranuclear palsy as determined by a qualified clinician b) "Definitely present" box checked on Clinical PSP features question on postural instability with falls < 1 yr after disease onset c) "Definitely present" box checked on Clinical PSP features question on slowing of saccades as determined by a qualified clinician Possible PSP= a, or b & c positive Probable PSP= a and b positive

Possible behavioural variant Frontotemporal Dementia (bvFTD) (from Rascovsky et al., 2011)[107]

Core diagnostic criteria	**Operationalized as**
At least 3 of 6 diagnostic features: - Disinhibition - Apathy / Inertia - Loss of sympathy / empathy - Perseverative / compulsive - Hyperorality - Neuropsychological profile	- Positive responses on gateway question and 3 items of the NACC FTLD module bvFTD features checklist OR Positive responses on gateway question and 2 items of the NACC FTLD module bvFTD features checklist and evidence of executive dysfunction on cognitive screen.
Functional disability	Positive answer to impaired functioning on the NACC FTLD module bvFTD features checklist.

Neuroimaging consistent with bvFTD (if available).	Frontal lobe atrophy on MRI or reduced frontal lobe metabolism on FDG or reduced frontal perfusion on SPECT

Diagnostic Criteria for Corticobasal Syndrome (CBS) (from Armstrong et al., 2013)[108]

Core diagnostic criteria	**Operationalized as**
Possible CBS • May be symmetric • 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus • plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation) **Probable CBS** • Asymmetric presentation • 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus • plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)	a) "Definitely present" box checked on Clinical CBS features question on limb rigidity and akinesia as determined by a qualified clinician b) "Definitely present" box checked on Clinical CBS features question on limb dystonia as determined by a qualified clinician c) "Definitely present" box checked on Clinical CBS features question on limb myoclonus as determined by a qualified clinician d) "Definitely present" box checked on Clinical CBS features question on orobuccal or limb apraxia as determined by a qualified clinician e) "Definitely present" box checked on Clinical CBS features question on cortical sensory deficit as determined by a qualified clinician f) "Definitely present" box checked on Clinical CBS features question on alien limb phenomena as determined by a qualified clinician **Possible CBS**= 1 of a-c and 1 of d-f present **Probable CBS**= 2 or a-c and 2 of d-f present plus symmetric presentation

Primary Progressive Aphasia (PPA), all forms (from Mesulam, 2001)[109]

Core diagnostic criteria	Operationalized as
Insidious onset and gradual progression	Report of informant of same.
Must have all 3: - Language impairment as the most prominent clinical feature - Language difficulty as the cause of impaired ADL's - Aphasia as the most prominent feature at onset and in early stages	- Report of informant of same - Positive response to the question: The language deficits interfere with independence in everyday activities such as work, hobbies, or interacting with friends Yes/No - Report of informant of same
Must not: - Be better accounted for by other neurodegenerative, psychiatric, or medical disorders - Have initial episodic memory, visual memory, and visuoperceptual impairments - Have prominent initial behavioral disturbances	- Medical history - Intact performance on clock and figure drawing on the MoCA and relatively normal Benson Figure Recall - Negative response to gateway question on NACC FTLD module bvFTD features checklist.

PPA-Semantic (from Gorno-Tempini et al., 2011)[110]

Core diagnostic criteria	Operationalized as
Both must be present: - Impaired confrontation naming - Impaired comprehension of single words	- "Definitely present" box checked on Clinical PPA features question on poor object naming; - "Definitely present" box checked on Clinical PPA

	features question on impaired word comprehension;
At least 3 of the following 4 features: - Impaired object knowledge	- "Definitely present" box checked on Clinical PPA features question on poor object/person knowledge;
- Surface dyslexia or dysgraphia	- "Definitely present" box checked on Clinical PPA features question on surface dyslexia and dysgraphia;
- Spared repetition	- "Absent" box checked on Clinical PPA features question on impaired speech repetition
- Spared syntax and motor speech	- "Absent" box checked on Clinical PPA features question on grammatical errors and effortful speech

PPA-Nonfluent/Agrammatic (from Gorno-Tempini et al., 2011)[110]

Core diagnostic criteria	**Operationalized as**
At least one must be present: - Agrammatism	- "Definitely present" box checked on Clinical PPA features question on grammatical errors;
- Apraxia of speech	- "Definitely present" box checked on Clinical PPA features question on effortful speech;
At least 2 of the following 3 features: - Impaired complex syntax	- "Definitely present" box checked on Clinical PPA features question on impaired speech repetition;
- Spared comprehension of single words	- "Absent" box checked on Clinical PPA features question on impaired word comprehension;

- Spared object knowledge	- "Absent" box checked on Clinical PPA features question on poor object/person knowledge

PPA-Logopenic (from Gorno-Tempini et al., 2011)[110]

Core diagnostic criteria	**Operationalized as**
Both must be present:	
- Impaired word retrieval and naming	- "Definitely present" box checked on Clinical PPA features question on impoverished word selection;
- Impaired repetition of sentences and phrases	- "Definitely present" box checked on Clinical PPA features question on impaired speech repetition;
At least 3 of the following 4 features:	
- Impaired complex syntax	- "Definitely present" box checked on Clinical PPA features question on speech sound/word errors;
- Spared comprehension of single words	- "Absent" box checked on Clinical PPA features question on impaired word comprehension;
- No apraxia of speech	- "Absent" box checked on Clinical PPA features question on effortful or halting speech;
- No agrammatism	- "Absent" box checked on Clinical PPA features question on grammatical errors.