Chronic Neuropsychiatric Sequelae of SARS-CoV2: Protocol and Methods from the Alzheimer's Association Global Consortium

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Abstract

Coronavirus Disease 2019 (COVID-19) has caused over 3.5 million deaths worldwide and affected more than 160 million people. At least twice as many have been infected but remained asymptomatic or minimally symptomatic. Though initially understood as a respiratory illness, COVID-19 includes central nervous system manifestations mediated by inflammation, cerebrovascular, anoxic and/or viral neurotoxicity mechanisms. Over one third of patients with COVID-19 develop neurologic problems during the acute phase of the illness, including loss of sense of smell or taste, seizures, and stroke. In a portion of affected persons, damage or functional changes to the brain result in chronic sequelae including and mounting evidence indicates that cognitive and neuropsychiatric complications may be independent from the severity of the original pulmonary illness. It behooves the scientific and medical community to attempt to understand the molecular and/or systemic factors linking COVID-19 to neurologic illness, both short and long term. This manuscript describes what is known so far in terms of links between COVID-19, the brain, neurological symptoms, and Alzheimer's Disease and related dementia, with a focus on risk factors and possible molecular, inflammatory, and viral pathways. It also provides an extensive description of the Alzheimer's Association Consortium on Chronic Neuropsychiatric Sequelae of SARS-CoV-2 infection (CNS SC2) harmonized methodology to address these questions in a worldwide network of researchers and institutions.

Introduction

SARS-CoV2 and the Brain. Coronavirus Disease 2019 (COVID-19) has caused over 3.5 million deaths worldwide and affected more than 160 million people. At least twice as many have been infected but remained asymptomatic or minimally symptomatic. Though initially understood as a respiratory illness, COVID-19 includes central nervous system manifestations mediated by inflammation, cerebrovascular, anoxic and/or viral neurotoxicity mechanisms.[1] Over one third of patients with COVID-19 develop neurologic problems during the acute phase of the illness, including loss of sense of smell or taste, seizures, and stroke. In a portion of affected persons, damage or functional changes to the brain result in chronic sequelae.[2,3,4] including an estimated 34% incidence of neurological or psychiatric disorder 6 months post infection.[5] Mounting evidence indicates that cognitive and neuropsychiatric complications may be independent from the severity of the original pulmonary and systemic illness. [6-16]

One possibility is that SARS-CoV2, the causal virus of COVID-19, actually invades the brain. Both SARS-CoV2 and SARS-CoV use human angiotensin-converting enzyme-2 receptors (ACE-2)[17] as the molecular mechanism for invading cells, and these receptors are richly expressed in the brain and olfactory bulb.[18,19] It is reasonable then to consider whether SARS-CoV2's affects on the olfactory bulb (resulting in anosmia) may extend into the olfactory cortical network,[20-27] especially since this has been shown to be the case in non-human primates[28] and rodents.[26] Concerningly, neuroimaging in sub-acute COVID-19 patients provides moderately strong evidence of regional involvement of the olfactory bulb and its 1st- and 2nd-order projections.[29-34] We note too that involvement of the olfactory cortical network in early Alzheimer's Disease (AD) is well established, and olfactory dysfunction is a strong clinical correlate of mild cognitive impairment in AD and other forms of dementia.[35-37]

Other possible (or additive) pathological mechanisms underlying chronic neurological consequences of SARS-CoV2 infection include cytokine-mediated inflammation, antibody-mediated autoimmunity, and cerebrovascular pathology. These play known roles in acute neuro-COVID and may act as predisposing factors or ongoing insults for chronic or progressive

neurological impairment.

Given these concerning findings, it behooves the scientific and medical community to attempt to understand the molecular and/or systemic factors linking COVID-19 to neurologic illness, both short and long term. The following review describes what is known so far in terms of links between COVID-19, the brain, neurological symptoms, and Alzheimer's Disease and related dementia, with a focus on risk factors and possible molecular, inflammatory, and viral pathways. We conclude with a description of the Alzheimer's Association Consortium on Chronic Neuropsychiatric Sequelae of SARS-CoV-2 infection (CNS SC2), which seeks to address these and other questions through an international consortium.

Evidence of Lingering Cognitive Impairment after SARS-CoV2 Infection. Significant evidence supports a connection between cognitive impairment and coronavirus infection. After the coronavirus pandemics of 2002 and 2012, 20% of recovered individuals reported memory impairment.[89] An early report during the ongoing pandemic found that one third of individuals with COVID-19 had dys-executive syndrome at the time of hospital discharge.[89] Not only can impaired cognitive abilities lead to poor occupational and functional outcomes, but they can precipitate or exacerbate existing mental health concerns, which in turn can further contribute to cognitive dysfunction.[90,91] In a recent meta-analysis and systematic review, the most common post-COVID-19 neurological symptoms were: headache, nausea, vomiting, muscular pain, anosmia, and ageusia.[12] The same study reported that SARS-CoV2 infection may result in cognitive impairment even after mild or asymptomatic infection.[12-15] Concerningly, asymptomatic COVID-19 subjects had lowered scores in visuoperception, naming, and fluency regardless of age, though older (over 60 years old) asymptomatic subjects fared the worst[16] and young, healthy individuals recovered in as short as 4 months following infection.[92] In a sample of COVID-19 patients discharged from critical care to rehabilitation, 80% had working memory, set-shifting, attention, and processing speed deficits,[93] and in two separate samples of patients discharged home, clinically significant cognitive impairment persisted in 60-70% of patients 3-4 months after discharge, with verbal learning, psychomotor speed, and executive function most

affected.[11,13] Finally, in two independent studies of patients assessed six months after hospital admission for mild to moderate COVID-19, olfactory dysfunction and cognitive impairment were linearly predicted by older age but not disease severity.[94,95] Thus, not only is a connection between COVID-19 and lingering cognitive impairment likely, it may affect significantly more people than the already staggering numbers now known to have been infected with the virus.

SARS-CoV2 and the risk of early Alzheimer's Disease. The idea that infectious agents may contribute to the risk of AD was recently reaffirmed.[38-43] A meta-analysis of over 100,000 participants found several viruses associated with a higher risk of AD,[44] and bacteria have also been implicated.[40,44] Immunity to Herpes Simplex Virus 1 (HSV-1), the best studied example, correlates with greater cognitive impairment[45] and increased neuropathological biomarkers of AD in humans.[46,47] In mice models, HSV-1 infection increases the expression of amyloid precursor protein,[48] triggers the accumulation of amyloid- β and hyperphosphorylated tau,[47,49,50] and impairs adult hippocampal neurogenesis.[45,49-52]

Of note, susceptibility to COVID-19 is driven in part by risk factors that overlap with those of AD and related dementias (ADRD), including older age[53,54] and ApoE4 status.[55-57] In regards to the latter, in vitro experiments show that human neurons derived from iPSCs are more susceptible to SARS-CoV2 infection and neurodegenerative changes if they carry ApoE4/4 genotypes.[58] Given that ethnic minorities in both the USA and UK,[59,60] as well as in individuals globally who have blood type A,[60,61] are at higher risk of COVID-19 complications and death, it appears that ancestry interacts (whether directly or through health disparities) with environmental factors to contribute to SARS-CoV2 related disease susceptibility, and therefore potentially also COVID-19-related ADRD risk. In short, after the acute pandemic recedes, its sequelae are likely to impact dementia research for years to come.[1]

The Complexity of Alzheimer's Disease Causation. The total number of people living with dementia worldwide approaches 50 million and is projected to surpass 130 million by 2050,[68] the majority of whom have AD. Despite massive investments, no effective treatments are

available.[69-72] Slow progress in understanding and treating AD may be due in large part to disease heterogeneity and the multiplicity of causal contributions.[68,73] However, dementia syndromes continue to be refined with contributions from neuropathology, longitudinal clinical assessments, advanced neuroimaging, and molecular markers,[68,72,74] and the emergent picture suggests overlapping phenotypes linked to multiple biological substrates.[75-76] Studies of causation reveal contributions from genetic variations, lifestyle choices, and environmental risk factors, including infections, plus the interactions of these factors.[68,73,77,78]

Identification of causal genetic variation was expected to guide development of disease-modifying treatments for dementia, yet at the time of this submission, the majority of heritability remains unexplained despite large lists of disease-associated genetic variants.[68] Risk prediction improves when large numbers of genetic variants are combined into polygenic risk scores (PRS), but these successes are largely limited to populations of European ancestry.[79-81] When applied across ancestry groups, or even across different segments of the same ancestry, PRS performance appears to deteriorate.[82] Under-represented minorities in genetic studies of ADRD therefore represent a severe knowledge gap that increasingly may result in greater health disparities as precision medicine becomes the prevalent paradigm.[83]

It is our firm belief that untangling the complexity of ADRD will require novel, data-driven strategies that take advantage of complex datasets (neuropsychological, environmental, neuroimaging, genomic, blood-based biomarkers),[84-86] deep learning and explanatory artificial intelligence,[87] and the inclusion of ancestral populations[88] in order to uncover naturally-occurring data structures or architectures. Such an approach is discovery-based and agnostic, allowing diagnostic heterogeneity and overlap to assist in the uncovering of specific biological mechanisms. A promising environmental factor that could be used in such an effort is SARS-CoV2 (SARS-CoV2) exposure,[18,20,28 ,64-67]

Epidemiological Factors Predictive of Cognitive Impairment. Though physical inactivity, smoking, and obesity (but not heavy alcohol consumption) are related to increased rates of hospital admission,[96] specific risks for transient or persistent cognitive impairment following

SARS-CoV2 infection have not yet been identified. Diabetes mellitus increases the risk for dementia and other severe outcomes after SARS-CoV2 infection.[91] Diabetes is highly prevalent in certain demographics, such as Black American/African Americans and Latino/Hispanic Americans, and these groups also appear to be at higher risk for the neurological complications of COVID-19.[97] Disparities in COVID-19 hospitalizations and mortality according to ethnicity remain even after correcting for neighborhood, household crowding, smoking, body size, diabetes, and mental illness.[98]

Age also appears to be a factor, as COVID-19 patients who are 65 years of age or older have more severe systemic disease and higher rates of neurologic complications. It is already well known that COVID-19 morbidity and mortality is very high in the elderly population, with 6 to 930 times higher likelihood of death compared to younger cohorts. The highest risks are among the most elderly (≥85 years) and, older person with medical comorbidities such as hypertension, diabetes, heart disease, and underlying respiratory illness.[53] Elderly patients with preexisting neurologic diseases are both more susceptible to severe COVID-19 infection and show higher rates of mortality than their neurologically healthy counterparts.[53,54] Most intriguingly, in a very large study of the UKBiobank, the ApoE e4e4 genotype was associated with COVID-19 test positivity at genome-wide significance in individuals of European ancestry, and the e4e4 genotype was also associated with a 4-fold increase in mortality after testing positive for COVID-19.[33] This finding, which was replicated in an independent community sample in Spain.[57]

Clinical Factors Predictive of Cognitive Impairment. Variations in host immune responses to SARS-CoV2 infection may partially explain age and sex differences in disease severity,[99,100] and possibly also the frequency and severity of chronic sequelae.[1] Levels of inflammatory markers, such as C-reactive protein,[101] ferritin,[102] and d-dimer[103] were associated with elevated risk of poor outcomes of COVID-19 in a dose-dependent manner, and a marker of heart failure was associated with increased mortality in COVID-19 pneumonia.[104] Delirium in hospitalized COVID-19 patients also correlates with elevated inflammatory markers.[10] However, in community cases, COVID-induced impairments in short-term memory, attention, and concentration did not

correlate with hospitalization, treatment, viremia, or acute inflammation.[92] Likewise, in patients discharged from critical care to rehabilitation, persistent executive dysfunction was not associated with mechanical ventilation or preexisting cardiovascular or metabolic disease.[13] On the other hand, in a small sample of community cases with mild symptoms, hyposmia was correlated with cognitive impairment.[105] And although younger patients (less than 60) may frequently complain of cognitive dysfunction, objective changes in performance are mild or absent and the best predictors include psychiatric complaints and physical symptoms (headache, diarrhea), with the only common risk factor being olfactory dysfunction.[6,14,105,106] Taken together, these findings hint at a role for inflammation in disease severity generally, but not necessarily for cognitive sequelae, and reinforce concerns about olfactory involvement in relation to cognitive impairment.

Overlapping Risk Factors Between COVID-19-induced Cognitive Impairment and Progressive Cognitive Decline and Alzheimer's Disease. Both ADRD and COVID-19 are age-dependent disorders, becoming much more frequent and severe with advancing age.[40] Morbidity and mortality of COVID-19 are also elevated in AD, and individuals suffering AD are more likely to develop COVID-19 and to die as a consequence of the illness.[40] Other risk factors potentially linking SARS-CoV2 infection with progressive cognitive decline and ADRD include: molecular pathway abnormalities, clinical profiles, and partially overlapping neuroimaging signatures. The Angiotensin-Converting Enzyme 2 (ACE2) receptor acts as the ligand for the spike protein of SARS-CoV2 mediating cell entry.[107] ACE2 expression declines with age, resulting in a pro-inflammatory state that may explain the increased severity and comorbid diabetic and hypertensive complications observed in older adults.[1] SARS-CoV2 specifically infects endothelial cells expressing ACE2, potentially leading to the observed deterioration of vascular architecture.[1] This could lead to brain hypoperfusion and accelerate cognitive decline in the elderly.[1,64,91] As a result of ACE2 downregulation, SARS-CoV2 infection in older adults induces aggressive secretion of pro-inflammatory cytokines.[1] Indeed, COVID-19 results in high levels of proinflammatory cytokines, acute respiratory distress, and hypoxia, each of which may

contribute to cognitive decline in healthy and in already predisposed individuals.[1,91,108,109] Pro-inflammatory cytokines increase oxidative stress, resulting in downregulation of excitatory amino acid transporters and elevated glutamate levels, which may in turn cause excitotoxicity. This pathway is already postulated to play a role in several neurodegenerative diseases, including ADRD. The olfactory bulb has one of the highest levels of ACE2 expression in the brain, and direct viral entry into neurons may create an additional cytotoxic insult.[109] Even a transient presence of the virus in the olfactory bulb may precipitate an underlying proteinopathy associated with age-related neurodegenerative disorders.[1,110,111,112,113] The neuroinvasive potential of SARS-CoV2 may result in senescence of several different CNS cell types, including oligodendrocytes, astrocytes, and neural stem cells that can differentiate into neurons that integrate into the granule layer.[1,114] Viral aggravation of underlying AD neuropathology has the potential to hasten the onset of, or further deteriorate, motor and cognitive deficits.[20,91,114]

In silico network-based relationships have been reported as pathways and processes that are implicated in ADRD, and they have been confirmed in transcription studies.[115] In addition, abnormal expression of AD biomarkers was found in the cerebrospinal fluid and blood of patients with COVID-19.[115] As already mentioned, ApoE4, a strong genetic risk factor for ADRD, has been associated with increased risk for severe COVID-19. Notably, the neurotropism and neurotoxicity of SARS-CoV2 in human-induced pluripotent stem cell derived neuron-astrocyte co-cultures and brain organoids was found to be much higher in ApoE4/4 neurons and astrocytes.[116] Systems biology approaches have predicted the interaction between prohibitins, a class of mitochondrial proteins, and SARS-CoV-2.[117] The same prohibitins have been shown to mediate altered mitochondrial bioenergetics in olfactory bulb neurons donated from AD patients,[118] possibly representing a common underlying molecular mechanism. A broader picture of overlapping mechanisms in the olfactory bulb includes equivocal disruption of MAPK cascades, which has been detected specifically in the olfactory bulb in AD[118] and is a hallmark of SARS-CoV-2 infection.[119] Furthermore, cases of persistent anosmia and parosmia may in fact reveal pre-existing neurogenesis defects, unmasked by SARS-CoV-2 infection and providing the niche for the onset of neurodegenerative disease.[21] Along with neuropathological

evidence of SARS-CoV-2's intraneuronal entry, its neuroinvasive potential may be defined by immune fitness on the cellular level.

Neuroimaging studies also provide possible links between COVID-19 and brain changes. A defined profile of brain PET hypometabolism in long COVID patients with biologically confirmed SARS-CoV2 and persistent memory impairment was shown more than 3 weeks after the initial infection symptoms. Alterations involved the olfactory gyrus and connected limbic/paralimbic regions, extending to the brainstem and cerebellum, and were associated with symptoms.[120] In older adults (average age 66), a significant reduction of frontoparietal and temporal glucose metabolism was related to cognitive impairment.[8] These reductions persisted with some improvement six months after COVID-19 diagnosis.[121]

The reviewed literature does not, however, prove a link between SARS-CoV2 infection and ADRD. Most specifically, no available evidence supports the notion that cognitive impairment following SARS-CoV2 infection is a form of dementia (ADRD or otherwise), because no data regarding the progression of neuropathological disease are available. Even though COVID-19 has significant, attendant lethality in the acute phase, death is not as a result of an extended, progressive neuropathological disease. Therefore, until and unless a clear progressive pattern of disease is demonstrated in at least some individuals as a direct sequelae of infection with SARS-CoV2, this will remain an open question. The longitudinal methodologies espoused by the consortium are intended to provide data to answer it as clearly as possible controlling for possible confounders.

The Alzheimer's Association Consortium on Chronic Neuropsychiatric Sequelae of SARS-CoV-2 infection (CNS SC2). Collectively, the reviewedThe information reviewed here results provides important clues and evidence to support oura hypothesis that cognitive impairment after SARS-CoV2 infection in older adults may be progressive in nature and associated with epidemiological risk factors (including genetic ancestry), biomarkers, and neurosignatures that are overlapping with, or identical to, those of ADRD. To test this hypothesis, our group has embarked on a large-scale, international collaboration to explore the association of SARS-CoV2 infection with neurological, psychiatric, and cognitive outcomes in an ethnically and

geographically diverse population. The underlying hypothesis is that the COVID-19 pandemic will increase rates of cognitive decline and dementia in older adults worldwide, presenting a very unwelcome but unique opportunity to understand interactions between the genomic risk of ADRD and relevant environmental factors, including viral exposure to SARS-CoV2.[18,20,63-67] The primary objective of this large-scale study is to clarify the pathogenesis of ADRD and to advance our understanding of the impact of a neurotropic virus on the long-term risk of cognitive decline and other central nervous system sequelae. The proposed research extends prior work to include under-represented racial and ethnic groups, creating a rich cohort for future studies of the pathophysiology, determinants, long term consequences, and trends in cognitive aging, ADRD, and vascular disease. *Our specific hypothesis is that SARS-CoV2 triggers ADRD-like pathology following the extended olfactory cortical network (EOCN) in older individuals with specific genetic susceptibility.* Of specific interest is the consequence that cognitive complaints in younger adult individuals may be of a different nature than those observed in older adults and obey different molecular mechanisms, clinical course, and outcomes. The proposed methods will allow us to address this and other questions.

Methods

Enrollment Countries. Member countries include (see Figure 1, Map of Consortium Members): Argentina, Australia, Austria, Bolivia, Brazil, Canada, Chile, China, Colombia, Cuba, Denmark, Dominican Republic, UK (England, Wales and Scotland), Ethiopia, Finland, France, Germany, Greece, Haiti, Honduras, Iceland, India, Israel, Kenya, Mexico, Netherlands, Nigeria, Peru, Philippines, Qatar, South Africa, Spain, Sweden, Tanzania, Thailand, and Uganda. Given the variety of countries involved, cohorts will include all major genetic backgrounds found in low, lower-middle, upper-middle and high-income countries. Data collection is already ongoing in several of the member countries.

Enrollment Criteria. We will recruit participants of age 50 years and above, with the lower cut-off being somewhat higher in some locations. About half of COVID-10 hospitalized patients are >55 years, making them a good population for investigating interactions between viral infections and the risk of cognitive decline and dementia.[1,18] Both males and females will be recruited.

Recruitment and sampling procedures. The principal objective of the CNS-SC2 protocol is to provide sufficient flexibility of recruitment and data collection to maximize sampling opportunities, while at the same time harmonizing procedures and methods enough to allow for meta-analytic approaches and other forms of appropriate data collation. Thus, participant recruitment processes are permitted vary somewhat depending on the site and study sample. Screening questionnaires will be used to determine eligibility and recruit participants via either telephonic and video interviews or during clinic and hospital visits. When possible, one informant (family member or close friend) will be enrolled per participant. We plan to use several complementary recruitment frameworks:

1. *Hospital-based Samples*: We will derive these from sampling frames constructed using current lists of hospital admissions for COVID-19 in academic centers. Participating academic groups with immediate access to hospital admissions data for patients who tested positive for COVID-19 allow recruitment of persons at relatively high risk of neurological complications, given that severity of infection warranted hospitalization. That is, while the relationship between acute severity and neurological complications does not hold as well for individuals with less severe disease, it is well established for cases that required hospitalization.(CITES) Following discharge, these patients will be contacted and offered enrollment in a cohort with a minimal longitudinal follow-up of between 12 and 24 months of the initial assessment. Representativeness of the sample will be determined by comparing characteristics of the full list of hospital admissions against those who enroll. Wherever possible, individuals discharged from the hospital but negative for COVID -19 infection (and matched for age range) will be recruited to represent the background risk of cognitive decline and neuropsychiatric pathology.

2. *Population Registry Samples*: Wherever they are available, we will establish new cohorts by sampling from existing national, regional, or local (e.g. city) population registries that include SARS-CoV2 testing data (regardless of hospitalization or the result of the testing) as part of the pandemic response. Such samples will include a wide range of outcomes, including respiratory or general symptoms severe enough to warrant hospitalization (with and without intensive care admission), mild symptoms (managed in ambulatory settings), asymptomatic positive individuals, and those who tested negative. From these lists, we will randomly invite participants stratified by testing status and regardless of symptom severity. This approach will make it possible to estimate population-level effect sizes, including error estimates that take account of, and are corrected for, each sampling fraction and the numbers successfully obtained, leading to greater external validity. To trim the samples, scores from semi-structured interviews may be used to determine the clinical severity of the COVID-19 and to populate the stratified sample from the cohort.
3. *Preexisting Population-based Cohort Samples of Aging individuals*: Wherever there are surviving participants of ongoing, longitudinal, community-based cohort studies already collecting biosamples, cognitive, behavioral, and neuroimaging data in populations that fit our age criteria, we will attempt to include them in CNS-SC2. COVID-19 status will be determined using both standardized Case Report Forms (CRFs) developed by the NeuroCOVID Forum of the World Health Organization and via antibody titer for SARS-CoV2 exposure. Participants in these cohorts already have pre-existing extensive baseline phenotyping, and in many cases have been extensively genotyped as well, allowing direct assessment of predictors of the short- and long-term effects of exposure to COVID-19 infection and complications from SARS-2. Because follow-up data collection in surviving participants of such historic samples are less likely to be representative of the original populations they were sampled from, analyses will check for lost to follow-up (nonparticipation) bias. However, as with comparisons with pre-COVID-19 samples (below) that are unlikely to have adopted the same measurement methods used in this protocol, synthetic data analysis methods will be required to combine findings newly enrolled samples (e.g. recruitment frameworks 1 and 2 above).

4. *Population-based Pre and Post COVID-19 Multiple, Cross-sectionally Representative (Probabilistic) Samples*: Where available, these may also be included in order to compare pre and post COVID-19 individuals. Such designs provide extensive pre COVID-19 population data for comparison with a new sample to be collected post COVID-19 in the same individuals. Whereas participant data in the pre COVID-19 samples can be presumed to be COVID -19 negative, it will be necessary in the post COVID -19 samples to determine their case status by questionnaire or COVID-19 test results. Such a design will be able to disaggregate the effect of viral infection from the social, economic, and psychological effects of living through the pandemic period.

Identification of SARS-2 Exposure. COVID-19 positivity will be categorized as definite, probable, and possible based on testing, documentation, and symptomatology (see Table 1). A positive PCR occurring within 3 months of enrollment will be exclusionary, as it could indicate current infection. Since the pandemic is still ongoing, seroconversion of participants in the uninfected comparison group is a potentially serious concern. Seroconversion could occur after the documented initial negative PCR but before the initial assessment or after the initial assessment but prior to the 24-month follow-up visit. The primary method for confirming seronegativity was initially planned as circulating antibodies against SARS-CoV2, but the introduction of successful vaccination programs all but excludes this tool to document lack of infection. We must therefore rely on clinical history documentation and monitoring of the registry for repeated PCR tests documenting active infection at a later time. Even with careful monitoring of both, we may fail to identify asymptomatic infections in some individuals. However, this limitation may improve the robustness of any findings of cognitive decline in the targeted population (i.e., participants with documented positive infection), since undetected asymptomatic infections would have the effect of increasing cognitive decline in the comparison group, reducing any potential group differences.

Stratification of COVID-19 Symptom Severity. For symptom severity, baseline evaluations of all enrollees will include detailed case report forms for COVID-19 developed by the World Health

Organization's NeuroCOVID-19 Work Group (several Consortium investigators are members of this group). These forms will be used to stratify COVID-19 severity according to a four-level scale: Care level 0: no treatment required; Care level 1: ambulatory treatment; Care level 2: hospital admission without or with oxygen supplementation; and Care level 3: intensive care unit admission with or without mechanical ventilation.

Data Collection Time Points. The initial plan calls for a minimum of two data points separated by 12 to 24 months. A schematic description of the planned data collection is provided in Figure 2.

Core Outcome Measures. Since the first cases of human infection by SARS-CoV2 are just approaching two years ago, it is impossible to predict the range of neuropsychiatric sequelae that may ensue from it. On the other hand, as reviewed above, acute and post-acute manifestations of COVID-19 disease commonly include cognitive impairment and, less frequently, overt psychiatric symptoms including mood abnormalities and psychosis. Therefore, we have chosen assessment instruments that allow an exhaustive assessment of neurological and psychiatric symptoms. Given the multinational nature of the consortium, we have also chosen instruments that are available and validated in as many languages as possible or, as is the case for cognitive assessment tests, are as unbiased as possible when used in individuals with varying mother tongues, literacy levels, or and cultural contexts. The following specific tools were selected (see Table 2):

1. *Phenomenological description*: In order to be able to capture novel patient descriptions and clinical signs, our assessment approach is flexible and semi-structured. Specifically, the World Health Organization semi-structured interview Schedules for Clinical Assessment in Neuropsychiatry (WHO SCAN) will be used to ascertain psychopathology and neurological symptoms.[122] Version 3 of WHO SCAN contains detailed semiquantitative (dimensional) assessments of the subject's report of behavioral neurology (cognitive efficiency, memory for recent events, executive function, language, etc), and psychiatry (anxiety, mood, hallucinations, delusions) phenomenology, as well as the interviewer's observations of interviewee behaviors.

WHO SCAN also provides automatized algorithms for all of the clinical diagnosis contained in Section F of the International Classification of Diseases revisions 10 (ICD-10) and 11 (ICD-11). When possible, and as provided for in WHO SCAN, informants will be interviewed for their impressions of the subject's cognition and to confirm the accuracy of the subject's responses. Pre COVID-19 data on historical clinical phenomena and the previous life course, both which are important in modelling future outcomes, are also assessed in SCAN and the SCAN 2.1 Clinical History Schedule, which takes account of externally provided data.

With the exception of personality disorders, the WHO-SCAN covers all forms of neuropsychiatric outcomes, including somatic complaints, anxiety, mood disorders, obsessional phenomena, neurodevelopmental phenomena (autism, ADHD), psychosis, drug, alcohol, gambling and eating problems and an assessment of cognitive decline. Outputs include pre-specified symptoms (e.g. delusion; panic; elation), dimensional symptom scores, and the determination of published diagnostic criteria. Experienced psychopathologists can be trained by means of a three-day online course that includes role play and interview rating sessions to ensure concordance and reliability. WHO-SCAN is coordinated by a WHO advisory group that can advise on training, translation, and research protocol specifications with the support of centers throughout the world.

2. *Neurological examination*: The neurological evaluation at each site is conducted and supervised by trained clinicians who are blind to neuropsychological test and PCR results and to SARS-CoV2 testing status and history. The evaluation includes semiquantitative assessments of visual and auditory perception, muscle strength and tone, eye and facial movements, coordination, gait and balance, and muscular fatique (after two minutes of walking). With participant consent, neurological exams will be videotaped. Diagnoses of parkinsonism and focality due to completed stroke will be noted, as will incidental diagnoses of non-cognitive neurological disorders (e.g., seizure neuropathy, headache). Finally, the WHO SCAN interview permits the collection all of the information needed to score the Clinical Dementia Rating Scale.[123]
3. *Cognitive assessment battery*. A customized neurocognitive assessment was developed to meet three criteria: (1) adapted to multiple cultural settings and languages, and therefore

minimally biased by formal education and native tongue; (2) robust to low levels of formal education or literacy, (3) reasonably brief. Details are provided in Table 2. The neuropsychiatric manifestations of SARS-CoV-2 infection have been characterized in the acute phase of the disease, but less is known about long term sequelae. Given this uncertainty, it is reasonable to include tests that probe multiple cognitive domains. Since both cortical and subcortical circuits may be affected, a broad cognitive assessment is warranted. Pictorial versions of most tests are proposed to minimize biases imposed by language of origin and literacy levels. The two tests that may need to be completed in a face-to-face format, as they require automatic understanding of natural language, are the ACE III (a short but comprehensive cognitive battery), and the shortened Boston Naming Test. All the other tests can be computerized easily. To our knowledge, there is currently no Visual Paired Associates Test that clearly mirrors the verbal version. Orbito-frontal functions will be assessed using the Iowa Gambling Task and the Reversal Learning Task. The classic test for psycho-motor speed is the Digit Symbol Substitution Task. The battery is completed by test for neglect, high order visual perception, and social cognition. We expect some degree of variation across sites on the specific tests used as a consequence of, among other things, the availability of local norms and validation, but every site will collect data on the same cognitive domains using analogous tests when the exact versions are not available. For meta-analytic assessments, we will use normalized z- scores of the performance for each domain.

4. *Emotional reactivity assessment*: The Perth Emotional Reactivity Scale (PERS), a self-report measure of trait levels of emotional reactivity, assesses the typical ease of activation, intensity, and duration of individual positive and negative emotional responses,[124] Concurrent validity has been demonstrated via congruent correlations with other emotion measures.[159]
5. *Supplemental measures*. To facilitate data sharing with ongoing studies, wherever feasible sites will collect information to fill the National Alzheimer's Coordinating Center Uniform Dataset (NACC UDS)[124-127] where feasible. The National Alzheimer's Coordinating Center (NACC) established the Uniform Data Set (UDS) for longitudinal data by means of a standardized clinical evaluation.[124-127] NACC is responsible for developing and maintaining a database of

participant information collected from all of the Alzheimer's Disease Centers (ADCs) funded by the National Institute on Aging (NIA). UDS defines an expanded, standardized clinical data set to provide ADC researchers a standard set of assessment procedures, collected longitudinally, to better characterize ADC participants with mild Alzheimer disease and mild cognitive impairment in comparison with nondemented controls. The UDS has data collection forms for initial and follow-up visits based on NACC definitions, a relational database, and a data submission system enhanced to provide efficient and secure access data submission and retrieval systems (https://www.alz.washington.edu).[127] The NACC UDS is validated for international Alzheimer's disease cohorts and is available in English, Spanish, and Chinese (Mandarin). Psychosocial measures, including quality of life, stressful life events, and poverty and financial hardship will also be collected where possible. Admittedly, this information is partially duplicative with other components of the proposed assessment. Local decisions over use will be driven by the availability of locally validated and culturally adapted assessment tools, as well as participant burden.

6. *Neuroimaging*.

a. 1.5 and 3 Tesla Scanners. To promote consistency in data analysis, we will follow standardized MRI imaging datasets developed for the acquired 1.5T and 3T scans by the Alzheimer's Disease Neuroimaging Initiative Study 3 (ADNI3). By so doing, we will optimize direct comparisons of various analysis methods, particularly given large variations among older MRI systems and the state of the art systems available at high-end academic centers. ADNI3 provides a two-tiered approach to accommodate the range of variability in scanners, including ADNI-3 Basic and ADNI-3 Advanced. The latter include structural T1-weighted, 3D FLAIR, T2* GRE, ASL, and high resolution images of the hippocampus. The Advanced Diffusion MRI and Resting State fMRI scans take advantage of simultaneous multi-slice acceleration for echo-planar images (EPI). For longitudinal consistency, Advanced sequences can be down-sampled postscan to match the Basic sequences. The standard ADNI3 sequence acquisitions are listed in Table 2. We will collect region-specific volumetric and cortical surface measures; white matter hyperintensities as a proxy for vascular disease; vascular lesion burden (including infarcts and

microbleeds); tract-specific fractional anisotropy and mean diffusivity; BOLD-derived voxel-based physiological (VBP) indices of neurovascular coupling; and, if positron emission tomography is available, region-specific glucose uptake as markers of tissue metabolism and synaptic integrity.

b. 7 Tesla Ultrahigh Field Scanners: The higher contrast and spatial resolution of 7T MRI provides submillimeter measurements, allowing study of small cortical and subcortical structures of the brain and providing superior detail to 3T. Enhanced anatomical detail at 7T allows higher sensitivity in measuring sub-structural volume loss, including hippocampal subfields[128] and the earlier detection of neurodegeneration implicated in ADRD. The UK 7T Network (which includes members of the CNS SARS-Cov2 consortium) have previously tested and proved the reproducibility of 7T scanners (Siemens and Phillips) across various sites.[129,130,131] The harmonized sequences, listed in Table 3, are designed to study volumetric assessment of: cortex, hippocampal subfields, and thalamus; quantitative cerebral white matter changes and inflammation; iron content from blood breakdown (cerebral microbleeds, microthrombi); markers of endothelial injury; and volume and injury to the sub-structures of the brain stem, including Locus Coeruleus. Comparative control groups with identical 7T MRI images include age, gender, and ethnicity matched participants who are both healthy or have an illness of similar severity (ICU admission, hospitalization without ICU, or no hospitalization). The study of 7T imaging precursors of Alzheimer's disease will further benefit from an independent 7T MRI study of patients with early onset Alzheimer's disease as an additional comparison group (clinicaltrials.org Identifier: NCT04992975). We will analyze the acquired data through data sharing agreements based on the local expertise of each site within the 7T MRI COVID Consortium.

7. *Biomarkers.* Collection methods for whole bloods, plasma, serum, anucleated blood cells, mouth swab for epigenomics, and cerebrospinal fluid are detailed in Supplementary Tables 1-2. Blood spot is recommended for all sites, and blood or salivary swab is recommended for DNA (GWAS). Participating sites will collect, store, use, share, and dispose of human biospecimens in accordance with the informed consent signed by the subject, or under a waiver of informed

consent granted by an independent ethical review body at each institution. When specimens are collected from humans for the study purposes, the collection and storage process should aim to adhere, as closely as possible, to harmonized study protocols and procedures appropriate for the type of biospecimen being collected and its intended uses. We will establish biorepositories within global regions where biospecimens will be collected. Raw data will be analyzed locally, such that only metadata will be shared across the consortium. Specific agreements between each repository and collection site will be (or have already been) established. All biorepositories, whether large or represented by individual freezers in laboratories, will follow best practices using effective facility environments that include ambient temperature controls, good air circulation, lighting, and security. Systems will be in place to allow for local and remote temperature monitoring of freezers, refrigerators, and other temperature controlled environments. Biorepositories will have emergency preparedness plans that cover equipment failures and power interruption that include back-up storage capacity and back-up power supplies such as generators. (https://oir.nih.gov/sites/default/files/uploads/sourcebook/documents/ethical_conduct/guidelines-biospecimen.pdf). Special attention will be paid to the appropriate packaging and shipping of human biospecimens between the collection site and the biorepository. This includes conforming to all applicable regulations and standards, including, but not limited to, those of the U.S. Department of Transportation (DOT) (DOT PHMSA PHH50-0079, 2006) and the International Air Transport Association (IATA) (IATA Dangerous Goods Regulations, 2019; IATA Infectious Substances Shipping Guidelines, 2019). All personnel involved in shipping biological materials should be trained properly for both air and ground shipments. A full list of the proposed biomarkers is included in Table 2.

8. *Genotyping*. Specific approaches will vary across sites, but at a minimum, each dataset will contain genome-wide genotypes from cohort individuals to address the role of ancestry and genetic variation on susceptibility to neuropsychiatric sequelae. When available, sites will obtain whole genome sequencing data. Our consortium is in a unique position to address the interaction between genetics (including ancestral DNA) and viral strain variation on CNS

sequelae of SARS-CoV2. If available, genotyping will be carried out using Illumina GSA (or equivalent chip) and imputation to best available panel for persons of specified ancestry.

Data Analysis. Longitudinal data analysis approaches, including time-to-event models and generalized linear models, will be used, depending on the outcome of our interests and data distribution. The cohort design will enable analyses employing survival and related regression and general linear models (depending on data distributions), using the full data set. There will also be ample scope for nested case control design approaches to analyze within selected subsets of the cohort data. These could be led by individual investigators, for example, in small sub-studies for which limited numbers of patients have undergone particular laboratory tests. When estimating the size of effects at the population level, and in particular for probabilistic cohorts, error estimates will take account of and be corrected for each sampling fraction, leading to greater generalizability and external validity. Where individual level data sharing is not possible, we will use meta-analytic approaches to compare findings across countries.

Stay-in-Touch Strategy. To maintain contact with participants after the initial assessment, we will use a cell phone-based technology developed by Prof. Sriram Iyengar, termed Txt2Info, which provides precision bidirectional mass communications during pandemics. Txt2Info combines judicious use of text-messaging and an easy-to-use REDCAP survey instrument in a simple, lightweight manner. English and Spanish are currently supported, but other languages can be easily and quickly added. Txt2info is designed to be rapidly customized and deployed for any scenario that requires real-time dissemination of information and community-sourced data collection.

Determining Pre-exposure Cognitive Status. A key consideration in the recruitment of new cohorts is the assessment of pre-exposure cognitive status, because pre-exposure decline (even in the absence of a clinical diagnosis of cognitive impairment or dementia) will result in exclusion from analyses. Since we will be collecting new cohorts, we will not have pre-exposure

assessments and will have to rely on indirect strategies to establish premorbid level of function. First, we will gather information about the pre-baseline functional ability of the participant through the SCAN interview. Second, where available we will interview a caregiver/informant using the CDR scale or the corresponding section of WHO SCAN. Finally, we will develop cognitive estimates of premorbid abilities.[132-136] These combination methods are necessary because measures typically used in the US (e.g., the National Adult Reading Test or the Weschler vocabulary subtest) are very limited in high illiteracy contexts such as Argentina. Most cognitive tests have robust norms established in our study population. In making diagnoses, we will incorporate clinical judgment of cognitive decline, particularly with respect to pre-morbid and baseline levels of cognition. Local norms that include age and education will also be routinely taken into account, both in making consensus diagnoses and in formal statistical analysis.

Mortality Endpoints. Efforts will be made to ascertain death certificates, contact significant others or to search the National Death Index (https://www.cdc.gov/nchs/ndi/index.htm) to track participants who are lost to follow-up. In Argentina we will track deaths in the registry of the provincial Emergency Operations Committee (http://coe.jujuy.gob.ar/noticias/). Other locations will track as available.

Consortium Agreement and Data Sharing Procedures. The Consortium is led by a steering committee. Multiple subcommittees address specific areas of focus, including clinical definitions, epidemiological designs, clinical evaluation, cognitive assessments, biomarkers, and neuroimaging. Subcommittees meet ad hoc based on specific needs. The entire Consortium meets every fortnight via remote conferencing. Funding opportunities and publication proposals are discussed in the open meeting, including invitations to collaborate, and interested parties can continue to meet at their discretion. All protocols, publication drafts, and minutes from subcommittee meetings are made available to all members through a digital board. Each local site will be led by 1-2 principal investigators (neurologists, psychiatrists, or epidemiologists) and

a team of trained clinical research associates. A data sharing agreement regulates (and allows collation of) deidentified results using meta-analytic approaches.

Discussion

The research described here aims to provide harmonized methodologies to better understand whether and how the SARS-CoV2 pandemic contributes to the risk (and mechanism(s)) of ADRD through a population-based, quasi experimental model. Through this network of study teams, we propose to characterize the neurobehavioral and neuropsychiatric phenomenology associated with SARS-CoV2 in harmonized, multinational, longitudinal cohorts of post SARS-CoV2 infection patients. Recruitment is ongoing in several cohorts. We plan to obtain core initial data within 18 months of recovery from hospital discharge or documented infection by PCR. Longitudinal follow up will be conducted at a minimum 24 months after the initial evaluation. A mHealth keeping-in-touch process is planned to minimize attrition rates. High rates of mutation in SARS-CoV2 (https://www.gisaid.org/phylodynamics/global/nextstrain/) strongly suggest that viral infectivity, including neurotropism, may not be uniform across countries impacted. However, regardless of the molecular mechanism(s) involved in chronic or progressive injury to the central nervous system, we assume that the fundamental biology driving disease development is largely the same across all human ancestries, even though redundant or parallel processes may result in diverse pathways leading to the same clinical phenotypes. Conversely, identical genetic variants may be associated with different phenotypes conditioned by the genomic context or ancestry, as well as by environmental influences. Therefore, variability, both in the effect of genomic variations and in the sources of risk for specific phenotypes, is expected to be inherently affected by contexts.[137-139] All members of the Consortium have agreed to share data for meta-analytic and replication efforts in the future. Ongoing data collection efforts using CNS-SC2 methodology in Argentina, Greece, Denmark, Sweden, Perú, Cuba, India and China will provide multiple opportunities to attempt replication or expansion of the findings.

Detecting Novel Symptoms. A critical caveat of this proposal is that the cognitive impairment triggered by SARS-CoV2 infection may resemble ADRD while differing from it in subtle but important ways. We therefore have chosen clinical assessment, imaging, and biomarker tools that will allow us to detect and describe even subtle differences. The semi structured interview WHO-SCAN makes use of a conversational interviewing approach, helping patients to describe in their own words their feelings, thoughts, and perceptions. The WHO-SCAN examiner is trained to determine which of these verbal and subjective descriptions represents abnormal psychopathological phenomena (pre-defined in a glossary of symptom definitions officially endorsed by WHO),[122] a technique that lends itself also to describing previously unrecognized phenomena or symptoms not catalogued as part of typical syndromes. Such novel emerging phenomena are often observed when the WHO-SCAN is translated into indigenous culture first languages that not only do not share all of Western conventional or universal experiences, but that also place importance on psychological experiences that are uncommon outside of that culture.[140] While there are useful structured (e.g. CIDI, CIS-R) and semi-structured (e.g. SCID, DIGS) interviews and short checklists (e.g. GAD-7, PHQ-9, EPDS) in widespread use in neuro-psychiatry, including clinical trial and epidemiological research, these more structured approaches are only capable of identifying established and recognized symptoms, syndromes, and pre-defined disorder categories. This is problematic because novel symptoms may prove crucial to tracking and predicting short and longer term CNS effects of novel viruses, including COVID-19 outcomes. Novel symptom discoveries could also lead to the development of new, more appropriate, brief structured assessments for wide spread taking to scale.

Minimizing Cultural Bias. Cultural variables can also exert a powerful effect on test performance through construct, method, and item biases,[141] but their impact is often underestimated. Indeed, the influence of culture on cognition poses great challenges to cognitive assessments in culturally diverse samples, not the least of which includes the difficulty of responding to the wide range of cultural contexts, conditions, and circumstances under which testing may occur around the world.[141] Thus, while a common neuropsychological assessment

is an essential component of the longitudinal assessments planned by the Consortium, we recognized that harmonization of testing procedures across cultures, educational attainment levels, languages and sociocultural environments is a very difficult task. Standard cognitive processes are biologically identical for all humans, but individual, social, and environmental differences may significantly change the way in which cognitive processes are engaged, resulting in different patterns of abilities across cultures.[142,143] For instance, studies in Aboriginal peoples show unique approaches to spatial relationships[144] and numerical and memory tasks.[145-148] To detect cognitive impairment and cognitive decline therefore requires a basic understanding of which skills are needed for normal function in a specific cultural context.[149] Culture-informed adaptations are made to the content and administration of instruments to reflect the experiences of the population being assessed and to retain within-population variance.[150]

The basic idea behind cross-cultural measurement is that the same aspect of cognitive abilities is assessed similarly in different cultural groups using tests selected, optimized, and normed for each individual group. In this case, absolute scores would not be directly comparable across groups, but deviance from norms would be comparable regardless of differences that may be present in a variety of important background characteristics that vary across and within cultures. To address these issues, a panel of experts from across the CNS-SC2 Consortium (including key personnel from each continent and with expertise in Aboriginal cognitive assessments) worked on harmonization of culturally appropriate conceptual tasks (e.g., content, sensitivity, and face value of the tools) to minimize three key sources of bias: fairness, instrument, and administration. Fairness, understood as equitable treatment throughout the testing process, refers to the manner in which the tool is administered. Instrument bias refers to all the properties associated with an instrument that are not the target of study but nonetheless can result in group differences in test scores. For instance, if a computer is used to measure reaction times in individuals who have never used a device and others who have lifetime usage, differential familiarity with computers is expected to influence the obtained results regardless of the construct being investigated. Administration bias refers to

group differences in test scores due to aspects of the interaction and communication between the examiner and examinee. Factors such as inappropriate testing conditions, unequal opportunity to familiarize oneself with the test format, unavailability of practice materials and unequal exposure to those materials, unequal performance feedback, and lack of standardized test administration can all lead to administration bias. We have created a Standard Operating Procedure manual to ensure equitable treatment throughout the Consortium.

Focus on Olfactory Impairment. Lastly, our semi-quantitative neurological examination is primarily focused on olfactory, motor, and cognitive function. Other aspects of the clinical examination (i.e. visual and auditory perception, muscle strength and tone, eye and facial movements, coordination, gait and balance, and muscular fatigue during six minutes of walking) are included to achieve broad characterization of concomitant complications. There are multiple sound reasons to pay particular attention to olfactory deficits in this context. First, increased amyloid-β (Aβ) burden is correlated with olfactory impairment in older adults with amnestic mild cognitive impairment (aMCI),[151,152] and both factors may be predictive of ADRD.[151,152] Olfactory impairment is also correlated with tau pathology and neuroinflammation in patients with ADRD[153] and predictive of dementia diagnosis in several pathologies.[36-37] As mentioned in the introduction, SARS-CoV2 invades the olfactory bulb and this is the likely explanation for the prevalent anosmia in infected patients.[20-22,24-27] This mechanism has been well established in experimental animals[26] and is well supported by imaging studies of sub-acute COVID-19 patients.[29-34] Fruit and flower odor categories have a graded structure that is a universal property retained across categories,[154] such that they can be stably tested. Second, the amygdala is one of the primary connections of the olfactory bulb,[155] has among the highest levels of ACE2 expression in the brain,[156] is a preferential target of COVID-19 in the post-mortem tissue of patients[157] and is affected in imaging studies of long-COVID patients.[158] Likely as a consequence of this involvement, changes in emotional reactivity have been reported as a prominent behavioral change after SARS-CoV2 infection.

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Figure and Table legends.

Table 1. Case Definitions

Table 2. Summary of Data to be Collected

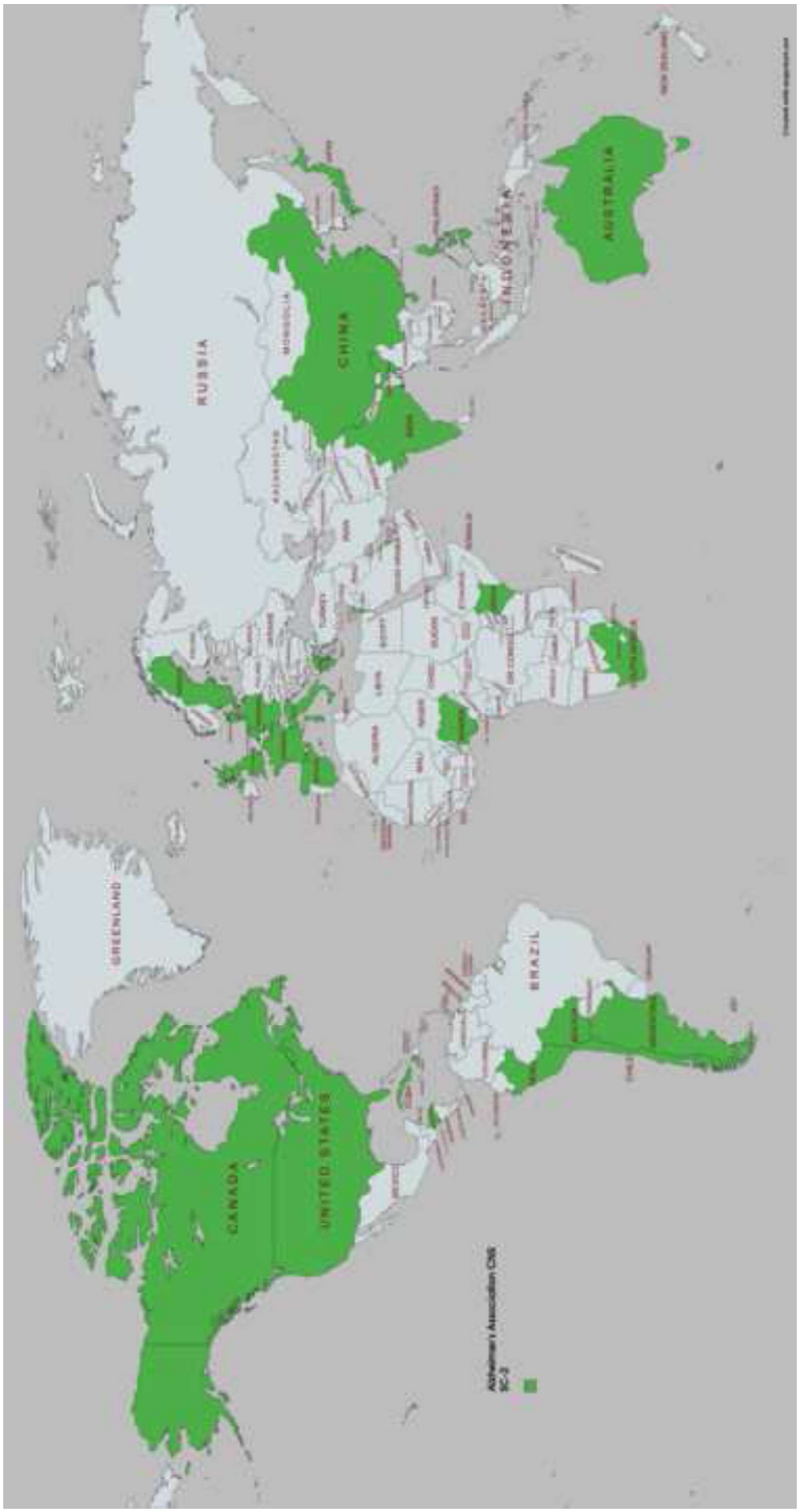
Harmonized measures will not be able to be collected as suggested at all sites. The intent of the list of measures is to secure harmonization of those measures that are locally available, to ensure maximum and optimum data shareability.

Table 3. Description of 7 Tesla High Field MRI sequences proposed

Figure 1. Map of Countries of origin of Consortium Members.

Figure 2. Proposed Longitudinal Schedule for Assessment of Cohort Members.

Methods consortium Figure 1.png



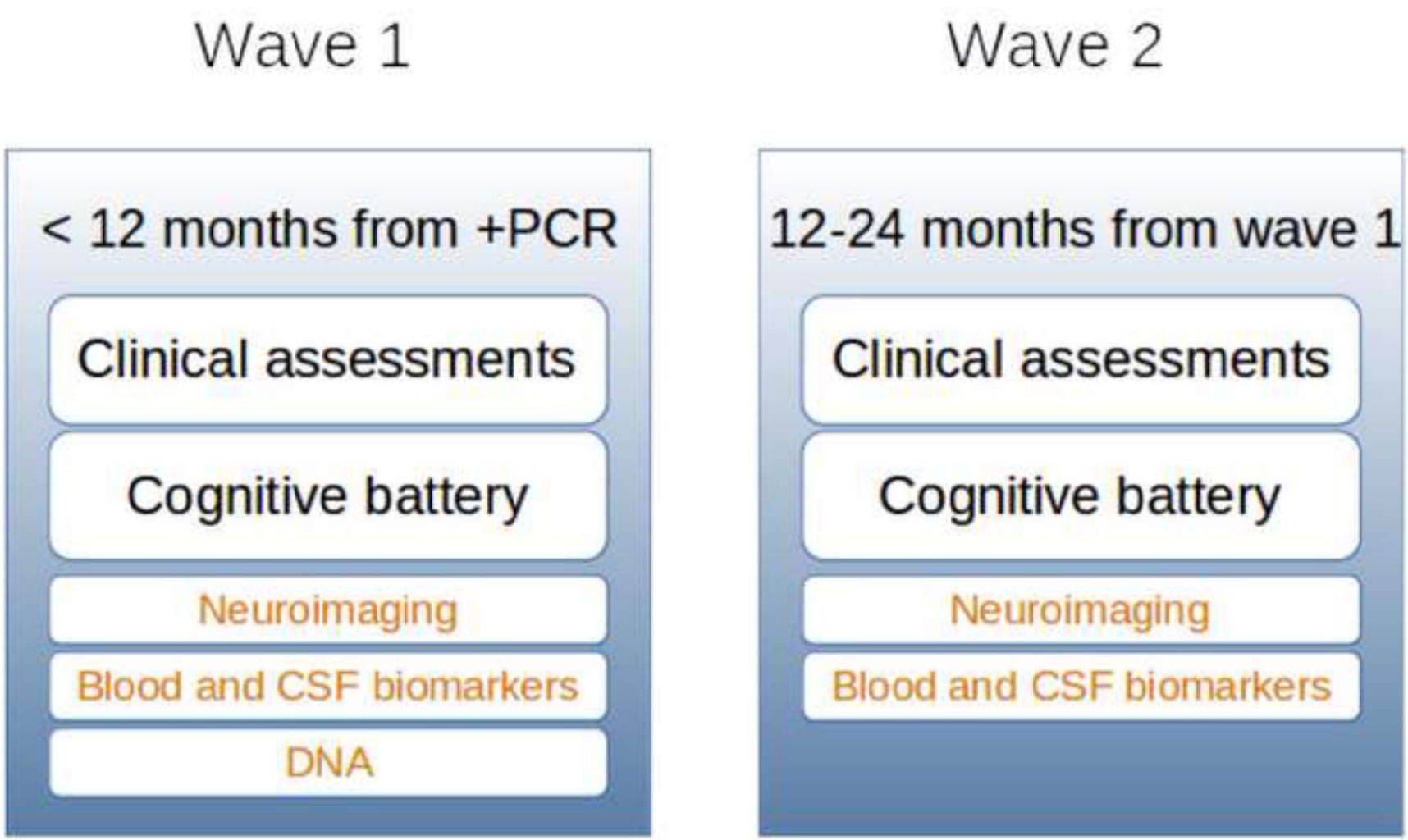


table and figure legends

Table 1. Case Definitions

Definite case definition variants:
Positive test
Positive test with a positive antibody test later
Positive test with at least 2 core symptoms*
Positive test with at least 1 core symptom* and 2 supportive symptoms**
Positive test, core symptoms and hospitalization, as an index of severity
Probable case definition variants:
Antibody test positive with two tests
Antibody test positive with at least 2 core symptoms or 1 core symptom and 2 supportive symptoms
Negative test with at least 2 core symptoms or 1 core symptom and 2 supportive symptoms with a positive chest CT
Possible case definition (e.g. drawn from population survey questionnaire or interview findings):
Single Core Symptoms alone
Self-reported, without testing confirmation
Only one positive antibody test
**Core symptoms: fever, chills, cough, sore throat, anosmia, SOB, hypoxia, muscle pain, fatigue, AMS, delirium*
***Supportive symptoms: diarrhea, headache, rash*

Table 2. Summary of Data to be Collected

Harmonized measures will not be able to be collected as suggested at all sites. The intent of the list of measures is to secure harmonization of those measures that are locally available, to ensure maximum and optimum data shareability.

Table 2. Overview of study measures

Domain	Measures	
Clinical, Cognitive and Psychosocial Assessments		
Cognitive domains	Orientation & language*	ACE III and Shortened Boston naming test
	Memory	Episodic: Visual Paired Associates
		Working: Corsi Block Test
		Semantic: Cactus & Camel Test
	Executive function	Inhibition (& psycho-motor speed): Color (or Size) Stroop
		Planning - Problem solving: Tower of Hanoi
		Decision making – Impulsivity: Iowa, Gambling task
	Psychomotor speed	Symbol substitution test
	Attention & Visuo-Spatial abilities	Search Neglect: Bell cancellation
		Perception Apperceptive Agnosia: Poppelreuter-Ghent's overlapping figures
	Social Cognition	Theory of Mind: Frith-Happé animations
Neuropsychiatriy and Behavioral Neurology	World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (WHO SCAN)	
Clinical evaluation of neurodegenerative disorders	The National Alzheimer's Coordinating Center Uniform Dataset (NACC UDS)	
Emotional reactivity assessment	The Perth Emotional Reactivity Scale (PERS)[51]	
Psychosocial measures	Quality of life measures; stressful life events; poverty and financial hardship	
Semiquantitative clinical variables	Anosmia/hyposmia smell recognition test; 2 min walk test for fatigability	
Neuroimaging		
Structural MRI	Region specific volumetric, cortical surface White matter hyperintensities as a proxy for vascular disease Vascular lesion burden: Infarcts, microbleeds	
Diffusion Tensor Imaging	Tract-Specific Fractional Anisotropy (FA) and Mean Diffusivity (MA)	
BOLD fMRI	Data from functional connectivity (FC) analyses BOLD-derived voxel-based physiological (VBP) indices of neurovascular coupling	
^{18}F-DG PET (Only at UTHSA site)	Region-specific glucose uptake as markers of tissue metabolism and synaptic integrity	
Blood-based biomarkers		
AD-specific biomarkers	Aβ42, Aβ40, P-tau$_{181}$, P-tau$_{217}$	
Neurodegeneration and neuronal activity/injury	NfL, GFAP, sTREM-2	
Inflammatory biomarkers	Bio-Plex Pro Human Cytokine panel: FGF basic, Eotaxin, G-CSF, GM-CSF, IFN-γ, IL-1β, IL-1ra, IL-1α, IL-2Rα, IL-3, IL-12 (p40), IL-16, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, GRO-α, HGF, IFN-α2, LIF, MCP-3, IL-10, IL-12 (p70), IL-13, IL-15, IL-17A, IP-10, MCP-1 (MCAF), MIG. β-NGF, SCF, SCGF-β, SDF-1α, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF, CTACK, MIF, TRAIL, IL-18, M-CSF, TNF-β	
Genetics		
DNA for GWAS or Whole Genome Sequencing		

Table 3.

Table 3. Sequences for 7 Tesla High Field MRI			
Sequence	**Acquisition Parameters**	**Measures Assessed**	**Time (mins)**
Set up/localizer	GRE	Positioning, Shimming	5.5
3DT1 MP2RAGE	348 slices (0.55 Iso.); TR~6000; TE~2.54;TI1/2~800/2500; AF=2	Morphometry;registration; hippocampus segmentatio	12.5
3D SWI	208 slices (0.375x0.375x0.75);TR~24; TE1/2~8.16/18.35; AF=2	Small vessel analysis, T2* mapping, QSM	9
T2 TSE	36 slices (0.375x0.375x1.5); TR~10060; TE~61; AF=2	Hippocampus segmentation	4
T2 FLAIR	80 slices (0.75x0.75x1.5); TR~14000; TE~99; TI~2900; AF=2	White matter hyperintensties	11
3D T2 Space	256 slices (0.6 Iso.); TR~3400; TE~367; AF=3	Morphometry, hippocampus seg, perivascular spaces	9.5
MT & non MT	60 slices (0.4mm iso); TR=538; TE=4.08;FA=8	Locus Coeruleus intensity, Contrast, MT	8
TOF (4 Slabs)	192 slices (0.375 Iso.);TR~14; TE~4.5; AF=3	Angiography, arteriolar analyses	6.5

Figure 1. Map of Consortium Members

Figure 2. Proposed Longitudinal Schedule

Table 1 editable version

Table 1

Table 1

Definite case definition variants
Positive infection test (PCR or rapid test)
Positive infection test with a later positive antibody test
Positive infection test with at least 2 core symptoms *
Positive infection test with at least 1 core symptom ^ and 2 supportive symptoms **
Positive infection test, core symptoms and hospitalization as an index of severity
Probable case definition variants
Antibody test positive on two occasions (without vaccination)
Positive antibody test (without vaccination) with at least 2 core symptoms * or 1 core + 2 supportive sympto
Negative infection test with at least 2 core symptoms * or 1 core + 2 supportive symptoms and typical chest
Possible case definitions (e.g. drawn from survey questionnaires or interview findings)
Single core symptoms
Self-reported without laboratory testing confirmation
Positive antobody test on just one occasin (without vaccination)
** Core symptoms: fever, chils, cough, sore throat, anosmia, dyspnea, hypoxia, muscle pain, fatighe, altered mental status or deliri*
*** Supportive symptoms: diarrhea, headache, skin rash*

Table 1

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Table 2. Overview of Proposed Measures Table 2

Domain	
Clinical, Cognitive and Psychosocial Assessments	
Cognitive domains	Orientation & language*
	Memory
	Executive function
	Psychomotor speed
	Attention & Visuo-Spatial abilities
	Social Cognition
Neuropsychiatriy and Behavioral Neurology	World Health Organization Schedules
Clinical evaluation of neurodegenerative disorders	The National Alzheimer's Coordinatin
Emotional reactivity assessment	The Perth Emotional Reactivity Scale
Clinical Cognitive Diagnosis	Mild Cognitive Impairment (amnestic
Psychosocial measures	Quality of life measures; stressful life
Semiquantitative Clinical Variables	Anosmia/Hyposmia smell recognition
Neuroimaging	
Structural MRI	Region specific volumetric, cortical su White matter hyperintensities as a pr Vascular lesion burden: Infarcts, micr
Diffusion Tensor Imaging	Tract-Specific Fractional Anisotropy (
BOLD fMRI	Data from functional connectivity (FC BOLD-derived voxel-based physiolog
^{18}F-DG PET (Only at UTHSA site)	Region-specific glucose uptake as m
Blood-based biomarkers	
AD-specific biomarkers	Aβ42, Aβ40, P-tau$_{181}$, P-tau$_{217}$
Neurodegeneration and neuronal activity/injury	NfL, GFAP, sTREM-2
Inflammatory biomarkers	Bio-Plex Pro Human Cytokine panel: 16, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, C (MCAF), MIG. β-NGF, SCF, SCGF-β, SD CSF, TNF-β
Genetics	
DNA collection for GWAS or Whole Genome Sequencing	

Table 2

Measures
ACE III and Shortened Boston naming test
Episodic: Visual Paired Associates
Working: Corsi Block Test
Semantic: Cactus & Camel Test
Inhibition (& psycho-motor speed): Color (or Size) Stroop
Planning - Problem solving: Tower of Hanoi
Decision making – Impulsivity: Iowa, Gambling task
Symbol substitution test
Search Neglect: Bell cancellation
Perception Apperceptive Agnosia: Poppelreuter-Ghent's overlapping figures test
Theory of Mind: Frith-Happé animations
s for Clinical Assessment in Neuropsychiatry (WHO SCAN)
ıg Center Uniform Dataset (NACC UDS)
e (PERS)[81]
or non-amnestic MCI), and dementia
events; poverty and financial hardship
test; 2-min walk test of fatigability
urface
oxy for vascular disease
robleeds
FA) and Mean Diffusivity (MA)
) analyses
ıical (VBP) indices of neurovascular coupling
arkers of tissue metabolism and synaptic integrity
FGF basic, Eotaxin, G-CSF, GM-CSF, IFN-γ, IL-1β, IL-1ra, IL-1α, IL-2Rα, IL-3, IL-12 (p40), IL- GRO-α, HGF, IFN-α2, LIF, MCP-3, IL-10, IL-12 (p70), IL-13, IL-15, IL-17A, IP-10, MCP-1)F-1α, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF, CTACK, MIF, TRAIL, IL-18, M-

Table 3 editable version

Table 3. Sequences for 7 Tesla High Field MRI	
Sequence	**Acquisition Parameters**
Set up / localizer	GRE
3DT1 MP2RAGE	348 slices (0.55 iso); TR~6000; TE~22.54; TI1/2~800/2500; AF=2
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T2 TSE	36 slices (0.375x0.375x1.5); TR~10060; TE~61; AF = 2
T2 FLAIR	80 slices (0.75x0.75x1.5); TR~14000; TE~99; TI~2900; AF = 2
3D T2 Space	256 slices (0.6 iso); TR~3400; TE~367; AF = 3
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TOF (4 slabs)	192 slices (0.375 iso); TR~14; TE~4.5; AF = 3

Measures Assessed	Time (min)
positioning; shimming	5.5
morphometry; registration; hippocampus segmentation	12.5
small vessel analysis; T2* mapping; QSM	9
hippocampus segmentation	4
white matter hyperintensities	11
morphometry; hippocampus segmentation; perivascular spaces	9.5
locus coeruleus intensity; contrast' MT	8
angiography; arteriolar analysis	6.5