## PROJECT SUMMARY/ABSTRACT

Deficits in abstract reasoning often accompany normal aging and are prevalent in age-related disorders including Alzheimer's disease (AD) and frontotemporal dementia (FTD). Abstract reasoning is largely supported by the frontoparietal control network (FPCN), a group of functionally connected brain regions including the inferior parietal lobule, anterior insular cortex, and dorsolateral and dorsomedial prefrontal cortices. The FPCN contributes to executive functioning and abstract reasoning by integrating information from two systems: the dorsal attention network (DAN) which regulates perceptual attention, and the default mode network (DMN) which regulates introspective processes. To date, most AD work has focused on episodic memory deficits and the DMN. However, understanding the structure and function of the FPCN and its interaction with networks including the DMN and DAN is critical for elucidating how age associated pathologies contribute to known cognitive deficits beyond episodic memory, including abstract reasoning.

The goal of the proposed research project is to advance our scientific understanding of how the FPCN enables abstract reasoning throughout the adult lifespan, and to understand how cognition is affected when the network is damaged by age and disease. This resubmission takes a network-centered, functional neuroimaging approach utilizing both MRI and PET modalities. Aim 1 of this proposal (PhD stage, F99) focuses on determining the contributions of the FPCN to abstract reasoning in healthy young adults. The goal of Aim 2 (postdoctoral stage, K00) is to extend this work to aging in order to elucidate the independent contributions of age and age-related disease to the network dynamics of the FPCN and associated abstract reasoning deficits. ***Training goals*** include developing expertise in 1) advanced fMRI and PET experimental methods and analysis techniques, 2) graph theoretical analyses of brain network dynamics, and 3) building a working knowledge of cognitive aging and dementia. The ***central research hypotheses*** are 1) that the FPCN supports abstract reasoning behavior by incorporating information from memory and attention systems, and 2) that the cognitive changes associated with normal aging, preclinical AD, AD, and FTD will be accompanied by uniquely modulated FPCN activation and connectivity patterns. This research will enhance the scientific understanding of the differential roles of age and disease on functional brain networks, an essential step in the development of better treatments and diagnostic techniques for age-related brain disorders.

## PROJECT NARRATIVE

Abstract reasoning skills are often impaired in normal aging and age-related disorders including Alzheimer's disease and frontotemporal dementia, but the neural mechanisms that support these important skills are not yet well understood. This project uses a network-centered fMRI and PET neuroimaging approach to investigate the effects of age and neuropathology on the brain networks that give rise to executive functioning and abstract reasoning behavior. Importantly, this project will investigate the differences between normal age-related cognitive decline and disease-related brain network dysfunction.

## INTRODUCTION TO REVISED APPLICATION

This is a resubmission of an F99/K00 grant entitled: “Abstract Reasoning and the Aging Brain: Neuroimaging of Frontoparietal Control Network Dynamics in Aging and Alzheimer’s Disease.” I thank the reviewers for their thoughtful critique of the initial application, and I am grateful for the opportunity to resubmit a revised application. The reviewers were enthusiastic about the initial proposal, speaking to the “intelligence and academic skill set” of the applicant (Rev 3) as well as the sponsor team who are “experts in their field, extremely well-funded, and have strong records of mentoring success” (Rev 2). Multiple reviewers spoke to the “excellent training environments” at BU and MGH, and the “strong, productive relationship the applicant has with his current primary mentor.” Particular emphasis was placed on the research training plan which targets a “relatively under-studied topic of high potential relevance to cognitive aging” with preliminary results that are “highly promising.” (Rev 1). Modifications have been made to address reviewers’ concerns and are summarized below.

**Reviewer 1:** “There is relatively limited description of the specifics of the K00 training plan as it relates to facilities and opportunities distinct from those provided at Boston University.” **Response**: The postdoctoral K00 phase at MGH offers the applicant access to two simultaneous MR/PET scanners, facilitating both fMRI and amyloid PET data collection and analysis training. Dr. Dickerson at MGH will provide training in understanding cognitive and neurological changes associated with aging, AD, and FTD. He also has existing datasets and patient pools that we will draw from for *Aim 2*. Additionally, at MGH the applicant will further develop his skillset beyond fMRI with expert mentoring in PET neuroimaging from Dr. Jacob Hooker, a newly added co-sponsor for this resubmission. These changes have been updated in the *Training Plan*, *Facilities*, and *Sponsor Statement*.

**Reviewer 1:** “The description of the institutional support available for the K00 phase of the training plan appears to be missing.” **Response**: Please see *Description of Institutional Environment* for newly added MGH support information, as well as a *Letter of Support* from Dr. Bruce Rosen, Director of the MGH Martinos Center.

**Reviewer 2: “**The candidate does not seem to have many first author publications.” **Response:** The candidate now has one first-author publication under review and a second one that will be submitted soon. In the past year, the candidate presented four poster presentations at international conferences (Society for Neuroscience, Cognitive Neuroscience Society, and Human Brain Mapping), and presented an invited lecture at Tufts University. The candidate has working data sets and is remaining productive through the pandemic.

**Reviewer 2:** “A minor weakness is that the candidate is not really branching out beyond fMRI.” **Response:** Prof. Jacob Hooker has been added as a co-sponsor to provide mentoring in PET neuroimaging. We have further emphasized the amyloid PET analyses proposed in *Aim 2* and updated *Training Goal #3* to include PET imaging.

**Reviewer 3:** “Dr. Dickerson lists involvement in 15 ongoing funded research projects. Given this level of involvement, it is not clear how he will have time to mentor the applicant during his 4-year K00.” **Response:** To supplement mentorship form Dr. Dickerson, we have recruited Dr. Jacob Hooker from the MGH Martinos Center as an additional co-sponsor for the postdoctoral K00 phase of this proposal. The applicant worked with Dr. Hooker as a research assistant from 2015-2017, and Drs. Hooker and Dickerson have collaborated on several projects previously. Dr. Hooker will offer expertise in PET neuroimaging, relevant to *Aim 2.*

**Reviewer 3:** “The preliminary data shown in Figure 2 are not compelling.” **Response:** Figure 2 originally showed fMRI activation maps for the 1D-Ravens Progressive Matrices (1D-RPM) task, developed for *Aim 1*. Results were originally displayed on selected slices of the MNI template brain. We have updated the figure with activation maps projected onto the cortical surface to provide a more complete and compelling view of the activity patterns. The surface maps show that activity is increased in anterior/prefrontal regions during symbolic reasoning, and in posterior/ventral visual regions during perceptual reasoning. Further evidence from a region of interest analysis is also included in the revised figure, showing that activation of the frontoparietal control network (FPCN) is greater during symbolic reasoning compared to perceptual reasoning. The regions uniquely activated by each task condition are uniquely damaged and AD and FTD respectively (see *Figure 3*), motivating the use of the 1D-RPM task to study these disorders in *Aim 2*.

**Reviewer 3:** “The plan to study “silent AD” is interesting but unusual.” **Response:** The term “clinically silent AD” was introduced by Braak & Braak (1998), but is uncommon. We have updated this proposal to use the more conventional term “preclinical AD.” Preclinical AD, defined by Sperling et al. (2011) as elevated levels of cerebral amyloid plaques in the absence of cognitive decline, is an active and important research field[57-64,93]. Our study will compare preclinical AD patients with controls to identify changes in frontoparietal control network (FPCN) connectivity that are related to normal aging. We predict that increased age will be associated with weakened connectivity within FPCN nodes, reflecting reduced long-distance structural connections. Prior work has also identified “compensatory” age-related strengthening of connections between the FPCN and other networks. We believe that this effect may be exaggerated due to the inclusion of older adults with preclinical AD pathology in these earlier studies, which the experiments described in this proposal will control for.

## SPECIFIC AIMS

Deficits in abstract reasoning are prevalent in older individuals and in age-related disorders including Alzheimer's disease (AD) and frontotemporal dementia (FTD). Abstract reasoning is largely supported by the frontoparietal control network (FPCN), a group of functionally connected brain regions including the inferior parietal lobule, anterior insular cortex, and dorsolateral and dorsomedial prefrontal cortices. The FPCN is thought to contribute to abstract reasoning by integrating information from two systems: the dorsal attention network (DAN) and the default mode network (DMN). To date, most Alzheimer's research has focused on episodic memory deficits and the DMN. Future work focusing on understanding changes in the FPCN and cognitive deficits beyond episodic memory are a necessary next step in aging research, and are the focus of this proposal. Using a network-centered approach with fMRI and leveraging PET imaging of neuropathology, I propose to study FPCN contributions to abstract reasoning in healthy young adults (Aim 1; F99), and to examine the effects of normal aging, preclinical AD, AD, and FTD on FPCN network dynamics and reasoning deficits (Aim 2; K00).

The ***primary research goal*** of this project is to advance our understanding of how the FPCN enables abstract reasoning behavior, and to understand how reasoning is affected when the network is damaged by age and disease. The ***training goals*** include building a strong understanding of graph theoretical network analyses, fMRI and PET methodologies, and applying this skillset to advance our understanding of the FPCN and cognitive changes associated with aging, AD, and FTD. The ***central research hypotheses*** are that (1) the FPCN supports abstract reasoning behavior by balancing activity in two opposing networks (the DAN and the DMN), and (2) that normal aging impacts the connectivity of nodes within the FPCN, while preclinical AD, AD, and FTD impact the connectivity of the FPCN with other functional networks (DAN and DMN). My long-term career goal is to develop better treatments and diagnostics for age-related brain disorders, by first improving our understanding of these functional networks, and then understanding the differential roles of age and disease on network connectivity.

**Aim #1 (Pre-doctoral Stage, F99): *Determine frontoparietal control network contributions to abstract reasoning behavior in healthy young adults using a novel reasoning task.***

Current Work: My dissertation work includes the development of a simple visuospatial abstract reasoning task to compare FPCN activity across perceptual and symbolic reasoning conditions. fMRI scans of healthy young adults (n=27) showed that the FPCN is activated for both symbolic and perceptual reasoning behavior, which differentially recruit DAN and DMN nodes in the two conditions.

Future Work: Using the data from the experiment described above, I will examine differences in task-related functional connectivity between the different reasoning conditions. My prediction is that the FPCN will become more strongly connected with the DMN during symbolic reasoning trials which require the incorporation of internal information, and more strongly connected with the DAN during perceptual reasoning trials.

**Aim #2 (Postdoctoral Stage, K00): *Examine changes in frontoparietal control network structure and abstract reasoning ability in aging, Alzheimer's disease, preclinical AD, and Frontotemporal dementia.***

*Rationale:* Normal aging, AD, preclinical AD, and FTD are associated with changes in FPCN functional connectivity and changes in abstract reasoning ability. My hypotheses are that the FPCN supports abstract reasoning by balancing activity in two opposing networks (the DAN and the DMN), and that this balance may be impacted by aging, preclinical AD, AD, and FTD. I predict that the balance of connectivity between the FPCN and other networks will be maintained in high functioning older adults, while AD and FTD, including preclinical AD pathology, will impact between-network connectivity of the FPCN with the DAN and DMN.

*Experiment A (Healthy Aging and Preclinical AD):* We propose an experiment using fMRI and PET data from cognitively normal older adults to examine age-related changes in FPCN connectivity. Our sample includes adults with preclinical AD pathology, characterized as cognitively normal older adults with elevated amyloid PET scans. I predict that FPCN nodes will show decreased connectivity with the DAN and DMN in subjects with greater amyloid burden (preclinical AD) compared to healthy middle-aged/older adult controls.

*Experiment B (Dementia):* We will draw from established cohorts of early-stage AD patients, FTD patients, and healthy middle-aged/older adult controls, and test them on the abstract reasoning task presented in Aim #1. Recruitment from several cohorts will facilitate specific associations between disorders or targeted brain structures and reasoning deficits. I predict that patients with FTD will perform worse on the symbolic conditions, with reduced BOLD signal in anterior portions of the FPCN, while patients with AD will perform worse on the perceptual reasoning conditions, with reduced BOLD signal in posterior portions of the FPCN.

The training goals outlined here will equip me with expertise in multimodal neuroimaging, and allow me to transition from a training program in basic cognitive neuroscience to a research career in cognitive neuroscience of aging. Completion of this research will improve our understanding of normal FPCN structure and function and the unique effects of aging, preclinical AD, AD, and FTD on frontoparietal control network dynamics.

## RESEARCH STRATEGY

**Aim #1 (Predoctoral Stage F99):** ***Determine frontoparietal control network contributions to abstract reasoning behavior in healthy young adults using a novel reasoning task.***

### SIGNIFICANCE (*Predoctoral Stage*)

Deficits in abstract reasoning often accompany normal aging[1] and are prevalent in age-related disorders including Alzheimer's disease (AD)[2–4] and frontotemporal dementia (FTD)[5,6]. Abstract reasoning is largely supported by the frontoparietal control network (FPCN)[7–10], a collection of prefrontal and parietal regions that exhibit strong functional connectivity[11,12]. However, the region-to-region interactions both within the FPCN and between the FPCN and other functional networks are not fully understood. *The goal of my dissertation work is to use fMRI to determine the role the FPCN plays in abstract reasoning.*

### *Activity of the frontoparietal control network during abstract reasoning*

FPCN nodes are activated in a variety of abstract reasoning paradigms including tasks of analogical reasoning, rule learning, and matrix reasoning[13–20]. Primary regions of the FPCN include the inferior parietal lobule (IPL), anterior insular cortex (AI), dorsolateral prefrontal cortex (dlPFC), and dorsomedial prefrontal cortex (dmPFC)[7,11,12]. Functional MRI studies of lateral parietal cortex have identified it as a region important for processing top-down directed attention[21], mental rotation and spatial reasoning[22,23], and magnitude processing[24–29] (including numerical, temporal, and spatial magnitudes). fMRI studies of dlPFC suggest a rostral-caudal axis of organization with the most rostral regions facilitating reasoning through the integration of long-term memory schemas[30–34].

The Raven's Progressive Matrices (RPM) task has been used by psychologists for almost a century as a test of fluid intelligence and relational reasoning[35]. Previous work by our lab and others has identified several regions of prefrontal and parietal cortices that are involved in the deduction, manipulation, and application of sequence rules during abstract reasoning tasks[14,16,19,37,38]. Computational models of these tasks divide reasoning into two stages: (1) the deduction of a relationship between stimuli, and (2) the application of that relationship to select an answer choice and produce a motor action[39–45]. However, several barriers exist to conducting fMRI studies with the traditional RPM task: (1) trials take subjects a relatively long time to complete, (2) a variety of strategies can be employed to solve the problems, and (3) the task requires intense working memory demands, which are often impaired in clinical populations. *In my dissertation work, we designed a simplified version of the RPM task, suitable for rapid presentation of trials in the scanner with reduced working memory demands for eventual application in a clinical population. We have completed an fMRI study of the task in healthy young adults and demonstrate FPCN activity during both symbolic and perceptual reasoning* (see **Fig. 1** and **2**).

### *Functional connectivity of the frontoparietal control network during abstract reasoning*

Cognitive task demands can influence the structure and connectivity of a cortical brain network[46]. Previous work has demonstrated the Dorsal Attention Network (DAN) becomes anticorrelated from the Default Network (DMN) when a subject is cognitively engaged in a task[9,47,48], and the magnitude of this anticorrelation is altered depending on the attentional demands across different cognitive states (e.g. at rest vs. watching a movie)[9]. Moreover, the anticorrelation between individual nodes of these two networks can vary systematically[8,9]. The FPCN is thought to integrate information from both memory and attention systems (DMN and DAN) to meet the demands of a particular task[7,48]. As task demands shift, one would expect functional connectivity between the FPCN, DAN, and DMN to shift in parallel. M*y F99 dissertation work will examine changes to FPCN functional connectivity associated with completion of an abstract reasoning task. We predict that the FPCN will become more strongly connected with the DMN during symbolic reasoning trials which require the incorporation of internal information, and more strongly connected with the DAN during perceptual reasoning.*

### APPROACH (*Predoctoral F99 Stage*)

The overall strategy of the F99 dissertation work is to use fMRI to observe changes in blood oxygenation level dependent (BOLD) signal associated with abstract reasoning. With fMRI, we can examine the entire brain at once to view large-scale changes in network activity and functional connectivity. My dissertation work focuses on healthy young adults (18 - 35 years old) to achieve a better understanding of the organization of the FPCN in the healthy human brain. These experiments will improve our understanding of how FPCN activity and functional connectivity contribute to abstract reasoning ability in humans.

### Current Work (*Predoctoral Stage*)

**Goals, Rationale, and Hypotheses:** During the first two years of my PhD, I developed a simplified version of the Raven's Progressive Matrices (RPM) task suitable for fMRI, and used the task to observe changes in BOLD signal associated with abstract reasoning behavior. Previous studies of the RPM task have focused exclusively on the symbolic version of the task. My design tested both symbolic and perceptual reasoning with an event-related design for fMRI. *Preliminary results support the prediction that the FPCN would be active for both symbolic and perceptual reasoning, and that we would see increased rostrolateral PFC activity for the symbolic condition, and ventral visual activity for the perceptual condition.*

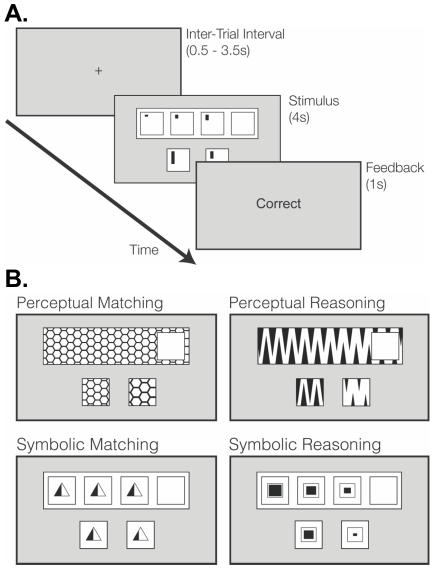

**Fig 1. (A)** Sample trial from the 1-Dimensional Raven's Progressive Matrices Task. **(B)** Task conditions.

**Participants:** Participants consisted of healthy young adults (18-35) of both sexes with normal or corrected-to-normal vision, no current or previous diagnosis of neurological or psychiatric condition, and no condition that would make undergoing an MRI scan unsafe. Sample size (n=27) was based on a literature review of fMRI studies of reasoning behavior[13,16,49], previous research in our lab[16], and a sample size calculation (G*Power 3.1, effect = 0.75, alpha = 0.05, power = 0.95).

**Experimental Design and Methods (Approaches Used)**

*Task and fMRI Acquisition:* We developed a simplified, one-dimensional version of the Raven's Progressive Matrices task (1D-RPM) suitable for fMRI. During the task, participants viewed patterns composed of either discrete symbols (symbolic condition) or detailed continuous textures (perceptual condition). Symbols or textures either vary from left to right according to a sequential rule (reasoning), or remain uniform throughout (matching) (see **Figure 1**). Subjects were required to determine which of two answer choices correctly completed the sequence. Participants were instructed on a paper version of the task prior to scanning and completed 384 trials of the task during fMRI scanning.

MRI data were acquired using a 3-T Siemens MAGNETOM Prisma scanner located at the Cognitive Neuroimaging Center at Boston University in Boston, MA. All data were acquired using a 64-channel head coil. For each subject, we collected (1) a T1-weighted (MEMPRAGE) anatomical image [$1.0\text{mm}^3$ resolution], (2) opposite phase-encoded echo-planar field-maps to be used for distortion correction of the functional images, (3) three runs of T2*-weighted echo-planar (BOLD) images covering the whole brain while the subject was at rest (*for use in Aim #1b, future dissertation work*), and (4) six runs of T2*-weighted echo-planar (BOLD) images covering the whole brain while subjects complete the 1D-RPM task.

*Preprocessing of fMRI Data:* Preprocessing of the functional BOLD images used AFNI for slice time correction, distortion correction, motion correction, spatial alignment of the functional data onto the subject's anatomical scan, spatial normalization and projection onto the fsaverage (MNI) cortical surface, voxelwise demeaning, and spatial smoothing (3mm FWHM). To ensure that this work is replicable, we wrote our preprocessing scripts with AFNI's `afni_proc.py` tool and posted the code publicly to GitHub.

*Data Analysis:* Single subject data was analyzed voxelwise using a general linear model (GLM) including a predictor (boxcar function) for each task condition (symbolic reasoning, symbolic matching, perceptual reasoning, and perceptual matching), a 3-degree polynomial (cubic) baseline term, and 6 nuisance regressors for motion (x, y, and z translations and rotations). To account for signal related to time-on-task, we also included four amplitude-modulated task predictors (one for each task condition) in the GLM. High motion time points were censored from the GLM analysis. Two-sided t-tests were conducted at each voxel to determine differences in activation between conditions. Group statistical maps were thresholded and corrected for multiple comparisons using AFNI's equitable thresholding and clustering (ETAC) method[50]. Thresholded activation maps were overlaid onto the MNI 152 (2009) standard template brain and the fsaverage (MNI) inflated cortical surface.

**Research Outcomes Obtained:** The work shown here builds off of previous work in our lab[16] by testing both perceptual and symbolic reasoning. Moreover, recent advances in MRI scanning technology, computing power, and statistical software allowed us to perform more robust statistical analyses, achieve better signal-to-noise ratio, and view results at a higher resolution. Results of the univariate group-analysis (n=27) are shown in **Figure 2a**. We observe that the frontoparietal control network is significantly activated during both symbolic and perceptual reasoning, and that it is activated more strongly during symbolic reasoning behavior (**Figure 2b**).

Increased activation of the FPCN during symbolic reasoning is likely driven by activity in the rlPFC, whereas during perceptual reasoning, activity in inferior temporal cortex is increased. These preliminary results confirm our hypotheses, suggesting similar FPCN network contributions to both symbolic and perceptual reasoning with notable differences in rlPFC (symbolic) and ventral visual regions (perceptual).

**Important Methodologies Learned:** I learned to design cognitive task suitable for fMRI. The task was repeatedly piloted to match response times and eliminate working memory confounds across conditions. I gained experience with fMRI experimental design, preprocessing, and univariate analysis methods. These skills form a strong foundation that will be invaluable during my postdoc.

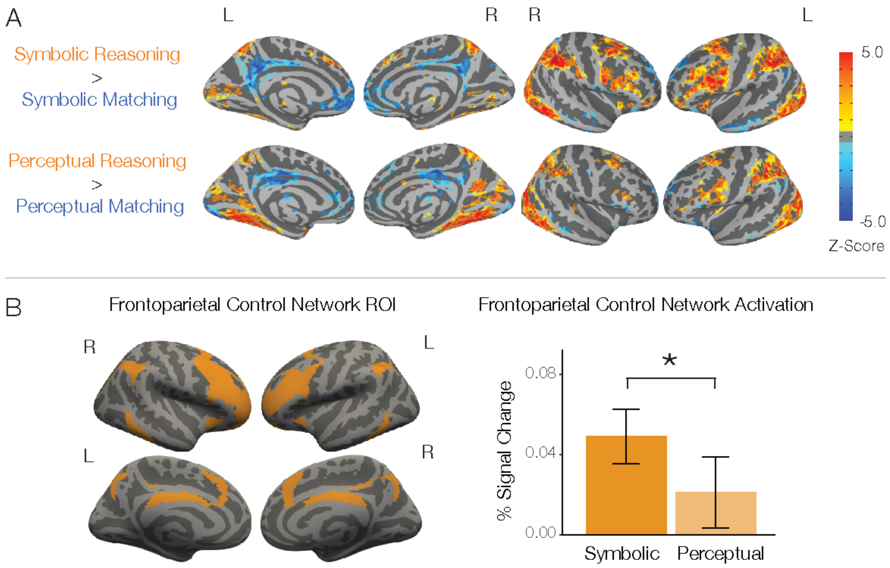

**Fig. 2** Preliminary data for the 1-Dimensional Raven's Task. (A) Activation maps on the inflated cortical surface. Warm colors represent greater BOLD signal for reasoning compared to matching, shown for symbolic (top row) and perceptual (bottom row) conditions. ($p < 0.05$, Cluster Size > 20 Vertices). (B) An ROI analysis showed that the frontoparietal control network (Left, defined by Yeo et al. 2011) is activated more strongly during symbolic reasoning compared to perceptual reasoning (Right, * = $p < 0.05$, Error Bars = 95% C.I.)

## Future Work (*Predoctoral F99 Stage*)

**Goal, Rationale, and Hypothesis:** The goal of my future dissertation work is to characterize local and global functional connectivity of the FPCN during abstract reasoning including interactions between the FPCN, DAN, and DMN. Previous work demonstrates that functional connectivity patterns of the FPCN can be altered depending on the cognitive task at hand[8,9]. According to this framework, during a memory retrieval task, connectivity will increase between the FPCN and memory nodes found within the DMN. In abstract reasoning, *we predict that the FPCN will become more strongly connected with the DMN during symbolic reasoning trials which require incorporating internal information, and more strongly connected with the DAN during perceptual reasoning trials.* Methodologically, our approach will define FPCN nodes in individual subjects because the precise topography of the FPCN is highly variable between individuals[11,51,52].

**Experimental Design and Methods:** The aim is to examine connectivity within FPCN regions (IPL, AI, dlPFC, and dmPFC) for individual subjects across conditions on the 1D-RPM task. This experiment will use the dataset I have collected for my dissertation work (n=27). Three 6-minute runs of resting-state fMRI data will be used to define individualized network parcellations for each subject.

*Preprocessing of fMRI Data:* Resting state data for each subject will be preprocessed using AFNI for slice time correction, distortion correction, motion correction, spatial alignment of the functional data onto the subject's anatomical scan, spatial normalization to the MNI-152 (2009) template brain, anatomical segmentation and nuisance regression to isolate gray-matter signal (regress out WM and CSF signal), bandpass-filtering to isolate low-frequency BOLD signal between 0.01 and 0.1 Hz, voxelwise demeaning, and spatial smoothing (3mm FWHM). Functional BOLD images acquired during the RPM task have already been preprocessed, as described above. The preprocessing pipelines will be made publicly available on GitHub to facilitate the reproducibility of this research project.

**Data Analysis and Predictions:** The precise topography of the FPCN can vary greatly between subjects, and some studies suggest that it may be the most variable of all the functional networks.[11,51,52] Therefore, investigation of FPCN structure and function should utilize parcellations of the network that are uniquely determined for each individual subject. Using the preprocessed resting-state fMRI data, individualized cortical network parcellations will be created for each subject[11,53]. A population-based functional network atlas[11] will provide a starting-point for an iterative clustering algorithm that will create a network parcellation for each individual's brain. The algorithm is described in detail by Wang et al. and their code is freely available on GitHub[54]. ROIs that make up the FPCN (IPL, AI, dlPFC, and dmPFC) will be identified for each individual and used as seeds in a subsequent task-based functional-connectivity analyses of the functional BOLD scans. Using the six task scans for each participant, a beta-series regression[46] will be completed in AFNI to analyze task-related shifts in functional connectivity during the 1D-RPM task. Briefly, this analysis will fit a separate beta-coefficient to each trial of the task, forming a voxelwise beta-series for each condition during the task. Average beta-series will be calculated for seeds in the FPCN (defined with each participant's unique network parcellation), and whole-brain voxel-wise correlation differences between conditions will be calculated for each seed region. Within-network structure will be mapped by creating a weighted-graph where FPCN ROIs are nodes and their seed-to-seed beta series correlations form weighted edges.

*We predict that the FPCN will show increased connectivity with the DMN during symbolic reasoning and increased connectivity with the DAN during perceptual reasoning. Cognitively, the symbolic trials require the incorporation of long-term internal representations of shapes and abstract knowledge, whereas perceptual trials require increased externally directed attention to the complex stimulus features.*

**Alternative Outcomes and Potential Pitfalls:** To account for between-subject variability in functional network structure, we will define the nodes of each network on an individual-subject basis. We will take a machine learning approach using a population-based functional network parcellation[11] as a starting point for defining the FPCN in individuals with an iterative adjustment clustering algorithm[54]. Because the precise topography of the FPCN can be highly variable between subjects, it is possible that some subjects could exhibit network structures that do not include previously reported FPCN nodes. To address this issue, we will outline strict criteria defining the general locations of specific nodes (e.g. dlPFC, IPL, etc.) that must appear in a subject's FPCN in order for that subject's data to be included in the analysis. Additionally, we have proposed the use of pre-existing code from the Yeo lab to create network parcellations in individual subjects[54]. We recognize that implementing code from another lab[54] at another institution is challenging, but it is also important for experimental replication and reproducibility. There are a variety of other algorithms that could be implemented for the same purpose, including a seed-based classification algorithm outlined by Braga & Buckner[55]. Alternatively, we could also implement our own k-means clustering algorithm.

**Important Skills to be Learned:** My future (F99) dissertation research will require me to learn network-driven fMRI analysis methods that extend beyond the traditional univariate methodology I have used to date. I have learned about the graph theoretical concepts behind these methods in my coursework, and have conducted dynamic network analyses on fMRI data unrelated to this proposal (recently these results were submitted as a first-author publication). I will continue to consult my thesis committee member, Dr. Joe McGuire, for assistance in learning these concepts. By exploring the brain through a network-driven approach, I will be prepared to study FPCN degradation and associated abstract reasoning deficits in AD, FTD, and healthy older adults as a postdoc.

## <u>Aim #2</u> *(Postdoctoral Stage K00): Examine changes in frontoparietal control network structure and abstract reasoning ability in aging, Alzheimer's disease, preclinical AD, and frontotemporal dementia.*

### SIGNIFICANCE (Postdoctoral Stage)

Previous work has investigated the differential effects of aging, AD, and FTD on the spread (or lack) of amyloid plaques, tau tangles, and gray matter thinning. To date, most AD work has focused on episodic memory deficits and the DMN. Future work focusing on understanding changes in the FPCN and cognitive deficits beyond episodic memory are a necessary next step in aging research, and are the focus of Aim #2. *The goal of the postdoctoral research project is to investigate the effects of normal aging, preclinical AD, AD, and FTD on FPCN network dynamics and abstract reasoning.*

### *Network connectivity in normal aging, Alzheimer's disease, and preclinical AD*

Resting state functional connectivity has great potential as a biomarker for AD and FTD[56]. However, research shows that brain network connectivity patterns can change simply due to normal aging, and the unique contributions of normal aging and age-related disease to resting state functional connectivity patterns are not yet fully understood. Overall, older adults tend to exhibit weaker functional connectivity <u>*within*</u> brain networks, with slightly strengthened connectivity <u>*between*</u> networks[65–67]. However, most previous research was unable to account for cerebral amyloid and APOE $\varepsilon 4$ genetic status. It is estimated that about 10% of cognitively normal 50 year-olds and up to 44% of cognitively normal 90 year-olds have abnormally high levels of cerebral amyloid plaques[68]. Previous studies have shown that a variety of factors including APOE $\varepsilon 4$ genetic status[57–59], and the spread of amyloid plaques[60–64] can influence the connectivity patterns of the DMN and FPCN. When testing for age-related changes in functional connectivity, it is essential to account for this preclinical AD pathology, which Sperling et al. (2011) define as elevated levels of cerebral amyloid plaques in the absence of significant cognitive decline[93]. *In Aim #2, Experiment A, we will use existing fMRI and PET data from cognitively normal older adults to examine the unique contributions of normal aging and preclinical AD pathology to changes in FPCN functional connectivity.* This experiment will use existing data available to the Dickerson lab as part of an ongoing longitudinal study, and will include a set of controls for genetic status, cerebral amyloid load, and cortical atrophy.

***Abstract reasoning in normal aging, Alzheimer's disease, and frontotemporal dementia***

Previous work indicates that abilities including abstract reasoning and executive functioning often decline with normal healthy aging, but the level of decline can vary considerably between older adults[77–79]. Prior behavioral work suggests that abstract reasoning is impaired in both FTD and AD[80,81], but the severity and precise type of reasoning impairment may vary with neuropathology. Moreover, the spread of AD pathology is often confined to the boundaries of the DMN and FPCN, and the precise signature of cortical thinning corresponds to the behavioral symptoms of particular subpopulations[3,4,67,69–73]. For example, damage to the posterior parietal cortex (common in posterior cortical atrophy) often impacts visuospatial skills[73–75], while damage to left prefrontal cortex (common in FTD) often impacts language function. Recent work in the Dickerson lab shows that gray matter thinning in AD can widely differ depending on the age of disease onset[76]. Patients with early-onset AD exhibit damage to parietal cortices, while patients with late-onset AD show damage in limbic and medial temporal regions. This study and others suggest a complex interaction between age and AD, which must be accounted for in future research. It is essential to conduct task-based fMRI studies in clinical populations, in order to better understand how brain damage and disease affect cognitive function. With an established cohort of subjects whose atrophy patterns and amyloid loads are already known, task-based experiments can be even more informative. *In Aim #2, Experiment B, we propose a task-based fMRI study on a cohort of previously-scanned patients, using the 1D-RPM reasoning task presented in Aim #1 to investigate abstract reasoning decline in AD, FTD, and healthy aging.*

## APPROACH (Postdoctoral K00 Stage)

The overall strategy of the postdoctoral research project is to study an established cohort of subjects from an **existing Longitudinal Study** cohort at the MGH FTD Unit and Alzheimer's Research Center using resting state and functional MRI methods coupled with cognitive and amyloid PET measurements. The project will examine existing amyloid PET and MRI data from healthy older adults (Experiment A), and will recruit participants from clinical populations in the Longitudinal cohort to complete a task-based fMRI study (Experiment B). This work aims to determine the unique contributions of normal aging, preclinical AD, AD, and FTD to changes in FPCN structure and function.

### Proposed Experiment A (Healthy Aging and Preclinical AD)

**Goal and Hypothesis:** We propose an experiment using existing data from cognitively normal older adults to examine age-related changes to FPCN connectivity. Preclinical AD pathology in cognitively normal older adults will be controlled for by examining the subjects' amyloid PET scans and their APOE $\varepsilon 4$ genetic status. *We predict that FPCN nodes will show decreased connectivity with the DAN and DMN in subjects with greater amyloid burden (preclinical AD) or positive APOE$\varepsilon 4$ status compared to healthy middle-aged/older adult controls.*

**Participants:** Based on a literature review of studies examining functional connectivity changes associated with age[65-67], studies accounting for cerebral amyloid[57-64], and a sample size calculation (G*Power 3.1, effect = 0.20, alpha = 0.05, power = 0.9, total predictors = 3) we determined that 50 subjects will be required for this study (Aim 2, Experiment A). We will use existing MRI and PET data from cognitively normal middle aged/older adults (ages 45 – 85) in an established cohort of subjects, including subjects with and without preclinical AD pathology or elevated AD risk, defined by elevated cerebral amyloid PET scans and APOE $\varepsilon 4$ genetic status.

**Experimental Design and Methods:** Resting state fMRI data will be preprocessed according to a standard preprocessing pipeline, as described in Aim #1. PET data analysis will be overseen by Dr. Jacob Hooker (co-sponsor). Amyloid PET data (acquired with the Pittsburgh Compound B radiotracer[36]) will be reconstructed using a MATLAB software tool developed at the Martinos Center[82] and registered to the subject's structural MRI using FSL and SPM software packages. Standardized uptake values will be calculated from the radioactivity measures at each voxel to quantify regional cerebral amyloid load. The FPCN will be identified in individuals by using the iterative adjustment clustering algorithm described in Aim #1. Specifically, we will compare the spatial extent/layout of the FPCN in older vs. middle-aged adults. We will also examine FPCN connectivity with other cortical networks including the DMN and DAN in older vs. middle-aged adults. Multiple graph-theoretical concepts will be used to fully characterize the FPCN including assortativity (the degree to which nodes of the FPCN connect to other nodes of the FPCN vs. other brain regions outside the network) and centrality (the degree to which information "flows" through the FPCN).

**Predictions:** We predict that increased age will be associated with weakened connectivity within FPCN nodes, reflecting reduced long-distance structural connections. Additionally, we predict that graph-theoretic metrics will demonstrate that the FPCN has less influence on other brain systems in older adults, with decreased assortativity (fewer between-network connections) and decreased centrality. However, we predict that the connectivity between networks will not be strengthened to the degree other studies have shown. This strengthening has been said to be compensatory, due to the weakening within-network-connectivity. We believe that this effect may be exaggerated in the literature due to the inclusion of older adults with preclinical AD pathology, which this experiment will control for.

**Alternative Outcomes and Potential Pitfalls:** Whenever participants are divided into groups, there is the risk of finding arbitrary differences based on arbitrary group assignments. Our proposed design divides participants into older/middle-aged adults, and as either positive or negative for elevated cerebral amyloid. The assignment to groups will be blinded as to not influence outcomes, and will follow strict criteria decided upon prior to analysis. As an alternative, we will also consider using amyloid status and age as continuous variables in a linear model. Regardless of the method used (grouping/linear model) we expect to find similar results.

### Proposed Experiment B (Dementia)

**Goal and Hypothesis:** The goal of Experiment B is to determine how age and disease-related brain changes affect FPCN structure and abstract reasoning ability. We will recruit healthy middle-aged and older adult controls, and AD and FTD patients from the established Longitudinal cohort (ages 45-85). These patients will be invited to participate in an fMRI study using the abstract reasoning task developed during my dissertation work (see *Aim #1*). *We predict that reasoning deficits will be associated with patterns of cortical atrophy in AD and FTD, with AD patients performing more poorly on the perceptual reasoning condition, and FTD patients performing more poorly on the symbolic reasoning condition of the task.*

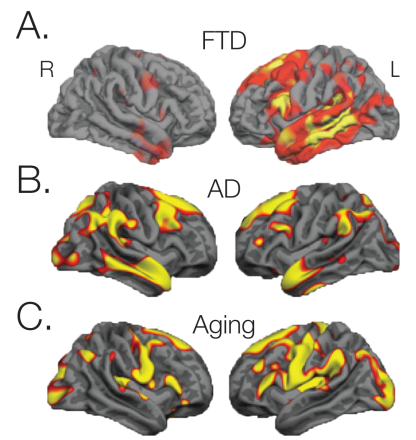

**Fig. 3** Cortical atrophy signatures of frontotemporal dementia (A), Alzheimer's disease (B), and normal aging (C). Used with permission from the Dickerson lab[83,84].

**Participants:** Based on a literature review of task-based fMRI studies of AD and FTD, and a sample size calculation (G*Power 3.1, effect = 0.20, alpha = 0.05, power = 0.8, Total predictors = 4, one tested predictor) we determined that 60 subjects will be required for the second fMRI study (Aim 2b). 20 patients with FTD, 20 patients with AD, and 20 healthy middle-aged/older adult controls will be selected from at the established Longitudinal cohort studied at the MGH FTD Unit and Alzheimer's Research Center (ages 45-85). Participants in the study will give informed consent and will be compensated for their time in accordance with the Partners Healthcare IRB.

**Experimental Design and Methods:** Participants will be selected from their T1 structural MRI scans. Full-brain cortical atrophy will be quantified with surface-based analyses in Freesurfer. Interested and eligible participants will be invited to complete an fMRI study in which they will complete the 1D-RPM task described in Aim #1. Additional structural images will be acquired so that up-to-date atrophy measures are collected at the same time as fMRI data.

**Data Analysis and Predictions:** Standard preprocessing will be conducted in AFNI (see *Aim #1*). Individualized BOLD signal maps will be produced using a GLM with regressors for each condition (see *Aim #1*). Group analysis will compare BOLD signal in AD patients with FTD patients and healthy controls. Patients will be grouped according to their symptomology and patterns of cortical atrophy (see **Figure 3** for typical patterns of atrophy ("disease signatures") for FTD[83], AD[84], and normal aging[84]). *We predict that patients with FTD will perform worse on the symbolic conditions, with reduced BOLD signal in anterior portions of the FPCN, while patients with posterior damage will perform worse on the perceptual reasoning conditions, with reduced BOLD signal in posterior portions of the FPCN.*

**Alternative Outcomes and Potential Pitfalls:** The abstract reasoning task was originally designed for use in healthy young adults (Morin and Stern). Before conducting the proposed postdoctoral work, we will re-pilot the task in a cohort of healthy middle-aged/older adults and dementia patients (Morin, Dickerson, Stern). We believe that patients in the early stages of AD and FTD should be able to perform the task but may consider extending trial duration or eliminating particularly difficult trials. Whenever participants are divided into groups, there is the risk of finding arbitrary differences based on arbitrary group assignments. In addition to traditional group-comparison, we will conduct a region-of-interest analysis with a linear model to assess the influence of atrophy in a given region (regardless of disease status) on BOLD signal associated with each task condition. This would also help to account for patients whose atrophy patterns are not necessarily stereotypical of their diagnosis.