Basic Information

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is the largest dataset of Alzheimer's disease (AD) brain and cognition in living participants. It includes a wealth of information in a large cohort of AD patients and older adults with high risk of developing AD. The data collected through ADNI include measures of cognitive function, clinical assessments, genetics, brain structure, brain pathology (using PET, CSF, and blood), brain metabolism, medication, vital signs, and biospecimen-based physical health measures. Since its launch in 2004, the ADNI dataset is widely used by researchers in the field of neuroscience for investigating AD, dementia and related conditions (Weiner et al., 2017). These modalities have been critical towards developing models of AD characterization and prognosis. However, absent in these models are measures of brain function, which are an important piece towards understanding the etiology and development of brain disease.

As cognition is supported by interactions between distributed brain regions in a large-scale brain network (Mesulam, 1990; S. E. Petersen & Sporns, 2015), a promising approach towards characterizing brain function involves formal study of the integrity of the brain's large-scale functional network organization. This organization can be measured using non-invasive functional brain imaging. Work by our lab and others have demonstrated the value of quantifying large-scale functional brain network organization towards AD characterization (Ewers et al., 2021; Zhang et al., 2023) and prognosis (Chan et al., 2021). These measures are highly informative beyond existing measures of pathology and brain structure.

We propose to provide rigorously defined large-scale functional brain network features that will enable the community to generate and evaluate better AD prediction models in the ADNI dataset. The ADNI dataset includes functional brain imaging data that can be incorporated into multi-modal and multivariate prediction machine learning (ML) analyses. Both cross-sectional and longitudinal data are available thus making this dataset well suited to longitudinal prediction and prognosis of dementia. Notably, ADNI's next phase will focus on recruiting under-represented racial/ethnic groups (Ashford et al., 2022). The ADNI dataset thus allows for establishing measures of brain function that contribute towards AD prediction, and promises to expand these observations in population representative cohorts of individuals.

Data Acquisition Protocols:

MRI Data: The ADNI dataset includes structural MRI (Jack et al., 2008), diffusion tensor imaging (DTI) and resting-state functional MRI (fMRI) (Jack et al., 2010). Critically, ADNI also includes measures of AD-related pathology (Aβ and tau), across several modalities (PET imaging, CSF and plasma). Participants in the dataset have also been characterized for AD genetic risk (APOE status). Additional scan protocols include FLAIR, ASL, and hippocampal T2 for different subsets of participants. For the present proposal, the focus is on processing functional brain network features, which are based on the resting-state fMRI data. Therefore, the data proposed in this proposal will be from several large cohorts of ADNI (i.e., ADNI-2, ADNI-Go, ADNI-3).

Across multiple sites, ADNI collects MRI and fMRI data using standardized protocols to ensure consistency across sites and scanners. Detailed information about the acquisition protocols across scanners can be found on the ADNI website: https://adni.loni.usc.edu/methods/documents/mri-protocols.

Processing of functional MRI Data:

The unique offering from the present proposal is rigorously processed resting-state fMRI data. The utility of incorporating measures of brain network function in novel models of AD prediction

necessitate careful processing and curation of the relevant data types. Functional MRI data is notoriously susceptible to artifacts from the scanner, cardiac and respiratory signals, and head-motion (Power et al., 2012; Van Dijk et al., 2012), which are known to alter the correlation of resting-state signal (Power et al., 2014; Satterthwaite et al., 2013; Van Dijk et al., 2012). Our team has helped develop processing pipelines for effectively cleaning this data (Han et al., 2018, in press; Savalia et al., 2017). The data we provide will undergo rigorous preprocessing and quality checking to ensure that they are free from known artifacts (Zhang et al., 2023).

In addition to the typical fMRI preprocessing steps (e.g., slice-timing, realignment, registration to anatomical data), a stringent protocol of quality checking and processing is applied to remove the known spurious variance in data. Resting-state functional correlation (RSFC) processing is applied to the preprocessed fMRI data using the following steps: (i) demean/detrend, (ii) multiple regression of tissue signal (grey matter [global signal regression], white matter, ventricle) and Friston 24 motion regressor (Friston et al., 1996), (iii) motion "scrubbing" (Power et al., 2014) where motion-contaminated frames that have > 0.3mm frame-wise displacement (FD; a measure of head-motion from one volume to the next, calculated as the sum of the absolute values of the differentiated realignment estimates) are interpolated and replaced, (iv) bandpass filtering (0.009-0.8Hz), and (iv) removal of interpolated frames used for preserving time series during bandpass filtering in step (iii). The functional data is then mapped to an atlas surface (fs_LR 32k). The resulting data are free of motion-related artifacts that could artifactually inflate functional correlation between brain areas that are close to each other in acquisition space (i.e., 3D voxel space).

A public set of brain parcellation with 441 brain nodes (Chan et al., 2014) will be used to construct brain networks for each individual. Specifically, the pairwise Fisher's z-transformed correlation of all nodes will be computed to create a correlation matrix (brain network). Based on this pipeline, each resting-state fMRI session that has at least 100 frames of data after motion-scrubbing will be retained (n total scans = 1104), where a 441 × 441 matrix is created to represent a functional brain network.

Greater details regarding the specific brain network measures that will be derived from this preprocessed data are included in the **Utility & Rigor** and **Innovation** section below.

Linking functional brain data to other modalities of brain structure and pathology:
Within ADNI, the raw MRI data undergo various preprocessing steps. For structural MRI, data has been processed by various groups (for details, please see https://adni.loni.usc.edu/methods/mri-tool/) and propagated back to the ADNI database (e.g., ADNI-3's FreeSurfer 6.0 data processed by UCSF, https://adni.loni.usc.edu/new-ucsf-cross-sectional-freesurfer-6-0-data-available). These data underwent standard structural MRI processing such as distortion correction, skull stripping, and segmentation via FreeSurfer. This provides researchers with ready-to-analyze brain anatomy variables such as whole brain and regional cortical thickness and grey/white matter volume.

Measures of Aβ and tau pathology are available for a large number of ADNI participants. The PET SUVR values of cortical Aβ can be used to categorize Aβ burden based on predefined cutoff values (^{18}F-Florbetapir: global SUVR > 1.11; ^{18}F-Florbetaben: global SUVR > 1.08) (Landau et al., 2012, 2013). Similarly for tau SUVR values, a predefined cutoff value sensitive to separating cognitively healthy adults from cognitively impaired individuals can be used to categorize individuals with high tau burden (meta-temporal ROI SUVR > 1.33) (Jack et al., 2017).

Number of Files, File Formats, and Size:
Only participants with at least one session of clean and usable fMRI brain network data will be included. Upon the most recent data download (9/14/2023), the number of unique participants with resting state data is 861. Of these, there are 413 participants with longitudinal data, ranging from 2 to 9 scans. After rigorous fMRI data processing, the number of unique participants with clean and usable resting-state data is 664. 257 participants have useable longitudinal data, ranging from 2 to 7 scans. The total number of available resting-state matrices will be 1104.

Resting-state functional brain network matrices (441 by 441) will be stored as a text file for each scan session, which are relatively small (~1.5MB). Given the approximated available sample of 1104 scans, the functional brain network data should be about 1.62GB.

Target Variables:
The primary target variables will be clinical diagnoses (i.e., AD status, clinical dementia rating [CDR], see **Utility and Rigor** section below for CDR's definition, utility and validity), and cognitive scores (e.g., Montreal cognitive assessment [MOCA], mini-mental state examination [MMSE]). For the purpose of applying prediction models for early prediction of AD, we recommend using CDR as the main target variable as it is directly linked to severity of AD. We also recommend using the continuous version of CDR (CDR Sum of Boxes [CDR-SOB]) for models that can support using continuous data as the target variable. In addition, these target variables can be constrained by presence of AD-related pathology and brain structure (described above).

Statistical Distribution of Target Variables:
The distribution of target variables can vary across different ADNI study cohorts and subpopulations. The proposed dataset is a subset of the ADNI cohort with usable resting-state fMRI after preprocessing and CDR scores assessed within a year of the resting-state fMRI scan. Cross-sectionally, the dataset includes 331 healthy participants (CDR = 0), 228 very mild dementia (CDR = 0.5), 47 mild dementia (CDR = 1) and 10 moderate dementia (CDR = 2) patients (age range: 55 – 96 years old). Because participants may have multiple scans and CDR scores available at different dates, this cross-sectional sample is stratified based on the highest CDR score associated with the resting-state fMRI scan.

The proposed dataset includes 255 longitudinal participants with CDR scores at multiple timepoints (ranging from 2 to 9 scans). Within the longitudinal cohort, 47 participants showed increased CDR scores (baseline CDR 0: N = 29, CDR = 0.5: N = 12, CDR = 1: N = 6). 199 participants exhibited no change in CDR status (baseline CDR 0: N = 128, CDR = 0.5: N = 68, CDR = 1: N = 3). 9 participants exhibited decreased CDR scores (baseline CDR = 0.5: N = 8, CDR = 1: N = 1).

Utility & Rigor

The Clinical Dementia Rating (CDR) is a widely used clinical tool for assessing the severity of dementia and cognitive impairment in individuals. The CDR score is assessed through an interview conducted by a trained clinician or healthcare professional. It provides a global rating of cognitive and functional impairment in six domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care (Hughes et al., 1982; Morris, 1993). The clinician assesses the individual's cognitive and functional abilities in each of the six domains mentioned above. Higher CDR score indicates higher dementia severity of the assessed individual. Each domain is scored on a scale from 0 to 3, with the following interpretation: 0=No impairment, 0.5=Questionable impairment (very mild), 1=Mild impairment, 2=Moderate impairment, 3=Severe impairment. The final CDR score (i.e., global CDR score) is

derived from the scores in each of the 6 domains, and assigned based heavily on the score of the memory domain (for details please see Morris, 1993).

In the past, the CDR has demonstrated good inter-rater reliability, indicating that different clinicians can assess the same individual and arrive at similar CDR scores (Morris, 1997; Morris et al., 1997). Importantly, the CDR has been shown to be valid in distinguishing individuals with AD and other dementias from those without dementia (Fagundes Chaves et al., 2007; Perneczky et al., 2006). Higher CDR scores are associated with more severe cognitive impairment and functional deficits (Balsis et al., 2015).

The secondary target variable is the sum of boxes of the CDR score (score range: 0 - 18). The CDR-SOB score is the sum of the CDR scores in all six domains, which provides a summary score for cognitive impairment on a continuous scale. Similar to CDR global score, higher CDR-SOB score indicates higher impairment.

For the participants in ADNI that has clean and usable functional brain network estimates, the CDR scores are as follow: (CDR mean=0.29, sd=0.38, range=0–2; N = 285 with CDR > 0).

Importantly, CDR scores can be combined with measures of amyloid- and tau-related pathology, which are available in the ADNI dataset, to confirm AD versus alternate dementia types. This allows for neurobiological verification of AD based on the presence of amyloid and tau burden.

Predictor Variables in the Dataset:
In ADNI, available predictor variables include a wide range of demographic, clinical, genetic, neuropathology, and neuroimaging derived measures. These variables can include age, gender, education, Apolipoprotein E (APOE) genotype, structural brain features (e.g., brain volumes, cortical thickness), cognitive test scores beyond CDR, and neuropathology (e.g., cerebrospinal fluid markers and PET SUVR for quantifying tau and amyloid-beta pathologies).

Many of these predictor variables are empirically linked to AD, where their validity in relation to AD/ADRD has been supported by past studies (Jack et al., 2018; Soldan et al., 2019). For example, age is a well-established AD-risk factor (Hebert et al., 2013), APOE genotype is associated with increased susceptibility to AD (Guerreiro et al., 2013; Jonsson et al., 2013; for review, see Roses, 1996), and neuroimaging measures from structural (Jack et al., 1997) and functional measures have been linked to AD (Brier et al., 2012; Ewers et al., 2021; Greicius et al., 2004; for review, see Yu et al., 2021). In the context of applying ML to these data, researchers have used validation techniques, such as cross-validation, to assess the generalization of predictive models to new data (Cullen et al., 2021; Moradi et al., 2015; Palmqvist et al., 2019).

Importantly, the present proposal introduces novel predictors previously not available to the public for the ADNI dataset, characterizing brain function. Functional fMRI data is used to characterize large-scale functional brain network measures. Both summary brain network measures, specifically “brain system segregation”, and the network matrices themselves have been shown to contain unique information dissociating AD-related brain patterns from healthy adults (Chan et al., 2021; Ewers et al., 2021; Zhang et al., 2023). This suggests that AD may involve a more extensive set of brain network interactions that span across multiple distributed brain systems, and is ideally analyzed by methods that incorporated this distributed information in its measure (see greater details regarding innovative data quality assurance and processing for the brain network data in the **Innovation** section)

In summary, the CDR is a widely used tool for assessing cognitive and functional impairment in individuals with AD/ADRD. Its reliability and validity have been demonstrated in clinical and research settings. Predictor variables in the ADNI datasets encompass various factors that are empirically linked to AD/ADRD and will include demographic, genetic, and brain-based measures.

Innovation

The dominant model of Alzheimer's Disease (AD) formalizes measurement of brain pathology and structural degeneration towards AD characterization and prediction (AT(N); Jack et al., 2016). However, at a given level of pathological burden and atrophy, there is variability in cognitive function; in fact, some individuals can exhibit a high degree of amyloid yet be cognitively healthy (i.e., "Reserve"; Stern, 2009). It is clear that missing variables related to brain function need to be accounted for to better understand disease expression, which would improve onset detection and diagnosis.

Functional brain networks are an innovative way of representing the complex organization and function of the brain (Rubinov & Sporns, 2010; Wig, 2017). Brain system segregation (Chan et al., 2014) is a graph-based measure of brain network organization previously shown to closely track healthy adult aging and is also prognostic of AD severity beyond known AD pathology and brain structure atrophy (Chan et al., 2021). The incorporation of this functional brain network measure in AD prediction models can provide greater accuracy as it explains AD severity beyond other known AD related measures. Furthermore, recent work has shown that beyond the summary measure of functional brain networks, the pattern of brain connectivity differs between healthy aging and AD severity (Zhang et al., 2023). This indicates that specific patterns of brain connectivity can provide unique information differentiating healthy and AD individuals.

One of the biggest challenges in introducing new features to a dataset used for prediction models (e.g., in ML) is to ensure that the prediction features are of high quality (i.e., avoiding the "garbage in, garbage out" scenario). Therefore, the rigorously processed resting-state fMRI data we propose to provide is valuable in ensuring the quality of these brain features and resultant models. Further, while there are other neuroimaging datasets with resting-state fMRI data that include AD patients and healthy control in smaller sample sizes, ADNI is unique in its size, extensiveness, and accessibility (see **Usability** section below).

Sample characteristics and representation

ADNI primarily focuses on collecting data via clinical research centers and academic institutions. A major key variable that was considered during the recruitment of ADNI is "Age", where they only recruited participants aged 55 and older. In the sub-sample of participants with clean and usable resting-state brain network data, the participant's age ranges from 55 to 96y. This age range aligns with the higher risk of AD and ADRD in older populations.

Ethnic minorities are disproportionally at risk for AD (Alzheimer's Association, 2021); however, studies in North America are underrepresenting minorities in their study sample (Lim et al., 2023). In 2020, ADNI announced a taskforce that focuses on diversity in its participant pool, recognizing the importance of addressing health disparities (https://adni.loni.usc.edu/announcing-the-adni-diversity-taskforce/). Although the initial phases of ADNI had limited racial and ethnic diversity (Lim et al., 2023), the latest phase (ADNI-4) aimed to improve representation by actively recruiting individuals from underrepresented populations (URPs) (Weiner et al., 2023). For the proposed data in this Challenge, the data will

be biased towards higher ratio of non-Hispanic Whites, however, the developed algorithms could easily be implemented on future ADNI data releases, which will include a more diverse participant sample. ADNI collects demographic information such as gender, education level, and socioeconomic status; however, these are not key variables considered during recruitment, thus some imbalances exist across the distribution of these variables.

The sampling approach in ADNI primarily involves recruiting participants from multiple academic institutions and clinical research centers. In ADNI-1, the recruitment style was designed to be similar to clinical trials, which resulted in generally well-educated and mostly white participants (R. C. Petersen et al., 2010). For additional details see Recruitment and Retention section in https://adni.loni.usc.edu/wp-content/uploads/2012/10/ADNI3-Procedures-Manual_v3.0_20170627.pdf). Because ADNI primarily focuses on North American samples, it may not fully represent the global diversity of individuals affected by AD/ADRD.

Usability

1. Data Storage: While ADNI data is collected across multiple sites, all data are entered into a shared data repository hosted at the Laboratory of Neuroimaging (LONI) at the University of Southern California, the LONI Image & Data Archive (IDA).
2. Ownership: The data is owned by ADNI, but qualified researchers can request access to de-identified data.
3. Data License: ADNI has made the data available to researchers under a data usage agreements and licenses.
4. Accessibility for Verification and Use: Researchers interested in using the ADNI data need to submit a data access request to ADNI, which is reviewed by the ADNI Data and Publications Committee (DPC; https://adni.loni.usc.edu/data-samples/access-data/#access_data). The review process does not judge the merit of the scientific question, but largely exist to ensure compliance that the data is being shared with the scientific community; thus, the review process is quick and is used to check whether the applicant is affiliated with a scientific or educational institution, or has a legitimate reason to request the data. Being part of this competition should meet the requirement for data access. Once the researcher is approved by the DPC, they will be provided with a login to access the IDA https://ida.loni.usc.edu/. After logging in, the researcher is free to access the relevant data in multiple formats (see # 5 below). The functional network products produced by our project team will be propagated back to ADNI and be available via the ADNI data access portal.
5. Data Readiness and Preparation: ADNI data can be accessed in its raw form and processed form. The processed data is typically well-prepared for research use, with standardized formats and documentation available for researchers. For example, clinical assessment, genotyping, demographic, and preprocessed structural MRI data from FreeSurfer are available for download as spreadsheets. The summary functional brain network measure offered by our team will be in spreadsheet format, and the brain network matrices are stored as plain text files (grouped together as a zip folder), ready to be analyzed by any software.
6. Known or Planned Restrictions: ADNI data may not be used for commercial product or redistributed in any way.
7. Sensitive and Personally Identifiable Information (PII): Personally identifiable information (PII) is collected as part of ADNI, but most of it is removed or de-identified in the accessible dataset to minimize the risk of re-identification. Information that directly identifies a participant such as name, contact info (e.g., phone, email) and address are not included in the de-identified data. Some information that may indirectly identify participants when combined with other information may be available (e.g., date of birth, race, gender).

Team introduction

Our team includes Dr. Gagan Wig, Dr. Micaela Chan, and Ziwei Zhang. All three team members are part of the 'Wig Neuroimaging Lab' at the University of Texas at Dallas, and will work together towards proposal goals. They have published several peer-reviewed publications with the exact approach outlined using both the ADNI dataset which is the focus of the present proposal, but also alternate related datasets. As such, they are well suited to the proposal aims.

Dr. Gagan Wig an Associate Professor of Behavioral and Brain Sciences in the Center for Vital Longevity at the University of Texas at Dallas. His research involves characterizing the organization of large-scale brain networks using neuroimaging, understanding how brain network organization differs and changes across the adult lifespan, and determining the impact of these changes on cognition and information processing. Prior to joining the UT Dallas, he was appointed as a Human Connectome Project post-doctoral fellow. During that time, his training involved developing and utilizing visualization and analysis tools for studying large-scale brain networks, with a particular emphasis on combining resting- state fMRI and network analysis to understand systems-level organization of the brain. Dr. Wig's research program at UT Dallas has built on this work and applied it towards understanding how brain networks and brain anatomy change across the adult lifespan. This research involves the application of formal network-models to patterns of brain connectivity measured in large samples of participants that vary in age (i.e., across the adult lifespan, including middle-age), cognition, and health (e.g., varying degrees of Alzheimer's Disease severity).

Dr. Wig's more recent research has been targeted on understanding how an individual's environmental exposures interact with their brain network organization to predict their resilience and vulnerability to age-related brain decline (in humans). This work is being conducted in cohorts of adult participants that exhibit greater representativeness of the population's health, racial, and socio-economic diversity.

Dr. Micaela Chan is a research scientist in the Wig Neuroimaging Lab. She completed her Ph.D. in the Cognition and Neuroscience program at UT Dallas, and her B.S. in Psychology from University of Illinois at Urbana-Champaign. Her research focuses on how our experience and environment interacts with the brain's functional network organization, and developing methods to represent individualized brain networks in a shared multivariate space. Her broader scientific interest includes network analysis, optimizing workflow and data-processing, and contributing to open-source projects/open science.

Ziwei Zhang is a Ph.D. student in the cognitive neuroscience program at UT Dallas, working under the supervision of Dr. Wig. Before joining the Wig Lab, she pursued a bachelor's degree in psychology and worked as a research assistant in a neuroimaging lab at UCLA. Her primary research interests involve using neuroimaging methods to study the mechanisms of neurodegenerative disease and psychopathology. Her dissertation project examines the effects of aging and Alzheimer's disease on functional brain network organization and cognition.

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