# BRAIN CONNECTIVITY AND NEUROCOGNITIVE HEALTH IN OLDER ADULTS: THE BALTIMORE EXPERIENCE CORPS TRIAL BRAIN HEALTH STUDY

by

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#### Abstract

**Background**: Cognitive aging is associated with cognitive decline and poor functional connectivity in the brain; however, the lengthening of life also presents additional potential to contribute to society. Addressing both these challenges and opportunities, we studied brain networks and cognitive functions within a randomized controlled trial of a senior service volunteer program, Experience Corps (EC).

**Methods**: Data are from the Brain Health Study (BHS), a longitudinal trial nested within the Baltimore Experience Corps Trial, randomizing 123 socio-demographically diverse community-dwelling adults over the age of 60. At Baseline, 12-month Follow-Up, and 24-month Follow-Up, functional magnetic resonance imaging (fMRI) brain data and neuropsychological test data were collected. We investigated two brain networks whose coupling is known to be associated with cognitive aging and dementia risk, the Task Negative Network (TNN) and the Task Positive Network (TPN). We studied the associations between these biologic measures and the cognitive domains of executive function and memory, which are also known to be important to dementia risk. In particular, we investigated (Aim 1) TNN-TPN functional connectivity at baseline; (Aim 2) how the connectivity between and within the TNN and TPN were associated with dementia-linked cognitive functions; and (Aim 3) how these connectivity scores and cognitive functions changed longitudinally in the EC and Control Groups.

**Results**: In Aim 1, we found that, the TPN and TNN were not strongly anti-correlated. In Aim 2, we found heterogeneous relations between functional connectivity and cognitive functions. In Aim 3, we found that these brain networks remained remarkably stable, and

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intervention effects were not statistically significant. Additionally, the EC group demonstrated an improvement in the executive functions domain of cognition compared to the Control group.

**Implications**: The BHS is the first of its kind, to have investigated cognitive aging with biological markers in the brain and cognitive measures in a randomized controlled trial design of a volunteer intervention. These results contribute to a better understanding of functional connectivity in older adults, its relations to cognitive functions, and how these outcomes can be modified by senior service. We also developed analytic methodologies that can be standardized and applied to other fMRI studies.

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To the participants of the Baltimore Experience Corps Trial, and to my parents:

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I dedicate this work.

Thy Lord hath decreed that ye worship none but Him, and that ye be kind to parents; whether one or both of them attain old age in thy life, say not a word of contempt, nor a sign of disrespect, but address them in terms of honor. Out of compassion, lower to them the wing of humility through mercy, and say: "My Lord! Bestow on them thy Mercy as they cherished me in childhood."

~ The Quran, 17:23-4

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~ The Quran, 14:34.

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# 1 Chapter 1. Introduction

#### 1.1 Public Health Significance

By 2050, the demographics of the United States will dramatically shift, with individuals 65 and up accounting for more than one in four adults in the population. This population shift means that diseases of the elderly will be directly relevant for everyone: one in four persons' will face a serious threat of acquiring Alzheimer's Disease, and all of us will know and care for a family member suffering from a stolen mind. If we could delay onset by 1-2 years, we would cut prevalence worldwide by over 20% (Brookmeyer *et al.*, 2007). Therefore, we have a public health responsibility to delay this degenerative trajectory, and to detect, treat, and prevent dementia. Perhaps we can transform the forecast for a silver tsunami to a better outcome.

However, we do not yet have the means to accurately detect or predict dementia in the brain, or the cognitive decline that precedes it by years. In our investigation, we aimed to detect changes in brain health prior to the onset of pathology. One emerging avenue to accomplish this feat is in the study of the organization of the brain. The human brain is organized in networks, collections of regions that work together. Models of connectivity between these networks demonstrate that within each network, the regions work together, and across network, the regions also exhibit a sense of synchrony, such that competing networks do not activate simultaneously. This harmony between and within networks in the brain may hold a promising key to detecting abnormalities in the brain before they become pathological.

Indeed, a host of recent studies implicate healthy functional connectivity with improved cognition and reduced dementia (Jones *et al.*, 2011; Jones *et al.*, 2012; Buckner *et al.*, 2007; Buckner *et al.*, 2008; Voss *et al.*, 2010; Vemuri *et al.*, 2012; Sandrone, 2012;

Hampson *et al.*, 2010; Sandrone *et al.*, 2012; Van De Ville *et al.*, 2012; Whitfield-Gabrieli *et al.*, 2012; Fransson *et al.*, 2006). However, these studies are based on cross-sectional data, which does not lend itself to the study of declines in cognition and subsequent development of a corresponding predictive model. Using longitudinal data, we investigated changes in functional connectivity and associated cognitive functions within the context of an intervention trial with preventative potential.

We assessed functional connectivity in the brain using functional magnetic resonance imaging (fMRI). This technology holds promise as a minimally invasive and easily standardized tool to aid in the development of a biomarker of preclinical changes in cognition. This tool can be adapted and incorporated in clinic settings, yielding major public health benefits for our aging society.

Lastly, the intervention trial, from which the data are drawn, presents a multimodal program of senior service. Differences between the intervention and control groups therefore suggest an intervention that older adults can take to improve brain health and cognitive functions. Furthermore, the nature of the intervention is a volunteer program, which places senior citizens as important members of society. This integration across generations benefits both senior volunteers and recipients of the services alike. This novel intervention takes the public health "problem" of shifting demographics, and turns it into a solution.

#### 1.2 Overview

In an average adult human, the brain occupies one fiftieth of the body's mass and devours one fifth of its calories throughout the day and night (Raichle and Gusnard, 2002; Clark and Sokoloff, 1999; Sokoloff *et al.*, 1955). The continuous metabolism of the

brain demonstrates that this organ is always at work, whether or not the person is engaged in a task. Indeed, the brain consists of intrinsic networks, representing groups of regions that work together and modulate one another continuously. Neuroimaging studies are beginning to map the functions of these networks in young healthy adults and in specific patient populations. However, data are lacking on the longitudinal behavior of intrinsic brain networks in community-based samples of older adults, and on what types of factors may promote improved functional connectivity in the aging brain.

This study sought to fill a void in the literature on functional connectivity in older adults. Our data were drawn from a randomized controlled trial (RCT) of the Experience Corps (EC) program, a model of senior volunteer service that increases physical, social, and cognitive activities. While pharmaceutical trials are failing to find a pill to preserve brain health and cognition, studies are demonstrating that lifestyle makes a difference (Daviglus *et al.*, 2010). Early evidence of the EC pilot RCT showed that relative to the Control individuals, participants of the intervention group exhibited increased activity in regions of the brain important for executive functions, including the prefrontal and anterior cingulate cortices (Carlson *et al.*, 2009). These neuronal changes in the participants of the intervention group were also substantiated by improvements on cognitive tests, which supports the idea that lifestyle could improve cognition, even in socio-demographically at-risk older adults.

We studied the functional connectivity between two fundamental brain networks, the Task Positive Network (TPN) and the Task Negative Network (TNN) in a community-based sample of older adults, and compared connectivity patterns between the intervention and control groups. Differences in connectivity patterns that correspond

with cognitive function outcomes help elucidate mechanisms of the Experience Corps program, and further support a lifestyle approach to protect against cognitive decline.

The Task Positive Network (TPN) includes regions of the brain that activate in the presence of a task, and the Task Negative Network (TNN) includes regions of the brain that activate in the absence of tasks. These two networks provide a model for the organization of the whole brain, working synchronously according to cognitive demand, such that when one is on the other is off. While this dichotomous association has been observed and replicated in young healthy adults, less is known about the accuracy of this conceptual model in older adults. Cross-sectional studies in healthy seniors demonstrate that in older adults, the regulating switch appears to decay, and some regions of the TNN activate even in the presence of a task, and conversely, some regions fail to activate in the absence of a task (Jones *et al.*, 2011). In Alzheimer's disease, this hyperactive pattern that naturally occurs with aging, is exacerbated and associated with cognitive decline (Jones *et al.*, 2011).

Figure 1.1 depicts an overview of the aims of the study. The aims sought to explain how TNN-TPN functional connectivity may impact cognition in older adults and how the association may differ for those enriched by the EC program. First we validated the locations of the TNN and TPN pathways discovered in our data with those that have been established in the literature, and studied the connectivity between and within each network. This validation study confirmed the integrity of our methods and provided conceptual support for further analysis. In my second aim, we studied the associations between functional connectivity and cognitive functions that are related to dementia risk. This aim links the novel connectivity fMRI results with results from tried and tested

measures of cognition from neuropsychological tests administered outside of the scanner. Together, the brain and behavior modalities helped to elucidate mechanisms of functional activity in cognition in the healthy aging brain. In the final aim, we characterized longitudinal changes in functional connectivity. We investigated the changes in TNN-TPN connectivity from one year to the next over the two-year period, including changes between the intervention and control groups. The following section explain each aim in detail, as illustrated also in Figure 1.1



#### Figure 1.1 Overview of Aims

At each time point, fMRI brain data and cognitive test data are collected. The goal is to investigate functional connectivity at baseline; how the connectivity between and within the TNN and TPN are associated with cognitive test outcomes in the Experience Corps (EC) Intervention and Control Groups;

and how these connectivity scores change longitudinally in each group. Specifically, in Aim 1, we extract the TNN and TPN from Baseline, and evaluate inter and intra-network connectivity. In Aim 2, we compare changes in functional connectivity with performance on cognitive tasks. In Aim 3, we use longitudinal analysis methods to study the effect of EC on the trajectories of functional connectivity scores and cognitive performance including each time point: Baseline, Year 1, and Year 2.

### 1.3 Specific Aims

Each of the three aims is listed in the sections that follow, together with corresponding hypotheses. We developed hypotheses based on the latest findings in the fMRI literature regarding functional connectivity and cognition.

#### 1.3.1 Aim 1. Functional Connectivity

**Aim 1.** Extract the Task Positive Network (TPN) and the Task Negative Network (TNN) at baseline and investigate the *inter*-network connectivity between these two networks and the *intra*-network connectivity within each of these networks.

#### *Hypotheses*:

 <u>Network Extraction</u>. The Task Positive Network will correspond closely with the well-known TPN set of pathways from the literature that are known to activate in the presence of a task, including regions of the frontal lobes and dorsal attention network; Similarly, the Task Negative Network will match the TNN pathways from the literature that remain active during rest, including the prefrontal cortex, the posterior cingulate, and the retrosplenial cortex.

- <u>Inter-Network Functional Connectivity</u>. The TNN and TPN will be anticorrelated, as exhibited by the negative correlations between the inter-network sub-network pairs.
- Intra-Network Functional Connectivity. Each network will be positively correlated with itself, as evidenced by the positive correlations between the intranetwork sub-network pairs.

## 1.3.2 Aim 2. The Brain Behavior Link

Aim 2. Investigate the baseline relationship between inter and intra-network functional connectivity and cognitive functions important to dementia risk, including memory (Rey Auditory Verbal Learning Test) and executive functions (Trail Making Test and Digit Span Test).

#### *Hypotheses*:

- <u>The effect of *inter*-network connectivity on behavioral outcomes.</u> Inter-network connectivity will be inversely associated with cognitive functions. In particular, larger anti-correlations between the TNN and TPN will be associated with better performance on neuropsychological tests of memory and executive functions.
- <u>The effect of *intra*-network connectivity on behavioral outcomes.</u> Intra-network connectivity will be positively associated with cognitive functions. In particular, increased correlations within each of the TNN and TPN will be positively associated with performance on neuropsychological tests of memory and executive functions.

## 1.3.3 Aim 3. The Intervention Effect

Aim 3. Investigate the effect of Experience Corps (EC) on the longitudinal trajectory of

1. inter and intra TNN and TPN functional connectivity patterns; and

2. cognitive functions in the domains of memory and executive functions

for baseline and two follow-up visits, capturing annual changes over a two-year period.

#### *Hypotheses*:

- 1. The effect of aging on longitudinal trajectories of functional connectivity.
  - A. *Inter*-network correlations will increase (become less negative) over the study period.
  - B. *Intra*-network correlations will decrease (become less positive) over the study period.
- 2. The effect of aging on longitudinal trajectories of cognitive functions.

Cognitive functions in the domains of memory and executive functions will decline over the study period.

3. The effect of EC on longitudinal trajectories of functional connectivity.

A. EC will halt the increase in *inter*-network correlations.

- B. EC will promote maintenance or increase in *intra*-network correlations.
- 4. <u>The effect of EC on longitudinal trajectories of cognitive functions.</u>

EC will halt the decline in cognitive functions in memory and executive functions.

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2 Chapter 2. Background

#### 2.1 The Integrationist Model of Brain Function

On September 13, 1848, Phineas Gage, a 25 year old foreman, known as among the best in the business of constructing American railways, set to work as usual. Colleagues described him as "very energetic and persistent in executing all his plans of operation;" and on that autumn day in southern Vermont, he planned to carve a roadbed out of a mountain for the new Rutland & Burlington Railroad (Harlow, 1869, p. 14). The routine procedure to blast rocks entailed digging a hole, adding blast powder, a fuse, and sand, and then setting charge using a large iron rod. Mr. Gage's rod was custom made at three feet seven inches in length and 1¼ inches in diameter, and smooth, like a javelin (Macmillan, 2002).

Around 4:30pm, as Mr. Gage set the rod into the hole, something terrible happened: the iron struck fire, shooting the rod out, and straight through Mr. Gage's "face ... passing back of the left eye, and out at the top of the head." Afterwards, Mr. Gage picked himself up, sat upright, and rode in an oxcart to the doctor's office, where he explained to the attending physician what happened. Dr. Edward H. Williams reported (Bigelow, 1850, p.16):

I did not believe Mr. Gage's statement at that time, but thought he was deceived. Mr. Gage persisted in saying that the bar went through his head. Mr. Gage got up and vomited; the effort of vomiting pressed out about half a teacupful of the brain, which fell upon the floor.

Phineas Gage is lucky to have survived the rock-blasting accident. However, the loss of the frontal portions of the left temporal lobes of his brain transformed his personality to someone who was "no longer Gage," (Harlow, 1869, p. 14). Legend has it that he went from being a kind and charismatic gentleman to an "unstable, impatient, foul-mouthed... wastrel," (Macmillan and Lena, 2010, p. 643).

The story of Phineas Gage serves as a foundation for the localization theory of brain function. From Mr. Gage's plight, one can infer that frontal lobes direct planning and executing, and controlling emotion. However, what is less known about Mr. Gage's story is that he underwent a recovery. He served as a stagecoach driver in Chile for the last six years of his life. Driving a stagecoach required being "reliable, resourceful, and possess[ing] great endurance. But above all, they had to have the kind of personality that enabled them to get on well with their passengers," (Macmillan, 2002, p. 106). While Mr. Gage never recovered the portions of brain that flew out of his head, his success as a stagecoach driver, working 13 hour days for several years suggests that he recovered a number of cognitive abilities. Recent evidence further supports Mr. Gage's social recovery: simulation studies incorporating his actual skull and the discovery of a photograph in 2009, depicting this man in a position of nobility, more like a king than a wastrel (Van Horn *et al.*, 2012; Wilgus and Wilgus, 2009).

Therefore, the full story of Phineas Gage actually disproves the localization theory of brain function, and **presents instead, the integrationist model.** Mr. Gage demonstrated that while the frontal lobes may command executive functions and emotional control, when an affront to this brain region occurs, the brain can re-wire itself to compensate for the loss. The functionality gained by the re-wiring presents the essence

of the integrationist model: while brain regions are important to function, the connections between regions are equally, and arguably, more important (Van Horn *et al.*, 2004). The integrationist approach posits that groups of regions that operate in synchrony form networks among themselves and with other brain networks.

The existence of networks in the brain to achieve function gives rise to the concept of functional connectivity, the study of relations between networks. The functional connectivity between two regions is defined as the correlation between the neural activities of these two regions, and characterizes the integrative state of the network (Marrelec *et al.*, 2008). Studying functional connectivity provides a global approach to charting the organization of the brain and subsequent behaviors.

Functional connectivity also makes room for plasticity in the brain. Plasticity posits that, contrary to commonly held beliefs that brain development ends by young adulthood, new connections can form throughout adulthood, and even into advanced ages. The story of Phineas Gage represents a classic case of plasticity in the brain. Parallels to the case of Mr. Gage have been made with modern cases of dementia. Individuals with dementia today exhibit atrophy and pathology in the same regions that Mr. Gage lost (Van Horn *et al.*, 2004). The miraculous recovery of Mr. Gage suggests a lifestyle model for promoting plasticity in the brain, and provides hope for those living with dementia. New technologies to image the brain in action can facilitate our understanding of functional connectivity and the potential for plasticity at all ages.

### 2.2 Functional Magnetic Resonance Imaging

*Background*. Functional magnetic resonance imaging (fMRI) is a non-invasive technology that provides a window into the brain in action. fMRI studies can establish how structures work together for various processes, and ultimately, help identify neuropathology related to subsequent clinical symptomology. This technology uses the fact that the magnetic properties of blood molecules vary according to oxygenation level. Each hemoglobin molecule can hold up to six molecules of oxygen, and the magnetic properties of blood molecules of oxygen are different than the magnetic properties of those with empty binding sites (Heller *et al.*, 2006). This discovery coupled with the theory that active regions of the brain have greater metabolic demands than inactive areas led to our ability to image the brain in action with fMRI.

*Mechanics*. While the theory of tracing oxygenation patterns in the brain is basic, the mechanics of the procedure are highly intricate. The data are collected by using a powerful magnet, which aligns with hydrogen atoms in the brain, and inducing a current in the receiver coil (Lindquist, 2008). The computer processes the resulting signals in the frequency domain, which lives on the complex plain, and therefore cannot be interpreted practically. Moreover, a single measurement of a signal from this domain is meaningless—one must obtain thousands of samples from this domain so that data can be transformed to the biologically meaningful image space. The more points that are sampled, the higher the resolution (Lindquist, 2008). The fMRI machine operates in this manner, collecting signals, sequentially one two-dimensional slice at a time. Ultimately, computer software programs integrate all of these pieces to display a three-dimensional image of the brain.

*The BOLD Signal.* The fMRI signal is known as the BOLD (blood-oxygen-leveldependent) signal because it is a measure of the ratio of oxygenated to deoxygenated hemoglobin. This signal is a measure of metabolism in the brain, representing a proxy for the desired measurement, neural activation. Blood flow in the brain corresponds with neural activity, and in fact, lab experiments show that the BOLD signal is related linearly to neural activation. This linear relationship between the BOLD signal and neural activation is a fundamental assumption of statistical analysis and subsequent interpretation of fMRI data.

*Noise*. Once the data have been acquired from the fMRI machine, reconstructed into image space, and summarized by a computer into a file, the problem of searching for meaning remains mathematically difficult. The data are highly dimensional, amounting to several gigabytes for a single subject. The data are full of correlations, both across space and time, with patterns that vary according to brain region. The data are noisy, consisting of different types of noise that must each be managed accordingly (Ashby, 2011). Before one can begin to analyze such data, we run it through a preprocessing pipeline so that it will begin to resemble signals from the brain that could convey useful information. Our lab uses a standard preprocessing protocol consisting of the usual steps of slice-time correction; motion correction, co-registration, and normalization; and spatial smoothing executed in SPM.

#### 2.2.1 Imaging the Aging Brain

The standard fMRI techniques to measure neural activation have been developed using populations of young healthy adults; therefore, imaging the aging brain presents

additional challenges. We present three chief challenges related to hemodynamics, neuroanatomy, and noise.

Firstly, the cerebral blood flow in older adults differs from that of younger adults; therefore, the canonical hemodynamic response function used to model the BOLD signal may not provide an accurate proxy for neural activation in aging brains (Samanez-Larkin and D'Esposito, 2008).

Secondly, the morphology of older brains differs from that of younger brains. Aging is associated with heterogeneous increased gray matter atrophy and sulcal expansion (Samanez-Larkin and D'Esposito, 2008). Therefore, the template brain used during spatial normalization may warp the brain images of older adults in ways that compromise accuracy (Raz *et al.*, 2007; Samanez-Larkin and D'Esposito, 2008; Buckner *et al.*, 2004). The template brain is based off an aggregate of brain images from young healthy adults. No standard template for older adults exists. Templates for the aging brain are more difficult to develop due to the increased neuro-anatomical variability in older adults (Samanez-Larkin and D'Esposito, 2008; Crinion *et al.*, 2007).

Lastly, fMRI data in older adults appear noisier than in younger adults. The increased source of noise is not fully understood, and could be due to increased anatomical variability or more difficulty breathing and staying still inside the scanner. Regardless, the results demonstrate that the signal is more difficult to detect in older adults. Compared to younger adults, the brain images of older adults show smaller clusters of functional activation and decreased correlations of interest (Samanez-Larkin and D'Esposito, 2008; Buckner *et al.*, 2000; Aizenstein *et al.*, 2004; D'Esposito *et al.*,

1999). These challenges of imaging the aging brain must be considered when seeking to compare results from older adults with those of younger populations.

#### 2.3 Cognitive Aging

Cognitive abilities underlie every action that one takes from reading the newspaper in the morning to preparing dinner in the evening. These abilities incorporate a range of domains, including attention, processing speed, executive functions, and memory, and entail mental skills that are required to accomplish both simple and complex tasks. While most of us take our cognitive abilities for granted, the degree of aptitude in each domain varies throughout the life course. From infancy through young adulthood, cognitive abilities in each domain grow rapidly. In the rhythm of adulthood, most cognitive abilities plateau, and slowly decline. Eventually, as adults advance in age, cognitive abilities deteriorate. This decline in cognition is generally accepted as cognitive aging. However, not every type of intelligence or class of cognition declines with age. While some processes in the brain lose efficiency over time, others cumulatively and continuously grow. Early Greek and Roman scholars noticed this phenomenon, describing the earliest models of cognitive aging:

> "Solon was under a delusion when he said that a man when he grows old may learn many things - for he can no more learn much than run much; youth is the time for any extraordinary toil." (Plato, Dialogs, Phaedrus, Section 536-D)

 "It is in old men that reason and judgment are found, and had it not been for old men no state would have existed at all." (Cicero, De Senectute, chap, xix, Section 67)

Plato's model describes the trajectory of fluid intelligence, which represents a native ability to think logically and solve problems, independent of acquired knowledge (Cattell, 1971). Cicero's model describes the trajectory of crystallized intelligence and wisdom, reflecting cumulative knowledge that grows with experience (Salthouse, 1988). Modern studies of cognitive aging continue to show that fluid intelligence declines with age while crystallized intelligence continues to grow or maintain a steady state (Salthouse, 1988). While the fluid versus crystallized dichotomy offers a hopeful perspective of cognitive aging, this perspective captures only one component of cognitive aging. To better understand the trajectory of cognitive aging, the trajectories of the different domains should be investigated.

After all, while cognitive decline is accepted as a normal part of aging, such declines do not occur uniformly across domain or across individuals. Some types of memory, such as semantic memory, reflecting general knowledge about the world, continue to improve well into older ages. Furthermore, a number of modifiable factors, such as education and physical health, are associated with maintenance of cognitive abilities with advanced age. Therefore, the normal trajectory of cognitive aging is complex and difficult to summarize neatly.

The abnormal trajectory of cognitive aging is characterized by severe deterioration that becomes pathological. The domains most affected are memory and

executive functions in ways that interfere with activities of daily life, making it impossible to read the newspaper or prepare dinner (Salthouse, 2004). This pathological deterioration manifests itself as dementia. However, the deterioration from normal aging to dementia is gradual, and if it can be pre-clinically detected, perhaps the decline can be put on pause, or even reversed.

Cognitive abilities are measured using a host of neuropsychological tests. These tests are designed to quantify abilities in specific cognitive domains. The tests are standardized and administered in an office environment so that performance of individuals can be compared to others across the population. Statistics are gathered and stratified by age and education level so that differences from these group-averages can help to detect irregular performances. Administering neuropsychological tests on the same individual repeatedly can help to detect and quantify declines in cognitive abilities. While these behavioral data are helpful, some argue that by the time the deterioration manifests itself in a test outcome, the biological change in the brain has already occurred. Therefore, we need studies in older adults that collect both behavioral data and brain data.

## 2.4 Dementia

Dementia is a syndrome beyond normal aging that is characterized by multiple cognitive deficits and memory impairments. The 2013 publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) replaced the term "dementia" with *major neurocognitive disorder* and *mild neurocognitive disorder*. Dementia comes from Latin roots that denote "mad" or "insane," and the updated terminology aims to reduce stigma. Given the recency of the change, most individuals and health professionals

continue to use the former name. Because communication is crucial in public health, we also use dementia, the more commonly understood name. The DSM-5 criteria for Major

Neurocognitive Disorder state:

- A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
  - 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
  - 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
- C. The cognitive deficits do not occur exclusively in the context of a delirium.
- D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

The fact that "decline" is a part of the DSM 5 diagnostic suggests a requirement for longitudinal measurements, before and after changes in cognitive abilities. The measurements can come in the form of an informant's report or a clinical assessment. The use of "decline" in the definition also allows room for person-specific variability. A deficit for one individual may not represent a deficit for another person, and each person can serve as his or her own standard for normal behavior.

The etiology of dementia is also variable. Because dementia is a syndrome, and not a single disease it arises out of multiple etiologies. The most common types of dementia are Alzheimer's disease, vascular dementia, frontotemporal dementia, semantic dementia, and dementia with Lewy bodies. The domains to be affected first vary in each of the dementia types, although ultimately, declines occur in multiple domains including executive functioning, language, working memory, spatial memory, and verbal memory.

Dementia is typically viewed as progressive and irreversible. Its symptoms exist

along a continuum and are often difficult to distinguish from normal aging (Whalley, 2002). Because the trajectory of aging varies from person to person and from one cognitive domain to another, there is no clear and standard definition of normal aging in the brain. Compounded by a progressive set of signs and symptoms that simultaneously targets multiple domains of cognition that naturally decline with age, the boundary between dementia and aging remains elusive. Furthermore, some patients are better than others at concealing the signs and symptoms of dementia. In particular, individuals with more cognitive reserve are able to withstand age-related pathologies for longer time periods (Whalley, 2002; Stern, 2002).

The cognitive reserve theory, linking dementia and cognitive aging, grew out of the observation that the amount of pathology in a brain does not correspond linearly with clinical expression of symptomology. While some people express signs and symptoms of dementia with little to no brain pathology, others exhibit normal levels of cognition although their brains are full of the hallmark plaques and tangles of AD. The cognitive reserve theory posits that as pathology accumulates in the brain, the mind copes by utilizing brain networks more efficiently; recruiting alternate brain networks; or compensating by using structures that are ordinarily not used for such functions (Stern, 2002). This model implies that each person has a different threshold for clinical expression of a pathology based on cognitive reserve. Factors associated with cognitive reserve include education levels, intelligence measures, language skills, and other proxies for cognitive outcomes. The fact that each person handles neuropathology differently further clouds the boundary between normal aging and dementia; nevertheless, it also suggests that preventative measures exist.
## 2.4.1 Prevention

The pervasive and growing epidemic of dementia coupled with the lack of curative treatment make prevention a primary objective. Even delaying dementia would result in massive public health benefits. Preventing Alzheimer's disease (AD) by five years would reduce the prevalence of AD in the United States by over four million patients by 2047, resulting in an annual savings of \$18 billion, and uncountable savings in quality of life preserved (Brookmeyer, 1998; 2007). However, how to prevent dementia remains unknown. Decades of epidemiologic studies have resulted in largely inconsistent findings. The majority of pharmaceutical trials have failed, with findings ranging from moderate benefits to harmful effects of drugs, including hormone replacement therapy, amyloid-  $\beta$  blockers, anti-hypertensives, and nonsteroidal antiinflammatory drugs (Pahnke et al., 2009). Studies on lifestyle factors, such as social networks, cognitive stimulation, leisure activities, physical exercise, and diet, have also yielded weak associations. However, the majority of these studies are not based on longitudinal randomized controlled trials with dementia incidence as an endpoint. Further epidemiologic studies are needed to help develop the most effective preventative strategies.

In the meantime, a number of studies on the cellular level and in animal models have helped to elucidate neuro-protective mechanisms for the aging brain. Two of the most consistent interventions found to improve brain health involve exercise and intermittent fasting (Martin *et al.*, 2006). Exercise increases secretion of brain-derived neurotrophic factor (BDNF), especially in the hippocampus, cortex, and basal forebrain, regions which are important in higher order thinking (Cotman *et al.*, 2002). BDNF

supports the survival of existing neurons and promotes the generation of new neurons and synapses (Huang *et al.*, 2001). Intermittent fasting improves brain health on the neuronal level through a number of pathways that stimulate the production of protein chaperones, molecules that assist with the unfolding of macromolecules; neurotrophic factors, proteins such as BDNF that support the growth of developing neurons; and antioxidant enzymes, molecules that inhibit the oxidization of other molecules (Martin *et al.*, 2006). These cellular mechanisms help the neurons cope with stress and resist pathology (Mattson and Wan, 2005). While the neuronal benefits of exercise and intermittent fasting have been modeled, in order to test their preventative efficacy in the general population, we need longitudinal RCTs incorporating these interventions with dementia as an endpoint.

### 2.5 The Quest for Biomarkers

One of the challenges of conducting RCTs with dementia as an endpoint involves the lack of homogenous diagnostic criteria, which currently rely on multiple modalities. The primary diagnostic modality involves traditional interviews and examinations, including the patient's medical and family history, physical exam, neurological evaluations, cognitive and neuropsychological testing, mental status exams, and psychiatric evaluations. Brain imaging modalities including MRI and CT scans, as well as blood tests, are also usually conducted to rule out other causes for dementia, including strokes or vitamin deficiencies.

Because brain pathology does not directly correspond with symptomology,

imaging the brain to visualize AD pathology is not included in the diagnosis protocol. In fact, there is no biomarker for dementia-related pathology. Jack et al. developed a model for biomarkers which includes a number of measurements of brain health (2013). Jack et al. graphically display the measurements as sigmoidal curves along a continuum with time to dementia onset on the x-axis and biomarker abnormality on the y-axis. Listed in order these markers include measurements of amyloid, as detected in cerebrospinal fluid (CSF) or positron emission topography (PET); CSF tau; brain volume and cortical thickness via MRI; and cognitive impairments from neuropsychological tests (2013). However, the sensitivity and specificity of these markers remains imperfect and measurements that rely on PET or CSF carry a health risk. PET involves injecting radioactive materials, which may pose a larger threat to vulnerable individuals who are already at risk for a neurodegenerative disorder. Extracting CSF can result in headaches, hemorrhage, or herniation, which could lead to further complications in the elderly. While changes in MRI-detected brain volume or performance on cognitive tests are not invasive, these modalities represent the last of the markers on the continuum towards dementia onset (Jack et al., 2013). They manifest themselves just before dementia onset, which may be too late to intervene.

We need biomarkers that are non-invasive and can detect early changes in cognitive abilities and pathology. Measuring abnormalities in brain network connectivity using fMRI could present an appropriate biomarker. Studies show that amyloid depositions alone do not cause AD, but perhaps in conjunction with malfunctions in functional connectivity, the pathology becomes symptomatic. An fMRI biomarker of brain network health could help to differentiate between levels of cognitive ability as an

initial step in the process, with the hope that one day such maps may offer clinical utility. This study will investigate the sensitivity of fMRI brain network maps to detect changes in cognition. A highly sensitive tool could detect the genesis of aging in the brain, and may serve as a preclinical tool to screen individuals at risk for dementia.

A brain network biomarker of cognitive decline would be especially valuable in our study because our data are drawn from a randomized controlled trial including a multi-modal intervention group. Differences between the intervention and control groups offer practical, protective lifestyle changes to preserve cognition.

# 2.6 Successful Aging

While aging may be portrayed as deterioration and decline, the extra time on Earth also presents a continued opportunity for development and growth. Successful aging presents a model for older adults to function comfortably and contribute to society. Rowe and Kahn defined successful aging in 1987 as being (1) free from disease and disability; (2) high functioning cognitively and physically; and (3) engaged and productive, socially. Definitions today range from Rowe and Kahn's stringent tripartite criteria to less restrictive criteria. These modern definitions expand upon Rowe and Kahn's third component, and include the older adult's perception in the concept of successful aging (Phelan *et al.*, 2004; Knight *et al.*, 2007; Von Faber *et al.*, 2001; Jeste *et al.*, 2010). Rather than the physical component, these definitions emphasize non-material elements such as life satisfaction, longevity, mastery, active engagement with life and positive adaptation (Phelan and Larson, 2002). Another emerging element of successful aging is the feeling of generativity, "the adult's concern for and commitment to the next generation, as

expressed through parenting, teaching, mentoring, leadership, and a host of other activities that leave a positive legacy of the self for the future" (de St. Aubin, McAdams, & Kim, 2004, p.4). These elements are more difficult to measure, and rely on the older adult's self-evaluation of his or her experiences. Nevertheless, we as a society can promote activities that foster this comprehensive and personal approach to successful aging. This paper proposes one successful model for successful aging, Experience Corps, which draws upon the experiences of older adults to serve society.

### 2.7 An Integrationist Model of Society

The primary element of emerging definitions of successful aging emphasizes the potential of older adults to serve as contributing members of society. Placing older adults in important community roles, rather than stowing them away in nursing homes or centers for senior living promotes inter-generational living. The integrationist approach contrasts with the segregationist model that has come with modernity, which celebrates youth and hides aging. Both the young and the old can benefit from living and working together.

Connecting infants, children, youth, young adults, and the middle aged with older adults provides advantages for everyone. Older adults have acquired a lifetime of knowledge and skills, which they can teach to others. Additionally, older adults can provide younger generations with a sense of purpose, an understanding of aging, an alleviation of the fear of aging, spiritual mentorship, an explanation of principles from the past, and lessons for the future. The young can also fill a void for the elderly. Younger individuals showing attention, care, and humility to seniors helps to reduce the isolation

that accompanies aging, reduce the likelihood of depression, provide a sense of purpose, and reinvigorate memories, ranging from family stories to real life chapters in history.

Developed nations forecast demographic transition that will turn society upside down, with the old outnumbering the young in some projections. This forecast tends to increase the stigma against the elderly and spark debates about what to do with all of the old people. The young today fear that older adults will leech the last of public resources. However, attaining old age represents a success, and the young of today will be old tomorrow (hopefully). A truly successful society welcomes everyone of all ages, and recognizes that the action or inaction of one individual influences that of others because we are all connected. If we choose to confine the elderly to centers out of sight, we would not only lose a valuable resource, but also suffer the consequences of living in suboptimal conditions ourselves.

The optimal brain functions in networks. No single neuron or region of the brain operates in isolation. Instead, the neurons operate in harmony, and when one cell or group of cells faces an injury, other cells from neighbors to those across the corpus callosum rush to the rescue. Successful human beings of all ages operate in this manner, as networks, too.

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3 Chapter 3. Functional Connectivity in Older Adults: An Investigation of the Task Negative and Task Positive Brain Networks (Aim 1)

# 3.1 Introduction

After decades of targeting structures in the brain as loci of function, the data have deemed the question null: brain activity cannot be localized by region. Rather than localization, the brain appears to operate using an integrationist approach: groups of regions operate together, forming networks among themselves, and modulating the activities of other networks. These networks characterize our present understanding of the organization of the brain, and exist intrinsically, whether at rest or engaged in a task, ready to fire before the blink of an eye. We studied two particular brain networks that are believed to provide a binary organization for the structure of brain anatomy and corresponding function. Our results reaffirmed some aspects of the literature on this network pair, and challenged others.

At rest, functional magnetic resonance imaging (fMRI) scans of the human brain exhibit activations in regions associated with the subconscious, such as memory formation; and deactivations, in other regions associated with conscious tasks, such as attention and executive control. These dichotomous networks, the task negative network (TNN) and task positive network (TPN), respectively, serve as a foundation for the organization of the brain: when one network is active, the other is inactive, and vice versa. The TNN represents the regions active in the absence of a task, including the posterior cingulate, medial and lateral parietal and medial prefrontal cortex; and the TPN represents the regions active in the presence of a task, including a set of frontal, parietal, and dorsal cortical regions (Fox *et al.*, 2005). The decoupling between these two

networks is hypothesized to operate in a balance according to cognitive demand, as illustrated in Figure 3.1 (Smallwood *et al.*, 2012).

The decoupling between the TNN and TPN has been replicated in study after study, and represents one of the most consistent and replicable results in the field of human neuroimaging (Greicius et al., 2003; Fox et al., 2005; Seeley, et al., 2007; Vemuri et al., 2012; Uddin, et al., 2009; Gusnard & Raichle, 2001; Shulman et al., 1997; McKiernan et al., 2003; Mazoyer et al., 2001; Fox et al., 2009). However, this canon of literature comes primarily from studies of young healthy adults. An emerging body of work on individuals in more diverse samples, such as those who have mental disorders or those who have lived to advanced ages, has found that the accepted pattern between the TNN and TPN does not always hold. For example, in individuals with Alzheimer's disease (AD), the decoupling between the two networks appears to breakdown, as the networks respond differently to cognitive demand (Andrews-Hanna et al., 2007; Jones et al., 2011; Lustig et al., 2003; Greicius et al., 2004; Wang et al., 2006; Sorg et al., 2007; Celone et al., 2006; Buckner et al., 2009; He et al., 2007; Gili et al., 2011; Zhang et al., 2010; Bai et al., 2009; Zhou et al., 2010; Damoiseaux et al., 2012; Wang et al., 2007; Wang et al., 2006; Supekar et al., 2008; Fleisher et al, 2009; Buckner et al, 2005; Sauer et al., 2006; Seeley et al., 2009). In AD patients, studies have found that the networks operate in reverse—the TNN is on in the presence of a task and the TPN is on in absence of a task, or even in tandem—both the TNN and TPN stay on either during a task or at rest.

While the collapse of the decoupling between the TNN and TPN has been investigated and replicated in clinical settings, few studies have explored this brain architecture within the context of normal aging. The purpose of this paper is to investigate the organization of the TNN and TPN in cognitively normal, communitydwelling older adults. In particular, we answer the question, to what extent do these networks operate dichotomously? Is it the case, that when the TNN is on, the TPN is off, and vice versa?





This figure shows the decoupling conceptual model: at rest, the TNN, in blue is activated, while the TPN, in red is deactivated. During a task, as indicated in the shaded gray blocks, the TPN is activated, and the TNN is deactivated.

We employed two methods to answer these questions: (1) a region of interest (ROI) method, which defines networks from the literature; and (2) an independent component analysis (ICA) method, which defines networks by a data-driven method. We then analyzed correlation coefficients for the TNN and TPN from each method to assess the extent of coupling or decoupling between and within the networks. The study of decoupling between networks and coupling within networks is commonly known as functional connectivity (Biswal *et al.*, 1995). In a brain at rest, the existence of these networks and how they modulate other networks is measured by the low-frequency correlations within and between the networks that persist intrinsically. Functional connectivity is defined as a group of neurons that act together coherently (Aertsen and Preissl, 1991). These actions are measured as temporal correlations between groups of anatomically defined spatial regions (Friston, 1997). We studied the functional connectivity between the TNN and TPN and within each network in the Brain Health Study (BHS), which is nested within the larger Baltimore Experience Corps Trial. We tested the decoupling diagram in Figure 3.1.

### 3.2 Methods

This investigation used data from the BHS, a longitudinal randomized controlled trial in community-dwelling older adults to establish the organization of brain networks. Using the Sternberg Task, a paradigm of working memory in the fMRI scanner, the task negative and task positive networks were extracted, and the connectivity between and within each network was assessed. In this section, we describe the data, the study sample, the cognitive outcomes, the imaging modality, and statistical methodology.

### 3.2.1 Brain Health Study Sample

The data were drawn from the Baltimore Experience Corps Trial (BECT), a randomized controlled trial of the Experience Corps (EC) program, a model of senior service in elementary schools. This trial included 702 participants who were recruited and randomized over four years into either the EC program or a low-activity control for two

years. To qualify for BECT, participants met the following eligibility criteria (Fried *et al.*, 2013):

- 1. Age 60 years or older;
- 2. English speaking;
- Minimum sixth grade reading level on the Wide Range Achievement Test (Wilkinson, 1993);
- 4. Score of 24 or higher on the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975);
- Clearance on criminal background check for those enrolled in the Experience Corps arm.

Prior to randomization in the larger BECT trial, 123 participants were recruited and randomized into the Brain Health Study (BHS), a sub-study nested within (BECT) focused on investigating the biological mechanisms in the brain underlying associated behavior changes by using structural and functional MRI (Carlson, Kuo, Chuang, Varma *et al.*, under review). Randomization into this sub-study occurred prior to interventional placement in order to avoid potential selection biases. Additional eligibility criteria for BHS include the following:

- 1. Right hand dominance;
- 2. No implanted pacemaker, defibrillator, or other electronic or metal devices; and
- 3. No history of atrial fibrillation, stroke, brain tumor, brain hemorrhage, or brain surgery for a cerebral aneurysm.

The Johns Hopkins Institutional Review Board approved of this study and all participants provided written and informed consent criteria (Fried *et al.*, 2013).

Table 3.1 summarizes the demographic and cognitive characteristics of the BHS participants, stratified by randomization group. The sample is representative of the urban population of older adults in Baltimore: over 90% are African-American; almost 70% are female; 20% are widowed; and the average education level represents about two years of post-secondary schooling. The average MMSE score indicates that participants are cognitively normal, as mandated by the eligibility criteria.

C1		<b>a</b> . 1 . 1
Characteristic	EC, Mean	Control, Mean
Ν	65	58
Female (%)	45 (69.2)	40 (68.96)
Age, in years (SD)	67.79 (6.32)	66.57 (5.72)
African American, n (%)	59 (90.77)	54 (93.10)
Education, in years (SD)	14.28 (3.01)	13.71 (2.76)
MMSE (SD)	28.23 (1.62)	28.32 (1.49)
Geriatric Depression Scale	1.31 (1.44)	1.31 (2.37)
EC, Experience Corps; MMSE, Mini-Mental State Examination.		

#### **Table 3.1 BHS Study Participants**

3.2.2 Paradigm Description

In the scanner, participants completed the Sternberg Task, a one-back test of working memory (Sternberg, 1969). In this task, participants view a set of four uppercase letters followed by a lower-case letter probe and the task is to indicate whether or not that letter has been previously viewed in the antecedent sequence. While lying in the scanner, the participant holds a button in each hand, and is instructed to press the button in the right hand if the letter was present in the preceding sequence; or to press the button in the left hand if the letter was not present, representing the match condition and non-match conditions, respectively. Each subject completed a total of 40 trials, consisting of 20 trials of the match condition, and 20 trials of the non-match condition. Figure 3.2 outlines an example of a match and non-match trial.



Figure 3.2 The Sternberg Paradigm

Each stimulus letter sequence was presented for 2 seconds, followed by an average of 3 seconds of a central fixation cross. The experimental design is jittered, so the actual time period of each inter stimulus interval (ISI) varied, ranging from 1.5 second to 18 seconds. The trials proceed throughout the entire scanning session without designated periods of sustained rest, representing an event-based paradigm. To investigate activity in the task negative and task positive networks, the entire time period inside the scanner is of interest: both the task itself and the short time periods between the trials, which represent the non-trial intervals of interest.

# 3.2.3 Data Acquisition

One hundred and thirteen BHS participants underwent an approximately 12minute (725 seconds) scan under the event-based Sternberg paradigm as described above. All imaging was performed on a 3T Intera Philips scanner (Best, the Netherlands).

This figure shows a snapshot of the Sternberg Task, as participants experience it in the scanner. The task periods, match and non-match, are indicated in light gray; the non-task periods, the inter-stimulus intervals, are indicated in light yellow. The time of each period is diagrammed along the x-axis in seconds.

Functional data were collected using T2\*-weighted a spin-echo, echo-planar sequence sensitive to detect the blood oxygen level (BOLD) contrast (repetition time = 1500 ms; echo time = 30 ms; slice thickness = 4 mm/1 mm gap; 30 slices, interleaved acquisition; flip angle =  $70^{\circ}$ ; matrix =  $64 \times 64$ ; field of view = 240 mm). Whole brain coverage was obtained with 30 interleaved slices. A total of 480 volumes were acquired for each participant in a single run.

A structural image was also collected for each participant using the magnetization prepared rapid-acquisition gradient echo protocol (repetition time = 8 ms, echo time = 3.6 ms, field of view = 256 mm, matrix =  $256 \times 256$ , slice thickness = 1 mm; 200 slices).

# 3.2.4 Preprocessing of Functional Data

A diagram of the preprocessing stream is shown in Figure 3.3. All fMRI data processing, unless otherwise noted, was carried out using SPM8

(http://www.fil.ion.ucl.ac.uk/spm/).



This figure diagrams the sequence of preprocessing steps that we used to preprocess the fMRI data in SPM. Slice time-correction accounted for the inter-leaved sequence of data acquisition. Motion correction involved rigid body transformations. Co-registration and normalizations involved standardizing each fMRI image to its structural image, and both images to the MNI template. Spatial smoothing was performed using a FWHM Gaussian kernel of 7.0mm.

Preprocessing of the functional data included slice-time correction to account for the different times that each volume is acquired during a sequence. Rigid body transformations were applied to correct for movement of the head in the scanner. Afterwards, each functional scan was co-registered to its corresponding structural image, and then normalized spatially into standard space, using the Montreal Neurological Institute (MNI) image. Lastly, spatial smoothing was conducted using a 7.0 mm full width at half maximum (FWHM) Gaussian kernel, and high-pass temporal filtering with a 50-second cutoff.

Additionally, preprocessing of the structural data entailed removal of non-brain structures using the brain extraction tool in FMRIB's (Oxford Centre for <u>Functional MRI</u> of the Brain) software library (FSL) 4.1.9 (<u>www.fmrib.ox.ac.uk/fsl</u>; Smith *et al.*, 2004; Smith *et al.*, 2002). Functional data were overlaid on the MNI template for presentation purposes.

**Final Sample:** After preprocessing, 90 participants remained in the study and were included in this analysis. Participants were dropped due to not having function data (n=9) or structural data (n=1), poor image quality (n=12), or severe atrophy (n=1), as outlined in Table 5.1.

#### 3.2.5 Assessment of Networks

Several methods exist for extracting the TNN and TPN from fMRI brain images, and these methods can be categorized into two types: a priori-region based methods and data-driven methods. We employed methods from each category to extract the TNN and TPN from the fMRI brain images of the BHS sample. While the two techniques represent different approaches, the analytic inferences that result, explaining the connectivity between and within the networks, should be comparable.

Most studies in this field use resting state or task-free fMRI protocols to extract intrinsic connectivity networks. However, in our study, we extracted networks from an fMRI protocol with an event-related design. Using data from an attention-demanding paradigm of working memory may actually facilitate the distinction between the TNN and TPN because of the presence of a task. Nevertheless, because the TNN and TPN are intrinsic to the organization of the brain, they exist whether or not there is a task. Studies support the inherent existence of these networks, and sensitivity to detecting each, both in resting state data and during cognitive processing tasks (Greicius *et al.*, 2003).

### 3.2.5.1 Region of Interest Method

The Region of Interest (ROI) method utilizes a priori regions that have been shown in the literature to belong to the TNN and TPN. These are regions that have consistently shown increased deactivations and increased activations during tasks, for the TNN and TPN respectively. The peak coordinates of these regions are used to form ROIs and in conjunction, they represent networks.

We used MNI coordinates defined by Yeo *et al* (2011) based on an fMRI study of 1,000 young healthy adults. This study served as the definition for our networks because of its very large sample size and use of other well-established studies as starting points in establishing ROIs. Additionally, to develop the networks, Yeo *et al.* reserved 500 subjects for validation purposes. Therefore, these networks that are ultimately established served as a sound basis for our study.

For the TPN, we adopted what Yeo *et al.* calls the Control Network, which is illustrated in Figure 3.4. This network is parcellated into 6 regions, labeled A-F. The anatomical regions of the TPN can be described as follows:

### **Task Positive Network (TPN)**

- A. Anterior control network
- B. Medial control network
- C. Lateral control network
- D. Dorsal attention network
- E. Premotor Cortex
- F. Superior Parietal Cortex

For the TNN, we adopted what Yeo *et al.* calls the Default Mode Network, as pictured in Figure 3.5. This network is also split into 6 regions, labeled A-F, representing the following:

### Task Negative Network (TNN)

- A. Prefrontal cortex (PFC)
- B. Inferior parietal lobule (IPL)
- C. Lateral temporal cortex (LTC)
- D. Dorsal medial prefrontal cortex (dMFC)
- E. Parahippocampal cortex (PHC)
- F. Posterior cingulate/retrospenial cortex (PCC/Rsp)

Each of the TNN and TPN networks, as defined in Figure 3.4 and Figure 3.5,

shows connectivity with itself and little or no connectivity with other regions of the brain.

This high intra-network connectivity and low inter-network connectivity support the use

of these networks to define the locations of the TNN and TPN in the BHS data. We will

use the MNI coordinates defined by Yeo et al. (2011) to construct TNN and TPN

networks using 6-mm spheres about each of the ROIs exhibited in Figure 3.4 and Figure 3.5. Then we will assess the resulting inter and intra-network connectivity.



# Figure 3.4 The Control Network (From Yeo et al., 2011)

This map shows the Control Network that Yeo et al., 2011 developed using a sample of 500 healthy adults, and validated on a similar sample of 500 other individuals. The map identifies 6 regions of this network, labeled A, B, C, D, E, and F. We refer to this network as the Task Positive Network (TPN).



Figure 3.5 The Default Mode Network (From Yeo et al., 2011)

This map shows the Default Mode Network that Yeo et al., 2011 developed using a sample of 500 healthy adults, and validated on a similar sample of 500 other individuals. The map identifies 6 regions of this network, labeled A, B, C, D, E, and F. We refer to this network as the Task Negative Network (TPN).

### 3.2.5.2 Seed Analysis Method

Building from the ROI method, seed-based techniques also employ an a priori assumption, using previous literature or data, to determine the location of the network. A seed consists of a region, such as a collection of voxels within a spheroid. The average time course of this seed is then incorporated as a regressor in first level analysis, a regression model for each subject, as displayed in Equation 1:

$$Y = X\beta + \varepsilon \tag{1}$$

where each matrix is defined as follows

$$\mathbf{Y} = [\mathbf{Y}_{1}, \mathbf{Y}_{2}, \dots, \mathbf{Y}_{N}]^{\mathrm{T}},$$
$$\mathbf{X} = \begin{pmatrix} x_{11} & \cdots & x_{1K} & 1 & \cdots & 1 \\ x_{21} & \cdots & x_{2K} & 1 & \cdots & 2^{q} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ x_{N1} & \cdots & x_{NK} & 1 & \cdots & 2^{q} \end{pmatrix},$$

$$\boldsymbol{\beta} = [\beta_1, \dots, \beta_K, \gamma_0, \dots, \gamma_q]^T$$
, and

$$\varepsilon = [\varepsilon_1, \dots, \varepsilon_N]^T.$$

In this level, an autoregressive model was used to specify the structure of the temporal correlation,  $\varepsilon_i = \rho \varepsilon_{i-1} + \zeta_i$ , where  $|\rho| < 1$  and  $\zeta_i$  are independent and identically distributed (i.i.d.). In the second stage, we regressed on the  $\beta$  parameters to summarize groups of subjects:

$$\beta = X_G \beta_G + \varepsilon_G \tag{2}$$

where  $\epsilon_G \sim N(0, I\sigma_G^2)$ .

T-tests were performed on the group level using the maps from the  $\beta$  corresponding with the seed region of interest. The results for the contrasts for the TNN

and TPN seeds yielded the regions of the brain that were correlated with the TNN and TPN, respectively. Essentially, this method outlines a procedure to use a seed, a region hypothesized to be highly connected with other regions in the brain, to grow a network over the entire brain, revealing the seed-to-brain connectivity.

In our implementation of the seed-based analysis, we included in the first analysis regression model additional variables to help maximize the signal of interest, and minimize the noise. We corrected for motion by including the six motion parameters from the SPM preprocessing, and we included the onset times for the task conditions, match and non-match, as well as corresponding errors.

Diagrams of seed-based maps of the TNN and TPN from Vemuri *et al.* (2012) are illustrated in Figure 3.6:



Figure 3.6 The Seed-derived network maps (From Vemuri *et al.*, 2012)

This map from Vemuri et al. shows the Task Negative Network (TNN) in the top panel and the Task Positive Network (TPN) in the lower panel that were derived using a seed-based approach in a group analysis of 341 elderly healthy control subjects. The TNN, the top panel, is the result of positive correlations to the 6-mm radius spherical seed in the posterior cingulate cortex (PCC). The TPN, the lower panel, is the result of the negative correlations to the PCC seed.

The top panel of Figure 3.6 exhibits the TNN and the lower panel exhibits the TPN. The seed region used is indicated in yellow, the 6 mm-radius spheroid in the posterior cingulate cortex. The top panel indicates the regions positively correlated with the seed, yielding the TNN. The lower panel indicates the regions negatively correlated with the seed, yielding the TPN.

#### 3.2.5.3 Independent Component Analysis Method

In Independent Component Analysis (ICA), instead of selecting regions in an a priori manner, the networks are determined by spatial patterns in the data. ICA is a method of blind source separation that can be used to recover the original sources from any multivariate signal. The original signals are recovered by using algorithms to make the multivariate signal as independent as possible. In fMRI brain imaging, the fMRI BOLD signal is a combination of multiple brain networks operating simultaneously. Applying ICA to these data separates the mixed signal into maximally independent components (ICs) that represent temporally coherent functional networks. That is, the regions included in each IC spatial map share similar time courses, and subsequently represent an individual brain network or sub-network, including among other networks, the TNN and TPN. Performing this algorithm on a group of subjects identifies the spatial maps that are shared across participants while also accounting for the individual boundaries of each subject.

Diagrams of ICA-derived TNN and TPN spatial maps from Vemuri *et al.* (2012) are illustrated in Figure 3.6.

We employed ICA using the GIFT toolbox (<u>http://icatb.sourceforge.net/</u>). We set the algorithm to estimate 40 components, which studies find sufficient for detecting the TNN and TPN (Kiviniemi *et al.*, 2003).



Figure 3.7 ICA-derived network maps (From Vemuri et al., 2012)

This map from Vemuri et al. shows the Task Negative Network (TNN) in the top panel and the Task Positive Network (TPN) in the lower panel that were derived using Independent Component Analysis (ICA) (20 components) with 341 elderly healthy control subjects. Three independent components within the TNN were detected by ICA in the upper panel; and four independent components within the TPN in the lower panel.

We used the maps in Figure 3.7 as guides in identifying the TNN and TPN

networks from ICA in our data.

# 3.2.6 Correlation Techniques

For both the ROI and ICA methods, the correlation analysis proceeded in an

identical fashion. After obtaining the networks from either method, we sought to

determine the extent to which each network is correlated with one another and with itself.

Each network consists of a set of time courses. The exact number of time courses

depended on the number of subcomponents of the network. We started by computing the

correlation coefficients between each of the subcomponent pairs both within and between the TNN and TPN for each subject. This resulted in a  $p \ge p$  connectivity matrix for each of the 90 subjects, where p represents the number of sub-networks. Then we took the average of the 90 matrices across all participants' networks, and plot the resulting average connectivity matrix.

The connectivity matrix contains the average correlation coefficients for each subnetwork pair, with possible values ranging from -1 to 1. Values close to 0 indicate that the two sub-networks exhibit no relation. Positive values indicate that the two subnetworks operate in tandem such that the activation of one network is associated with the activation of the other network. Negative values indicate that the two sub-networks operate in opposition such that the activation of one network is associated with the deactivation of the other network. We expected that intra-network, the sub-networks will exhibit positive correlations; and inter-network, the sub-networks will exhibit negative, or, anti-correlations (Vemuri *et al.*, 2012; Raichle, 2010; Fransson, 2006; Whitfield-Gabrieli *et al.*, 2012).

To visualize which networks serve as hubs of connectivity, we also visualized the correlation coefficients using a network graph. We used a threshold of  $\pm 0.35$ , representing a moderate correlation, for the calculation of edges on the graph. Correlation coefficients between (-0.35, 0.35) remain important, as well; however to help identify the sub-networks that are the most connected, we omitted these nodes from the network graph visualization.

### 3.3 Results

This section details the results from the ROI and ICA methods. While each method produced quantitatively and qualitatively different networks, the results converged to reveal a congruent pattern of TPNs and TNNs.

### 3.3.1 Region of Interest Method

Figure 3.8 is a plot of the time courses for each of the sub-networks for the 90 participants. The participants are stacked horizontally along the x-axis, and the BOLD signals are indicated on the y-axis. While the plot reflects the variable nature of the raw data, some patterns are visible. For instance, Control Network D, illustrated in teal-blue, consistently has a BOLD signal higher than any of the other sub-networks. Similarly, Default Mode Network B, illustrated in royal-blue consistently has a BOLD signal lower than any of the other sub networks. This pattern suggests that these two networks should be anti-correlated, a finding supported by a negative correlation between the TNN and TPN.



### Figure 3.8 ROI Time Courses

This plot shows the raw time courses for each of the sub-networks for the 90 participants. The x-axis represents the participants, which are concatenated side by side; and the y-axis represents the fMRI BOLD

signals. The legend on the right indicates how the time course are color coded according to the sub-network including Control A - F and Default A-F, representing the TPN and TNN respectively.

Figure 3.9 provides individual raw time course data for four random subjects from Figure 3.8. The shades of orange represent the TNN and the shades of purple represent the TPN.





This set of plots shows the raw time courses for four randomly selected participants at Baseline. The x-axis indicates the scan number from 1 to 480 and the y-axis indicates the fMRI BOLD signal. The purple shades represent the TPN and the orange-shades represent the TNN.

These illustrations of raw time courses provide an indication of the connectivity between the networks; however, to quantify and visualize the connectivity more clearly, we compute the correlation between each network pair. Figure 3.10 exhibits the average correlation values across all study participants. Hot colors (shades of red) indicate positive correlations and cool colors (shades of blue) indicate negative correlations, also known as anti-correlations. The connectivity matrix is equivalent along the diagonal, and the upper triangle exhibits a visualization of the correlation coefficient values, while the lower triangle exhibits the precise coefficient values. In the upper triangle, the diameter of the circle represents the magnitude of correlation.

Figure 3.10 shows that there are substantial anti-correlations between the TNN and TPN. In particular, networks 4 and 8, Control Network D and Default Network B, which stood out immediately from the plot of the raw time courses in Figure 3.8, are indeed anti-correlated. Networks 4 and 12 (Control Network D and Default Network F) are also substantially negatively correlated. These anti-correlations provide support for the hypothesis that the TNN and TPN are decoupled, according to the conceptual model in Figure 3.1. However, there are also strong positive correlations between the networks. Networks 2 and 8 (Control Network B and Default Network B); 2 and 12 (Control Network B and Default Network F); 3 and 8 (Control Network C and Default Network F) are each positively correlated with each other.

Intra-network, Figure 3.10 also exhibited both positive and negative correlation coefficients. Within the TPN, there were no anti-correlations larger than 0.35, and there were four correlation coefficients with positive values larger than 0.35, indicating a

stronger intra-network connectivity. Within the TNN, there were two substantial anticorrelation coefficients: the correlation between networks 8 and 10 (Default Network B and D) and that between 10 and 12 (Default Networks D and F) is -0.35. This suggests the inferior parietal lobule (IPL) and dorsal medial prefrontal cortex (dMFC); and the IPL and PCC, each pair representing components of the TNN, were not operating simultaneously. However there are also four positive correlations within the TNN.



#### Figure 3.10 The ROI Connectivity Matrix

This connectivity matrix shows the average correlation values across the 90 study participants. Subnetworks 1-6 represent the TNN and sub-networks 7-12 represent the TPN, as indicated in the legend on the right. Rows 1-6 crossed with columns 1-6 represent the intra-task positive network. Rows 7 - 12crossed with columns 1-7 represent the inter TNN-TPN network. Rows 7-12 crossed with columns 7-12 represent the intra-task negative network. Shades of red indicate positive correlations and shades of blue indicate negative correlations.

Figure 3.11 shows a network graph portrayal of the connectivity, which leads to three key observations. Firstly, within the TNN, networks 8 and 12, the IPL and PCC,

stand out as hubs, each with 7 connections to other regions. Secondly, network 10 the dMFC, is also a hub, with 5 connections. Thirdly, within the TPN, the network with the greatest number of connections is network 4, Control Network D, which connects to 5 other sub-networks. Overall, the TNN sub-networks are more connected to other sub-networks than the TPN sub-networks. After factoring in the 0.35 threshold used for the visualization of nodes, two networks stand out for not having any connections: Control Network E and Default Network C, representing the lateral temporal cortex (LTC).



Figure 3.11 ROI Network Graph

This network graph shows the connections between sub-network pairs that have average correlation values greater than |0.35|. Nodes 1-6 represent the TPN, and nodes 7-12 represent the TNN.

Figure 3.8-Figure 3.11 exhibit the results of the ROI method to assess functional connectivity between the TNN and TPN at increasing levels of reduction. Figure 3.8 shows the individual time course data for each subject, presenting all of the information without any modifications or reductions. This raw display shows the variability in the

data, and that despite this variability certain sub-networks appear to consistently exhibit higher or lower values than other sub-networks, indicating that a pattern exists and warranting further statistics. Thus, Figure 3.10 provides an average of the correlations of each sub-network pair across all subjects. This connectivity matrix provides a group-level display of the sub-network pairs that are the most positively correlated and those that are the most negatively correlated. The value of the average correlation coefficient is also provided for each sub-network pair. Figure 3.11 further summarizes this information by focusing in on only the sub-network pairs with average correlation coefficients of at least 0.35. Therefore, only the sub-network pairs with moderate correlations are displayed, and to aid identification of regions that are the most connected, and which regions are disconnected with others in the brain. Together, this sequence of figures reveals the connectivity results, from the raw data to our interpretations.

#### 3.3.2 Seed Analysis

The seed analysis incorporated behavioral measures and motion parameters in the subject-level regression models. Therefore, we took additional preprocessing steps to account for these measures. Namely, we examined the behavioral performance of each participant, and removed from this analysis those who performed below chance. Six participants were dropped from the analysis at this stage. Additionally, we re-examined the echo planar image quality, and removed from analysis those with significant imaging artifacts that interfered directly with the seed regions. The final sample for the seed-based analysis included 82 subjects.
The seeds were selected based on the results of the ROI connectivity analyses. We selected the seed region as the one with the most connections from each of the TNN and TPN, as illustrated in Figure 3.11. The region with the most connections in the TPN is labeled node 2, which connects to seven other sub-networks in Figure 3.11, and represents Control B. The region with the most connections in the TNN also connects to seven other sub-networks, and is labeled node 12 in Figure 3.11, representing Default F, which is also known as the PCC. The time courses from Control B and Default F are used as regressors in the first level analysis, and Figure 3.12 exhibits the results of second level analysis containing the seed-to-brain connectivity results.

The T-statistics in Figure 3.12 are ultra-thresholded using the family wise error rate for multiple corrections with P = 0.000000005 to exhibit only the regions that were highly correlated with each seed. Figure 3.12A exhibits the group level result of regions that are correlated with Default F, the PCC. Figure 3.12B exhibits the group level result of regions that are correlated with Control B. Figure 3.12A maps the TNN and Figure 3.12B maps TPN, demonstrating that each network can be recovered by using an a priori seed from within that network. That is, each network is appropriately correlated with itself. However, the parallel T-tests to obtain the regions that are negatively correlated with each seed resulted in a null finding—that is no, or very few voxels survived the significance threshold. Therefore, the seed-based approach generated each map from its respective seed; but neither generated its hypothesized complementary map, indicating that the anti-correlations were not observed in these data.

# A. The seed-based TNN



#### Figure 3.12 Results of Seed-Based Analysis

These images show the results of the seed analysis. (A), the upper panel, shows the TNN, the regions positively correlated with the posterior cingulate cortex seed. (B), the lower panel, shows the TPN, the regions positively correlated with Default B. All seed regions were constructed using 6-mm spheres. The results are ultra-thresholded using P = 0.000000005, and displayed on the standard MNI structural template.

# 3.3.3 Independent Component Analysis Method

Figure 3.14 exhibits the TNN derived from ICA. This network is parcellated into three

components, consisting of the anterior DMN, posterior DMN, and anterior/ventral DMN.

The figure is a group level map of the average spatial components; however the analysis

was conducted on back-reconstructed time courses corresponding to the networks of

interest for each individual.

Figure 3.14 exhibits the TPN derived from ICA. This network is parcellated into eight components, consisting of the upper left executive control network (ECN), lower left ECN, upper right ECN, lower right ECN, and dorsal attention network: Upper Left Executive Control Network (ECN), upper right ECN, lower left ECN, lower Right ECN, Bilateral ECN, Dorsal Attention Network (DAN) I, DAN II, and DAN III.

The connectivity matrix in Figure 3.15 shows the average correlation pairs across participants. Sub-networks 1-3 represent the TNN and sub-networks 4-12 represent the TPN. Overall, most correlation coefficient values are smaller than those in the parallel connectivity matrix from the ROI method. Also, like in the ROI results, the ICA connectivity matrix shows both positive and negative inter-network correlations. The strongest inter-network anti-correlation is between the anterior DMN I and the dorsal attention network, which represent two regions that are located far apart in the brain. The largest inter-network positive correlation is between the posterior DMN and DAN III, suggesting that these two geographically proximal regions of the brain operate together. Similarly, intra-network, there are both positive and negative correlations; however, the majority of correlation coefficients within each network have low values of less than 0.20. Within the TPN, the three DAN components are highly correlated with one another, as expected.



Figure 3.13 The ICA-derived TNN

This figure shows the results of Independent Component Analysis (ICA) (40 components) using GIFT (http://mialab.mrn.org/software/gift/). Three TNN components were detected: components 9, 11, and 14.



Figure 3.14 The ICA-derived TPN

This figure shows the results of ICA, from the same run as. Eight TPN components were detected: components 5, 8, 10, 13, 18, 24, 27, and 29.

1				•						•
	2					•				
		3						•	•	
			4							
				5						
					6					
						7				
							8			
		27						9	•	۰
		27						34	10	٠
28		43						34	34	11

# Key

- 1. Component 11. Anterior Default Mode Network (DMN) I
- 2. Component 14. Anterior DMN II
- 3. Component 9. Posterior DMN
- 4. Component 5. Upper Left Executive Control Network (ECN)
- 5. Component 13. Upper Right ECN
- 6. Component 27. Lower Left ECN
- 7. Component 18. Lower Right ECN
- 8. Component 29. Bilateral ECN
- 9. Component 8. Dorsal Attention Network (DAN) I
- 10. Component10. DAN II
- 11. Component 24. DAN III

# Figure 3.15 The ICA Connectivity Matrix

This figure shows the results of the average correlations across all 90 participants from Independent Component Analysis (ICA). Sub-networks 1-3 represent the TNN and sub-networks 4-11 represent the TPN.

# 3.4 Discussion

The functional connectivity results from the various methods converge on common findings: the intrinsic correlations in the brain map spatially to the TNN and TPN as expected. In the ROI method, the regions of the TNN were correlated with other regions of the TPN, and regions of the TPN were correlated with other regions of the TPN. In the seed-based method, the entire TNN was recovered using a single seed from this network; similarly, the whole TPN was recovered using one seed in the TPN. Our results from the seed-based approach match the corresponding maps from the literature fairly well. The TNN map that we obtained, Figure 3.12A, closely resembles Figure 3.6 from Vemuri *et al.* (2007). The TPN map, Figure 3.12B, also resembles the TPN map from Figure 3.6, although the match is not as close as in the TNN. The increased difference between the TPN in the literature and the results from our data could be due to the different study designs. Vemuri *et al.* utilize resting state data. The consistency of the finding for the TNN compared to the relative inconsistency of the results for the TPN indicates that the TNN is more robust and homogenous than the TPN.

In ICA, the TNN and TPN are produced without any a priori assumptions, and while the correlations within each network were lower than in the other methods, they tended to be positive. Thus, regardless of the method, we can be confident in the existence and generation of these brain networks in our community-based sample of older adults.

However, the relation between the two networks did not replicate the canonical findings from the literature, as hypothesized in Figure 3.1. Namely, in each method, we found that while some anti-correlations between the networks were observed, the nature

of the relation between the two networks can be described more accurately as a variety of correlations types including positive, negative, and null. In the ROI method, there were a number of positive correlations between the networks, indicating that the TNN and TPN may operate simultaneously rather than one at a time in turn. The ROI method also yielded a subset of negative correlations, indicating that there were a few sub-network pairs that appear to operate in the binary fashion that the literature predicts. In the seedbased method, there were no negative correlations, indicating that the two networks were not sufficiently anti-correlated at the group level. In the ICA approach, most of the correlations between the two networks were null. A correlation coefficient of zero can occur in two cases: (1) if the two networks indeed have no associations; or (2) if the data arise from a bimodal distribution such that some subjects have positive correlations and others have negative correlations, and the average is therefore zero. While further analysis is needed to determine the reason for the null correlation coefficients between the two networks, this finding is consistent with the results from the ROI and seed-based methods, that the TNN and TPN appear to display little to no anti-correlations.

The lack of anti-correlations between the TNN and TPN suggests that these two networks were not decoupled in our sample of socio-demographically diverse community-based older adults. The majority of findings in the literature with conclusions to the contrary are based on studies of young healthy adults. **Therefore, it may be that while the TNN and TPN are decoupled in young healthy adults, the two networks become less decoupled during aging.** In fact, other studies in children and older adults are also finding that the relation between the TNN and TPN may be more complicated than the common binary understanding. Fair *et al.* found that in children ages 7-9 years old, the TNN exhibits only sparse correlations with itself (2008). Developmental models of neuroanatomy demonstrate that the last areas to develop are also the first to deteriorate, which suggests that functional connectivity in the brains of children may provide a model helpful for the understanding of brain networks in older adults (Fair *et al.*, 2008). Also, Steffener *et al.* found that in older adults, the TNN remains active during task performance, and they hypothesize that the functioning of this network, in parallel with the TPN may actually serve to enhance performance for older adults (2012). We test the association between TNN-TPN connectivity and cognitive performance in Aim 2. The speculation that the TNN and TPN operating together may enhance performance suggests that for older adults, these networks may function in a compensatory mechanism. Perhaps the binary organization of the brain exhibited in young healthy adults is not optimal for older adults, and in fact the coupling of the two networks is a natural part of cognitive aging.

# 3.4.1 Strengths & Limitations

The Brain Health Study includes a number of significant features that make it suitable to answer the questions of interest and subsequent future implications. Extracting networks from an event-related paradigm represents a strength of the design and suggests a protocol for future studies. Because the networks match maps of the TNN and TPN from the literature, our study shows that it is possible to probe TPN and TNN activity in virtually any fMRI study. Usually, selecting or constructing the proper paradigm of interest for the desired outcomes represents the chief challenge for nearly every study design. Our study finds that because the networks represent intrinsic activity in the brain,

they can be extracted in both event-related and resting state designs. Thus, this simple protocol is straightforward to replicate.

Participants from the BHS also distinguish this investigation and add value to the literature. While most fMRI studies of older adults consist of white, educated, and uppermiddle class individuals, this sample consisted primarily of black, variably educated, and lower income individuals. This sample represents an often neglected target population, the at-risk community-dwelling older urban denizen. Results indicated that our approach is flexible in diverse samples, compared to other more homogenous samples of well-educated young and older adults, and specific patient samples. This approach thus has important implications for vulnerable and diverse groups of individuals.

A limitation in our study design is the event-based protocol. Most studies on functional connectivity collect long periods consisting of several minutes of "resting state." Here, we studied brain networks in the context of a working memory paradigm. This work fits with new and evolving precedent for evaluating functional connectivity using the Sternberg paradigm, such as (Fransson *et al.*, 2006; Metzak *et al.* 2012). However, studies using resting state data to assess brain networks argue that because these networks exist intrinsically, they ought to be measured optimally in the absence of a task.

The validity of using data from event-related study designs compared to task-free protocols has also been previously studied. In 2007, Fair *et al.* concluded that interleaved resting-state data (such as that from blocked event related fMRI designs) yielded resting state connectivity patterns that were both qualitatively and quantitatively similar to

continuous rest data (Whitfield-Gabrieli and Ford, 2012). The similarities in findings across study protocols adds further support to the intrinsic existence of the networks, and suggests that for a more nuanced understanding of the relationship between networks task-based fMRI, rather than task-free designs ought to be utilized.

Thus, while the literature is based on resting state fMRI, we propose that if these networks exist spontaneously, then their presence ought to be magnified in the presence of a task. Therefore, using data from an event-based paradigm may represent a strength rather than a limitation. The consistency in findings across both event-based and resting state fMRI studies provides further support for the underlying biology of the relation between brain networks, and suggests that one day, this tool can be developed as a robust measure of brain health.

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Zhou, J., Greicius, M. D., Gennatas, E. D., Growdon, M. E., Jang, J. Y., Rabinovici, G. D., ... & Seeley, W. W. (2010). Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain*, awq075. 4 Chapter 4. The Association Between Functional Connectivity and Cognitive Outcomes in Older Adults (Aim 2)

### 4.1 Introduction

Which patterns of connectivity in the brain are associated with better cognitive outcomes? If we could answer this question, the clinical and public health implications would be tremendous. We would be able to predict, in advance, declines in cognition in the elderly, and develop targeted interventions to preserve optimal functional connectivity. Using functional magnetic resonance imaging (fMRI), we aim to answer this question for a particular pair of networks, the task-positive (TPN) and task negative (TNN) networks. Our findings supplement the body of work linking brain network connectivity to cognitive outcomes, and demonstrate that in older adults the story is neither linear nor straightforward. Unearthing biology from artifact using a technology in which the noise is often louder than the signal, and relating the results to cognition, presents challenges. Indeed, we have a long way to go to map the brain-print of cognitive aging; nevertheless, our investigation provides a conceptual model, statistical methodology, and practical application representing one step forward in the effort to solve a part of this brain-behavior paradigm.



#### **Figure 4.1 The Brain Behavior Paradigm**

This diagram shows the conceptual model of the relation that we modeled: the association between brain network connectivity, as measured by correlations in fMRI BOLD signals; and cognitive functions, as measured by neuropsychological tests outside of the scanner.

The decoupling hypothesis of network connectivity posits that for optimal brain function, the TNN and TPN operate in separate phases according to cognitive demand. In the presence of a task, the TPN activates, and the TNN deactivates; in the absence of a task, the reverse occurs—the TNN activates, and the TPN deactivates. Previous studies have found that the binary organization of these brain networks is related to cognitive function in the direction that supports decoupling: better cognitive function is associated with more negative correlations between the TNN and TPN (Kelly *et al.*, 2008; Hampson *et al.*, 2010).

The focus of previous studies has been to establish the relation between functional connectivity and cognitive function in young healthy adults or in special patient populations. We investigated this association in a diverse population of community-based older adults. We studied the cross-sectional association between TNN-TPN connectivity and cognitive function, as well as the respective associations of intra-network connectivity within each of the TNN and TPN pathways. We selected cognitive outcomes from classic behavioral tests that are linked with dementia risk. By carrying out this investigation in a community-based sample of cognitively normal older adults, our results

have important implications for the aging population across the world. We predicted network pairs that are associated with better cognitive performance, and identified those that are associated with poorer cognitive performance, providing a framework for the prediction of cognitive decline, and the development of biomarkers to predict dementia pathology before it occurs. This analysis could lead to standardizable brain imaging tests that will allow older adults to examine the health of their brain connections, and take subsequent steps to improve brain health and preserve cognition.

### 4.2 Methods

In this section, we describe the methodology used to investigate the association between brain network connectivity and functional outcomes in the Brain Health Study (BHS), an imaging trial nested within the Baltimore Experience Corps Trial (BECT). Using the Sternberg Task, a test of working memory in the fMRI scanner, we extracted the task negative and task positive networks, assessed the connectivity between and within each network, and then lastly tested the association between the functional connectivity measures and outside-of-scanner cognitive outcomes. Figure 4.2 diagrams this procedure. In this section, we describe the data, the study sample, the brain networks, the cognitive outcomes, and statistical methodology. The imaging modality and technical specifications have been described in 3.2.3.



**Figure 4.2 Diagram of Methods** 

#### 4.2.1 Study Sample

The data are drawn from the BHS, a study nested within BECT, a randomized controlled trial of the Experience Corps (EC) program, a model of senior service in elementary schools. Details about EC and study participants are included elsewhere (Section 5.2.2). The sample included in this analysis consists of those participants with both usable fMRI data as well as complete behavioral tests outside of the scanner, which included 85 participants.

Table 4.1 summarizes the demographic and cognitive characteristics of the study sample. The sample is representative of the urban population of older adults in Baltimore: over 90% are African-American, almost 70% are female, and the average education level represents about two years of post-secondary schooling. The average MMSE score

indicates that participants are cognitively normal, as mandated by the eligibility criteria.

Characteristic	Mean
Ν	85
Age, in years (SD)	67.44 (6.2)
Male, n (%)	23 (27.1)
African American, n (%)	79 (92.9)
Education, in years (SD)	14.03 (2.75)
MMSE (SD)	28.46 (1.35)
Geriatric Depression Scale	1.02 (1.80)
MMSE = Mini-Mental State Examination	

# Table 4.1 Brain-Behavior Study Sample

#### 4.2.2 Brain Networks

After preprocessing the data according to the previously described protocol in Section 3.2.4, we extracted each brain network of interest using the region of interest (ROI) method that is outlined in Section 3.2.5.

We utilized a priori regions that have been shown in the literature to belong to the TNN and TPN from based on an fMRI study of 1,000 young healthy adults (Yeo *et al.*, 2011).

These are regions that have consistently shown increased deactivations and increased activations during tasks, for the TNN and TPN respectively. Next we describe these regions, and their known associations with cognitive outcomes.

### 4.2.2.1 Task Positive Network

For the TPN, we used what Yeo *et al.* (2011) characterize as the "Control Network," listed below:

#### **Task Positive Network:**

- A. Anterior control network
- B. Medial control network
- C. Lateral control network
- D. Dorsal attention network
- E. Premotor cortex
- F. Superior parietal cortex

Because the TPN represents regions of the brain that exhibit increased activations during tasks, this network is believed to be involved directly in cognitive function. Previous studies have found increased activation in TPN regions to be associated with improved performance on cognitive tasks. For instance, Song *et al.* found that the strength of connections in the dorsolateral prefrontal cortex is positively correlated with performance on the Wechsler Adult Intelligence Scale, an overall measure of intelligence (Song *et al.*, 2008). Additionally, Seeley *et al.* found that the connectivity within the intraparietal sulcus is positively correlated with performance on the Trail Making Test, a measure of executive function (Seeley *et al.*, 2007). The literature shows that stronger intra-network connectivity within the TPN is associated with better cognitive outcomes (Hampson, 2010).

#### 4.2.2.2 Task Negative Network

For the TNN, we use the MNI coordinates identified by Yeo *et al.* (2011) as the Default Mode Network, which is also parcellated into six regions:

### Task Negative Network:

- A. prefrontal cortex (PFC)
- B. Inferior parietal lobule (IPL)

- C. Lateral temporal cortex (LTC)
- D. dorsal medial prefrontal cortex (dMFC)
- E. parahippocampal cortex (PHC)
- F. posterior cingulate/retrospenial cortex (PCC/Rsp)

We adopted the term "task-negative," as introduced by Fox *et al.* over "default mode" network (DMN) because of the meaning that each name implies (2005). "Default mode" implies that these regions are constantly activated, such that they may be engaged in processing that is critical to brain functioning at all times. However, neuroimaging studies demonstrate that these regions are activated in the absence of a task, and deactivated in the presence of a task, as implied by the term "task-negative." Therefore, while some studies use the terms interchangeably, we opt for TNN instead of DMN to be more descriptively accurate based on the current state of research findings.

Many TNN regions appear relevant to cognitive function because of their consistent reductions in activity during tasks, across different types of tasks. For instance, meta-analyses repeatedly show that regions of the prefrontal cortex (PFC) and posterior cingulate cortex (PCC) exhibit decreased blood flow during tasks (Shulman *et al.*, 1997; Mazoyer *et al.*, 2001). Task engagement appears to suspend activity in TNN regions. In the absence of a task, these regions are active, and the correlations between TNN regions are high, demonstrating that these regions form an integrated functional network (Greicius *et al.*, 2003). The functions of this network are not fully known, and are believed to be involved in self-referential processes such as memory formation, the integration of the past and the present, daydreaming, planning, and decision-making. The TNN is believed to be involved in the functioning of types of processing that represent the converse of task-related paradigms. For example, in order to read and digest this paragraph, the reader would benefit from focusing on this paragraph, rather than on planning activities for tomorrow. The neuroimaging literature supports this hypothesis that decreased activity in the TNN during tasks is associated with improved cognitive performance.

#### 4.2.3 Behavioral Measures

Study participants completed tests outside of the scanner to measure performance in the domains of executive function and memory, two cognitive domains that exhibit declines with the onset of dementia (Carlson *et al.*, 2009). BHS participants were healthy community based adults; and we evaluated their performance in the absence of dementia in order to establish the brain-behavior link in healthy aging and among older adults at an elevated socio-demographic risk for dementia.

#### 4.2.3.1 Executive Functions

Executive functions supervise all cognitive operations. Functions in this domain include planning, assembling, coordinating, problem solving, sequencing, strategizing; shifting; inhibiting; and goal-directed behavior (Salthouse *et al.*, 2003). Like all other functions, there is no one-to-one anatomical structure in the brain responsible for executive function; however, the structures in the brain commonly implicated include the frontal lobes, and particularly the prefrontal cortex (PFC). The PFC is the last region of the brain to develop in young adults, as it does not complete myelination until the late 20's for males; and the prefrontal cortex is typically the first to deteriorate in older adults (Craik and Bialystok, 2006). This set of functions is both extremely sensitive to aging and especially important for mental health, as a disruption in this central command system affects all of the other domains. Recent studies have further supported the chief role of

executive functions, and demonstrated that this domain may mediate the effects of age on cognition (Salthouse *et al.*, 2003; Carlson *et al.*, 2009).

The regions believed to be implicated for executive functioning overlap with both regions of the TNN and TPN. Therefore, establishing the link between TNN-TPN connectivity and executive function will help to better provide an integrated understanding of how this domain operates.

To assess components of executive functions, we used a test of set shifting entitled, the Trail Making Test (TMT), and a test of working memory entitled, Digit Span Test (DST). Both of these neuropsychological tests are completed outside of the scanner. The TMT is a visuomotor search task consisting of two parts, A and B, to measure psychomotor speed and task switching, respectively. In Part A, participants are instructed to connect a random dispersion of numbers, 1-25, on a page in sequentially ascending order by one. In Part B, the points on the page include both letters and numbers, from A-L and 1-13, and the task is to connect each number with the corresponding letter, and continue onto the subsequent number letter pair (i.e., 1-A-2-B-3-C, etc.). Participants are instructed to complete the task as quickly as possible. Performing Part B successfully requires working memory, mental flexibility, attention, task switching, and rapid visual processing (Seeley et al., 2007). Both parts of this task are completed on paper with a pencil, and the time and accuracy for each participant are recorded. A lower score on TMT-B indicates a faster completion, and subsequent better performance. While TMT-A does not require executive function capabilities, it serves to ensure that the participants understand the task, and have the visuomotor skills necessary to complete TMT-B.

To assess the working memory component of executive function, we administered the Digit Span Test, a subtest of the Wechsler memory scale. It also consists of two parts, Forward and Backward. DST Forward consists of recalling a sequence of numbers in order, representing a control to the second measure of working memory. DST Backward consists of recalling a sequence of numbers in reverse order, which requires an additional manipulation of the information, and therefore represents a measure of Executive Function (Groeger *et al.*, 1999; Lezak, 2004). DST Forward does not require executive function capacities; however, it is necessary to conduct as a baseline measure of performance, and to ensure that participants can proceed to DST Backward. A higher score on DST Backward indicates that more digits were appropriately computed, and subsequently, a better performance.

We developed a score for Executive Function by aggregating the scores from TMT-B and DST Backwards, the two tests that capture the domain of interest. Each score was normalized by subtracting the mean and dividing by the standard deviation. The resulting z-score has mean zero and standard deviation of one, essentially eliminating the original unit of measurement such that the resulting scores can be compared. Additionally, the TMT-B score was multiplied by negative one so that in can be interpreted in the same manner as DST Backwards, in which a higher score indicates better cognitive performance. The executive function score that was used in this analysis consisted of the average of the normalized and sign calibrated TMT-B together with the normalized DST Backwards score as indicated in Box 1:

**EF Score = mean[(-1)\*(Normalized Trails B) + (Normalized DST Backwards)]** 

#### 4.2.3.2 Memory

Memory, one of the most often studied and poorly understood domains, includes both long-term and short-term memory, and encompasses both verbal and visuospatial abilities. Types of long-term memory include episodic, semantic, procedural, and implicit (Tulving, 1983). Overall, each of these subtypes declines linearly with age, beginning in the mid-20s, except semantic memory, which is considered a crystallized type of intelligence (Tulving, 1983). Several regions of the brain are implicated in memory, and these regions, such as the hippocampus and hippocampal formation, also overlap with both the TPN and TNN, respectively.

To assess memory, we employed the Rey Auditory Verbal Learning Test (RAVLT), which has been utilized since its development in 1958 (Rey, 1958). The purpose of this test is to assess verbal learning and memory (Spreen & Strauss, 1991; Spreen, 1998; Lezak, 2004). The test includes a number of components to measure immediate memory recall, new learning, susceptibility to interference, and long-term memory. Participants are read a list of 15 words, and asked to remember as many words as they can. Each participant completes five learning trials, an immediate recall, and a delayed recall after 15 minutes. The first five trials assess sequential learning, the immediate recall trial assesses short-term memory, and the delayed recall trial assesses long-term retention. The number of items recalled correctly in any order is recorded.

We developed a score for memory by aggregating the five trials of RAVLT together with the immediate recall and delayed recall trials, as indicated in box 2:

Box 2. Development of Memory Score

Memory Score = mean[(Normalized Trial 1) + ... + (Normalized Trial 5) + (Normalized Immediate Recall) + (Normalized Delayed Recall)]

### 4.2.4 The Brain-Behavior Link

The literature shows that the increased activity of TPN and the decreased activity of TNN during any cognitive task is associated with better cognitive outcomes. Seeley *et al.* reported significant inverse correlations between time on the Trail Making Test and intra-network connectivity within the executive control network, indicating that greater functional connectivity in the TPN is associated with faster performance (2007). Similarly, Rissman *et al.* found that intra-network connectivity within some components of the TPN is associated with better performance on a test of delayed recognition (2004). Miller *et al.* established a similar finding in a working memory recognition test: coupling of regions within the TPN, the prefrontal cortex and frontal fusiform area (FFA), and of the bilateral hippocampus and FFA occurs during the task (2012).

While the regional results for TNN activity during tasks and cognitive outcomes tend to converge upon an inverse relation, the brain-behavior results using TNN connectivity rather than simple activation, are more nuanced. Esposito *et al.* found that the results depend on the sub-networks under investigation—connectivity in the anteriormost region of the DMN is positively correlated with the level of task difficulty, and that connectivity in the posterior cingulate cortex (PCC), a posterior portion of the DMN, is negatively correlated with the level of task difficulty (2009). This finding that the association between TNN connectivity and task performance is not homogenous, and depends on the sub-networks in question, has been replicated. Leech *et al.* found that as task difficulty increases, the ventral PCC shows reduced integration within the DMN and less anti-correlation with the cognitive control network activated by the task (2011). On the other hand, Leech *et al.* found that another region of the PCC exhibited the opposite pattern: the dorsal PCC showed increased DMN integration and more anti-correlation with the cognitive control network of the TPN (2011).

These heterogeneous results from the literature helped us to develop hypotheses about what we expected to find between functional connectivity and cognitive outcomes within and between the TNN and TPN. While few studies have investigated the connectivity between TNN and TPN together, the results on this subject, and on intranetwork connectivity from the literature suggest that the trend may depend on the particular sub-networks under investigation. Furthermore, the majority of studies investigated the effect of connectivity on activation during task, not on the performance of the task. Therefore, our hypotheses come from the literature on the classic regional studies relating regional activation with task performance, coupled with the findings relating the activation of TNN versus that of the TPN to task performance. These findings indicate that the TPN activates during tasks; the TNN deactivates during tasks; the TNN activates in the absence of tasks; and the TPN deactivates in the absence of tasks. Additionally, the literature shows that increased TPN and decreased TNN activity during task is associated with better cognitive performance. Taken together, we hypothesize that larger anti-correlations between the TNN and TPN will be associated with better

cognitive performance. Larger anti-correlations indicate that the two networks are more decoupled, and ascribing to the model of functioning suggested by the literature such that the TPN is activated only during the task, and the TNN is activated only in the absence of the task.

Similarly, we expect that larger *intra*-network correlations, correlations between sub-networks within each network, will be associated with better cognitive performance. The more connected each network is with itself, the more efficiently that network is operating.



Figure 4.3 presents a cartoon of our hypotheses.

#### **Figure 4.3 Brain-Behavior Hypotheses**

This cartoon demonstrates our hypotheses that inter-network correlations will be associated inversely with cognitive performance, and intra-network correlations will be positively associated with cognitive performance on tests of Executive Function and Memory.

While these hypotheses provide a helpful starting point through which to view our results, the reality may reflect the heterogeneity of findings from the literature. The

association between cognitive scores and inter-network and intra-network connectivity may depend on the specific pair of networks, and on the cognitive domain, as well.

The domains of executive function and memory are not measuring the same thing, and it may be that one is more sensitive to inter or intra-network connectivity than the other. While both measures of cognition ought to be associated with network connectivity, executive function may serve as a particularly sensitive measure, compared to memory. After all, executive control represents the converse of the default mode. Better control of executive function would indicate a greater ability to overcome the automatic default mode of the brain, and complete the task at hand (Craik and Bialystok, 2006). Less control of executive function would indicate that the TNN may remain activated during the task. Furthermore, other studies have observed that declines in executive function precede declines in memory (Carlson *et al.*, 2009). Therefore, we expect stronger findings for executive function, compared with memory.

#### 4.2.5 Statistical Methods

The statistical methods that we utilized to establish the brain-behavior link are outlined in

Figure 4.4. On the left hand side of the figure, we outlined the steps taken to analyze and condense the neuroimaging data into useful markers of functional connectivity. First, the data were preprocessed according to the protocol described in Chapter 3.2.4. Next, the networks were extracted using the region of interest (ROI) method, which decomposed each the TNN and TPN into six sub-networks. Lastly, a correlation analysis was performed to obtain measures of connectivity between the two

networks and within each network. The measure of choice is the correlation coefficient, as described in Section 3.2.6.

On the right hand side of

Figure 4.4, we outlined the steps taken to condense the cognitive outcomes into useful measures that are representative of cognitive domains that we sought to quantify. For each of the executive function and memory domains, we collected the relevant tests, and normalized and aggregated them to form the Executive Function and Memory Scores.



#### **Figure 4.4 Summary of Statistical Methods**

The connectivity between the brain networks is assessed using the procedure outline in the box on the left. The resulting connectivity scores are then used as regressors to model their association with the normalized executive function and memory scores.

Linear regression was used to link brain connectivity with cognitive outcomes.

There were a total of 6 TNN sub-networks and 6 TPN sub-networks, which yielded 12 x

12, or 144 intra and inter-network correlation pairs. Since the connectivity matrix is

symmetric along the diagonal, and each sub-network is perfectly connected with itself, this left only 66 unique correlation pairs to investigate. Of these, 15 correlation pairs represent connectivity within the TPN, 15 represent connectivity within the TNN, and 36 represent inter-network connectivity. We ran a linear model to answer each question of interest: the association between intra-TPN connectivity and cognitive outcomes; between intra-TNN connectivity and cognitive outcomes; and between inter TNN-TPN connectivity and cognitive outcomes. Because there are two cognitive outcomes of interest, EF and memory this yields a total of six models as listed in Table 4.2.

<b>Table 4.2 Summary</b>	of Br	'ain-B	Sehavior	Models
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	Memory	<b>Executive Function</b>
Inter-network	Model 1	Model 2
Intra-TNN	Model 3	Model 4
Intra-TPN	Model 5	Model 6

Each model also includes sex, education, and age, which are covariates that are known to be linked with cognitive aging (van der Elst, *et al.*, 2006). By including these covariates, we hoped to account for their effects, and obtain a more accurate model for the relation between the variable of interest, brain network connectivity, and cognitive outcomes.

# 4.3 Results

In this section, we describe the behavioral results followed by the results for the linear models that relate brain connectivity with cognitive outcomes. The results are structured according to the listing of models in Table 4.2, by connectivity type.

# 4.3.1 Behavioral Results

Raw data for the neuropsychological exams of interest are summarized in Table 4.6 in the Appendix. However, the cognitive outcomes that were used as the behavioral
measure of interest in the linear regression are the aggregated and normalized cognitive scores. Figure 4.5 exhibits the distributions of these scores. Each outcome is approximately Gaussian and centered at 0, which reflects the manner in which these scores were developed. For EF, the distributions of males and females were similar, as indicated in pink, and blue respectively. However for memory, the men's performance is lower than that of the women.





This figure shows the histograms of the scores for executive function on the left and memory on the right. Men are represented in pink and women are represented in blue.

The Gaussian distribution of these behavioral measures helps to ensure the validity of using these measures as outcomes in the linear regression model. In the next section, we describe the results of the linear models.

#### 4.3.2 Brain-Behavior Results

Prior to conducting the formal linear models to assess the association between brain network connectivity and cognitive outcomes, we first performed an exploratory analysis. We computed the correlation between each pair of sub-networks' correlation coefficient with each cognitive outcome, EF and memory, stratified by sex. These correlations are illustrated in Figure 4.6. Larger circles indicate larger correlation values. Smaller circles indicate smaller values. The correlation values range from -1 to 1, and in color from red to blue, with white falling at 0. For females for both EF and memory, the values representing the association between brain network connectivity and cognitive outcomes hover closer to zero, than for males. The cells with larger circles indicate that that sub-network pair has a stronger association with a given cognitive outcome.

#### A. Executive Function in Females

#### **B. Executive Function in Males**



#### Figure 4.6 Exploratory Analysis of Brain-Behavior Associations

This set of matrices shows the average correlations between the functional connectivity score and cognitive outcome for each sub-network. The upper row, panels A and B, shows the average correlations for the executive functions outcome for women and men respectively. The lower row, panels C and D, shows the average correlations of functional connectivity with memory scores for women and men respectively.

#### 4.3.2.1 Inter-Network

Models 1 and 2 investigated the effect of inter-network connectivity on Memory

and Executive Function respectively. In the following section, results from the linear

models are provided, including estimates of the coefficients, measures of their variability, and scatterplots to illustrate the trends.



**Figure 4.7 Overview of Inter-Network Connectivity Models** 

This pair of plots shows the results of the inter-network connectivity models for memory on the left and executive function on the right. The coefficient estimates, labeled on the left of each plot, for each of the inter-network connectivity pairs is plotted together with its 95% confidence interval. Covariates that are significant at the 0.05 level are indicated with an asterisk.

*Memory*. In Model 1, we investigated the relation between inter TPN-TNN connectivity and the Memory score. We included all 36 TPN-TNN sub-network correlation pairs, and the panel on the left of Figure 4.7 shows an overview of the results. To simplify the explanation of the results, these sub-network correlation pairs will be referred to as *connectivity scores*. The graph of the coefficient estimates for the connectivity scores illustrates that 20 out 36 of the coefficients are negative, indicating that these connectivity scores are inversely associated with the memory score. Figure 4.7 also includes the 95% confidence intervals for the coefficient estimates, and most of these horizontal lines cross zero, indicating a large amount of variability in the data. The statistically significant coefficients, at the P-value of 0.05, are indicated with an asterisk in Figure 4.7. The significant findings are also highlighted in Table 4.3. Out of the five connectivity scores that are significant, three are negatively associated with the memory score. In the subset of connectivity scores that are statistically significant from Table 4.3, a couple of sub-networks appear multiple times: Control B and Default E, indicating that these sub-networks are highly integrated with corresponding sub-networks from the TNN and TPN respectively.

Scatter plots of the significant connectivity scores and their association with memory are displayed in Figure 4.8. The scatter plots illustrate that memory scores increase with V24 and V25, and decrease with each of V36, V57, and V71.

Variable	Meaning/Unit	Coefficient Estimate	Standard Error	P-Value
Education	Years	0.10	0.04	0.03
V24	Control B, Default E	1.05	0.51	0.05
V25	Control B, Default F	1.73	0.89	0.05
V36	Control C, Default E	-0.92	0.46	0.05
V57	Control E, Default B	-1.59	0.61	0.01
V71	Control F, Default D	-1.80	0.77	0.02

# Table 4.3 The Effect of Functional Connectivity on Memory



# Figure 4.8 The Effect of Functional Connectivity on Memory

This figure shows scatter plots of the five connectivity scores that were found to be significant in Model 1. Starting on the upper panel, and going from left to right to the lower panel, these functional connectivity scores are V24, V24, V36, V57, and V71. The x-axis indicates the inter-network correlation value and the y-axis indicates the memory score.

*Executive Function*. In Model 2, we investigated the relation between inter TPN-TNN connectivity and the EF score. The results are exhibited on the right side panel of Figure 4.7. The figure shows that 23 connectivity scores have negative coefficient estimates, indicating an inverse relation with the executive function score. However, the 95% confidence intervals are very long, and only one connectivity score is significant at the 0.05 level, as indicated in Table 4.4. This connectivity score represents the correlation between sub-networks Control E and Default B, and has a coefficient estimate of -1.95. This connectivity score also turned out to be significant in Model 1. The scatterplot for this coefficient is exhibited in Figure 4.9.

Variable	Meaning/Unit	Coefficient Estimate	Standard Error	P-Value
Education V57	Years Control E & Default B	0.94 -1.95	0.05 0.67	0.05 0.005

**Table 4.4 The Effect of Functional Connectivity on EF** 



#### **Figure 4.9 The Effect of Functional Connectivity on Executive Function**

This figure shows scatter plot of the single connectivity score, V57 that was found to be significant in Model 2. The x-axis indicates the inter-network correlation value and the y-axis indicates the executive function score.

#### 4.3.2.2 Intra-TNN

Models 3 and 4 investigated the relation between intra-TNN connectivity and Memory, and EF, respectively. For both the models on memory and executive functions, we found that while most (10 out of 15) connectivity scores have positive coefficient estimates, none are significant (p's > 0.05). These results are displayed in the Appendix.

#### 4.3.2.3 Intra-TPN

Models 5 and 6 investigated the relation between intra-TPN connectivity and Memory, and EF, respectively. Like in the Intra-TNN results, we found that for memory, the majority (11 out of 15) of the coefficient estimates are positive; however, none attain statistical significance (p's > 0.05). The results for executive function turned out differently: only 7 of the 15 connectivity scores are positive; and while none of the positive coefficient estimates are significant, two of the negative coefficient estimates are significant. The intra-TPN results are also displayed in the Appendix.

### 4.4 Discussion

The results of this cross-sectional analysis show that neither the TNN nor TPN behave homogenously; and that together, the ways in which these networks were integrated to affect cognitive outcomes were also variable. In this section, we discuss overall trends in the association between brain network connectivity and cognitive outcomes, and situate these highlights within findings from the literature. The results demonstrate that the association of brain connectivity on brain outcomes differs for intranetwork connectivity versus inter network connectivity. The results also show that sex may modify the nature of the relation—in some brain networks, connectivity is positively associated with cognitive performance in females and the opposite in males. Additionally, the cognitive outcome of interest matters—the trends differ for executive function and memory. These patterns are discussed in detail below. Lastly, we discuss the strengths, limitations, and public health significance of applying these methods to develop a biomarker.

#### 4.4.1 Inter vs. Intra Network Connectivity

Our hypothesis stated that inter-network connectivity would be negatively correlated with cognitive performance, and intra-network connectivity would be positively correlated with cognitive performance. The results support this hypothesis for select sub-network pairs, and show that in general, both positive and negative associations exist for both types of network pairs.

The models for inter-network connectivity fit the data better than those for the intra-network connectivity. The R-squared values, measuring the amount of variability that the model accounts for, for each model are summarized in Table 4.5. Model 1, the effect of inter-network connectivity on memory has an R-squared value of 0.6, indicating a good fit. Model 2, the effect of inter-network connectivity on EF has an R-squared value of 0.41, indicating a moderately good fit. While both of the inter-network models account for a large proportion of the variability for both of the memory and EF outcomes, the intra-network models all have R-squared values hovering below 0.28, indicating a less than moderate or poor fit. The fact that the inter-network models fit the data better than the intra-network models indicates that perhaps it is not the integration of each network with itself that promotes better cognitive performance, rather it is the connectivity between the TNN and TPN that function together to modulate cognitive performance. On a statistical level, this finding also explains why the inter-network models resulted in a number of significant connectivity scores, whereas these scores of interest were not significant in the intra-network models.

Model	Description	<b>R-squared</b>
1	Inter-network connectivity on memory	0.61
2	Inter-network connectivity on EF	0.47
3	Intra-TNN on memory	0.22
4	Intra-TNN on EF	0.27
5	Intra-TPN on memory	0.27
6	Intra-TPN on EF	0.28

In Model 1, there were five connectivity score coefficients that are significant. Control B appears twice, and in Section 3.3.1 (Aim 1), this network exhibited the greatest number of connections with other networks. Control B is a sub-network located in the anterior portion of the TPN. The connectivity pair (Control B, Default E) and (Control B, Default F) are both positively associated with the memory score. Default E and Default F represent sub-networks located in the posterior portions of the TNN, centered at the parahippocampal cortex (PHC) and posterior cingulate/retrospenial cortex (PCC/Rsp), respectively. The positive association between these TPN-TNN network pairs and memory suggest that the anterior regions of the TPN are communicating with the posterior regions of the TNN in the functioning of memory. Indeed, in studies that aim to localize structure to function, the PHC has been found to be associated with memory formation. Our results suggest that this sub-network of the TNN actually integrates with sub-networks from the TPN in the formation of memories. Similarly, the PCC is also implicated in memory retrieval, and known to be one of the most highly connected regions of the brain, representing a node of the TNN (Nielsen et al., 2005). Our results showed that the integration between the PCC, and an anterior sub-network within the TPN is associated with memory. Although we hypothesized that inter-network connectivity would be anti-correlated with cognitive outcome performance, due to the known functional roles of the PHC and PCC, the result should come as no surprise. Because these regions of the TNN are implicated in memory formation, it is logical that we found that the more coupled these sub-networks are with an anterior sub-network of the TPN, the better the memory outcome.

The remaining connectivity scores in Model 2 were negative, supporting the hypothesis that increased decoupling between the networks is associated with better cognitive performance. These connectivity scores represented sub-networks located at multiple points in the brain, from the anterior to the posterior, to the lateral. These results replicate those from the literature that have shown that better cognitive function is associated with smaller or more negative correlations between the TNN and TPN. In a study on the effect of brain connectivity on working memory, Hampson *et al.* found that the connectivity between dorsolateral PFC, a region in the TPN, and medial PFC, a region in the TNN, is negatively correlated with cognitive performance (Hampson *et al.*, 2010). Thus, these findings support the decoupling hypothesis between the TNN and TPN and TPN, as a mechanism for cognitive health.

In Model 2, the effect of inter-network connectivity on EF, only one connectivity score was statistically significant. The sub-network pair (Control E, Default B) was inversely related to the EF score. Control E is located in the medial portion of the TPN. Default B is also known as the inferior parietal lobule (IPL), a key region of the TNN. Because EF consists of a number of processes, there are fewer studies in the literature that investigate the effect of brain connectivity on EF. Nevertheless, our results are consistent with the current state of the literature. Kelley *et al.* found that the anti-correlation between task-positive and task-negative networks was inversely associated with response time (2008). Our EF score is an aggregate of different tests to capture this domain more comprehensively, and response time from the Trail Making Test is incorporated into the EF score used in our analysis.

The intra-network models, did not yield any significant results of interest. Findings from the literature indicate that the strength of connectivity both within the TNN and within the TPN is positively related to task performance (Hampson, 2010). Such findings suggest that each network works with itself to facilitate cognitive processing. Although there are a number of positive connectivity score coefficients in Models 3-6, the lack of statistical significance suggests that the *intra*-network connectivity within each model does not account for the behavioral outcomes of the cognitive performance for the Memory and EF scores that are measured. This finding may suggest that inter-network integration is more important than intra-network integration for mediating cognitive processing necessary for memory and EF outcomes. Alternatively, the null results from Models 3-6 may indicate a lack of power to detect differences, a lack of variability in the intra-network correlations used in the models, or measurement error. Further studies are needed to investigate the effect of intra-network correlations on cognitive performance.

#### 4.4.2 Executive Function vs. Memory

The models show that brain connectivity is both positively and negatively associated with EF and memory. However, the inter-network connectivity models fit the memory score outcome better than the executive function outcome (R-squared 0.61 vs. 0.47), suggesting that synchrony between the TNN and TPN is more important in the modulation of Memory than EF. Regions in both the TNN and TPN are implicated in Memory, while regions implicated in executive functions tend to be restricted to the TPN. Therefore, the inter-network connectivity models utilizing memory as an outcome may fit the data better than EF because memory requires stronger synchrony between these two networks.

#### 4.4.3 Males vs. Females

A consistent finding in the neuroimaging literature has been that differences exist in the connectivity of male and female brains (Schmithorst *et al.*, 2007; Kilpatrick *et al.*, 2006). In the brain-behavior models, sex was included as a covariate, and being male was associated negatively with the EF and Memory scores. This association achieves statistical significance (P < 0.05) in the model where we tested the effect of Intra-TPN connectivity on the memory score.

While formal analyses stratified by sex were not conducted, graphical displays of the data revealed different qualitative patterns for men and women. Figure 4.10 provides an example of this phenomenon in which gender appears to modify the relation between brain connectivity and behavioral outcomes. For the inter-network correlations displayed in Figure 4.6, women, in red, exhibited the expected pattern: correlations between the TNN and TPN were inversely associated with cognitive scores; and men, in blue, exhibited the opposite: inter-network correlations were positively associated with cognitive scores. These findings in men suggest a different mechanism is operating. Since men consistently scored lower than women on the cognitive tests, perhaps the differences in connectivity patterns represent a biological explanation for these behavioral differences. Longitudinal change models would allow us evaluate whether the reverse connectivity patterns in males precedes performance on the EF and Memory tests.



Figure 4.10 The Effect of Sex on Brain-Behavior Outcomes

This figure shows the relation between inter-network correlations and cognitive performance, color coded by sex with women in red and men in blue. The x-axis represents the connectivity scores and the y-axis represents the cognitive performance scores. The panel on the left shows the association between V37 connectivity scores and executive function. The panel on the right shows association between V33 connectivity scores and memory.

## 4.4.4 Biomarker Development

The methods outlined in this paper provide a potential framework for using fMRI imaging to detect pre-clinical changes in brain connectivity. By studying the association between functional connectivity and cognitive outcomes, we outlined connectivity patterns that were associated with better cognitive functions, and suggested a method to predict which connectivity trends are associated with poor cognitive functions.

An fMRI biomarker would be optimal compared to other imaging technologies because fMRI is minimally invasive and can be easily standardized to measure preclinical changes in cognition, which can help to differentiate between normal aging and Alzheimer's Disease (AD) pathology. Recent evidence that brain pathology corresponds poorly with clinical symptoms greatly weakens present understanding of AD etiology. This schism suggests that perhaps amyloid deposition is not central in the pathogenesis of AD (Whalley *et al.*, 2002). This disappointing result of the amyloid cascade hypothesis leaves us searching for the pathology of the signs and symptoms of dementia in the brain. Another useful approach will be to search more closely for markers of aging in the brain, such as those suggested by Jack et al. in his 2013 model laying out the time course for preclinical biomarkers of brain aging such as cerebrospinal fluid (CSF) tau, a protein implicated in maintaining the structure of cells; brain volume and cortical thickness via MRI; and cognitive impairments from neuropsychological tests. It may be that factors and biomarkers of aging are different from those that indicate pathology. Such a neuroanatomical distinction would help to reveal the boundary between normal aging and pathology.

#### 4.4.5 Strengths & Limitations

One strength of this study arises from the study design. Because the data come from an event-based fMRI trial design with a cognitive task rather than resting state, the differences between the TNN and TPN can be measured within the same protocol and differences may be easier to identify. Larger differences between the networks,

engendered by the task, would create larger correlations and anti-correlations, which would exceed the spontaneous correlations, due to physiological noise, present in fMRI, and make it easier to detect true signals.

Another strength is seeking to relate brain network connectivity with behavior. This quest presents a significant question, and the answer probes at not only mechanisms in the brain, but also their relation to behavior, outside of the scanner. Furthermore, this answer will contribute to the development of standardizable tools to detect pre-clinical changes in cognition to help predict dementia pathology while there is still time to intervene.

The results present a nuanced relation between brain connectivity and cognition. We did not observe full support for the hypotheses predicted, which suggests that in older adults, the relations are more complicated than is commonly appreciated based on similar data in young adults.

A future direction to definitively map the brain connectivity – behavior relation in older adults would be to use a data-driven approach. Instead of using a priori seeds for the connectivity scores, every possible seed voxel in the brain could be used, and those that correlate the most with cognition could then be tested using the methods we developed. However, a strength of the ROI approach that we used is that the selected regions represent constituents of brain networks with known connectivity trends. Therefore, using these ROIs makes it easier to expand to the literature and to standardize results in the landscape of findings.

To further compare results better with the broader literature, it would be helpful in future studies to perform the same analyses on resting state fMRI data.

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# 4.6 Appendix

# Table 4.6 Behavioral Data (Mean ± SD)

Neuropsychological Exam	Unit	Total
Digit Span (Forward)	Number	7.74 ± 1.72
Digit Span (Backward)	Correct	5.14 ± 2.34
Trail Making A	Time in	45.44 ± 15.63
Trail Making B	seconds	131.8 ± 74.72
RAVLT (learn)		39.23 ± 7.67
RAVLT (Short Delay)	Number Correct	6.63 ± 2.77
RAVLT (Long Delay)		6.46 ± 2.85 <sup>±</sup>



#### Figure 4.11 The Effect of Intra-Network Connectivity on Memory

This pair of plots shows the results of the intra-network connectivity models for memory. The left panel shows intra-TNN model and the right panel show the intra-TPN model. The coefficient estimates for each of the intra-network connectivity pairs is plotted together with its 95% confidence interval.



Figure 4.12 The Effect of Intra-

#### **Network Connectivity on Executive Function**

This pair of plots shows the results of the intra-network connectivity models for executive function. The left panel shows intra-TNN model and the right panel show the intra-TPN model. The coefficient estimates for each of the intra-network connectivity pairs is plotted together with its 95% confidence interval.

5 Chapter 5. The Effect of Experience Corps on Brain Connectivity and Neurocognitive Health in Older Adults (Aim 3)

### 5.1 Introduction

Older adults, over the age of 60, are the largest growing demographic group in the United States (Administration on Aging, 2010). While this statistic represents a triumph of modernity for adding decades to the lifespan, many people view aging with trepidation. In the absence of diseases of the elderly, normal aging is associated with cognitive decline and poor functional connectivity in the brain. However, advancing age also represents a lengthening of life, and an additional potential to contribute to society. This paper presents neurobiological and behavioral changes in older adults who participated over two years in a randomized controlled trial of a senior service volunteer program, Experience Corps (EC). EC places teams of older volunteers in neighboring inner city Baltimore Schools to provide literary, scientific, and behavioral support. EC provides a model to promote cognitive health and to harness older adults' wisdom as a naturally growing resource to benefit the community. This paper evaluated the impact of EC on cognitive outcomes and functional connectivity in the Task Negative Network (TNN) and Task Positive Network (TPN), and suggests a new view of aging as a solution rather than a problem.

### 5.1.1 Cognitive Aging

Declines in cognition found in older adults is known as cognitive aging, and occurs across multiple domains of cognition, including memory, processing speed, language, attention, and executive functions. Characterizing the trajectories of decline in particular domains might offer insight into the mechanisms of pathology. Cross-sectional

studies show that the domains most affected by aging include memory, processing speed, attention, and executive control (Salthouse, 2004). In our longitudinal investigation, we studied the effect of EC on memory and executive functions.

Memory includes both long-term and short-term memory encompassing both verbal and visuospatial abilities and can be characterized into multiple sub-types including, long-term memory include episodic, semantic, procedural, and implicit (Tulving, 1983; Baddeley, 1992.). Each of these subtypes declines linearly with age, beginning in the mid-20s, except semantic memory. In order to study cognitive decline, we included only tests that require episodic and semantic memory.

Executive functions monitor all cognitive operations. Functions in this domain include planning, assembling, coordinating, problem solving, sequencing, strategizing; shifting; inhibiting; and goal-directed behavior (Salthouse *et al.*, 2003). While there is no one-to-one anatomical structure in the brain responsible for executive function, the structures in the brain most implicated are the frontal lobes, particularly the prefrontal cortex. This region of the brain is the last to develop in young adults, as it does not complete myelination until the mid-20's for females and late-20's for males; and the prefrontal cortex is typically the first to deteriorate in older adults (Craik and Bialystok, 2006). This domain is both extremely sensitive to aging and especially important for mental health, as a disruption in this central command system would affect all of the other domains. Recent studies have further supported this chief role of executive functions, and demonstrated that this domain may mediate the effects of age on cognition (Salthouse *et al.*, 2003).

Some investigators argue that because executive functions serve as the control processes for a number of other domains, it is difficult to measure each domain independently, and determine the corresponding trajectories of each with aging (Salthouse, 1996). However, ultimately each of the domains of cognitive functions interacts with another, and the difficulty in measuring the domains separately identifies a limitation of current neuropsychological tests and statistical methods. By developing better methodology, it is possible to differentiate the trajectory of executive functions from the other domains. Carlson *et al.* developed standardized scores for multiple domains, which showed that declines in executive functions precede declines in memory (Carlson *et al.*, 2009).

#### 5.1.2 Aging Brain Networks

Aging is associated with altered functional connectivity between and within each of the TNN and TPN (Eyler, Sherzai, Kaup, & Jeste, 2011; Rajah & D'Esposito, 2005; Ghazes *et al.*, 2012; Biswal *et al*, 2010; Damoiseaux *et al.*, 2008; Andrews-Hanna *et al.*, 2007; Jones *et al.*, 2010). The decoupling hypothesis of functional connectivity posits that the TNN and TPN are negatively correlated, and that each network is positively correlated with itself. While neuroimaging studies provide support for this hypothesis in young healthy populations, emerging studies in the elderly suggest that aging alters this model of network connectivity in complex ways that we have yet to fully understand.

*Intra-TNN connectivity*. Some studies report increased intra-TNN connectivity with age, while other studies report the opposite (Damoiseaux *et al.*, 2008; Andrews-Hanna *et al.*, 2007; Jones *et al.*, 2010; Jones *et al.*, 2011). One common trend reports age-related differences in intra-TNN con nectivity according to the loci of the sub-networks—

advancing age is consistently associated with declines in frontal-occipital sub-networks within the TNN (Wang *et al.*, 2010; Jones *et al.*, 2011; Andrews-Hanna *et al.*, 2007). Furthermore, in studies investigating functional connectivity across the life course, the strength of association within the TNN has served as a marker for brain maturity that follows the trajectory of cognitive aging—in a study of children through young adults of 30 years old, Dosenbach *et al.* found that intra-TNN connectivity parallels the maturation of the brain with a peak in positive connections at age 22, followed by a reduction in connectivity with increasing age (2010). However, others have observed no differences in intra-TNN connectivity throughout adulthood from ages 17-58 years (Bluhm *et al.*, 2008).

In studies restricted to older adults over 60 years old, the majority have shown that aging is associated with a decline in intra-TNN connectivity; however, this trend does not apply homogeneously throughout the TNN. In a study of older adults, Jones *et al.* also found that anterior sub-networks within the TNN exhibit both declines and increases in within-network connectivity (2011). The majority of functional connectivity results come from cross-sectional studies; we performed a longitudinal investigation to help provide a more complete representation of the complex association between functional connectivity and aging.

*Intra-TPN connectivity.* The effect of aging on intra-TPN connectivity also appears to be heterogeneous. There are fewer studies on this topic; however, the consensus from the literature reflects that of intra-TNN connectivity: young adults, compared to older adults, show increased connectivity. Additionally, investigators have also found that the location of the TPN may be different in older adults compared to

younger adults, which makes it difficult to compare functional connectivity in crosssectional samples (Gazes *et al.*, 2012).

Inter-Network connectivity. The relation between the TNN and TPN has been described in detail in Section 4.2.2. Studies demonstrate that in young healthy adults, these networks are anti-correlated (Greicius, et al., 2003; Fox et al., 2005; Seeley, et al., 2007; Vemuri, et al., 2012; Uddin, et al., 2009; Gusnard & Raichle, 2001; Shulman et al., 1997; McKiernan et al., 2003; Mazoyer et al., 2001; Fox et al., 2009). However, in older adults and individuals with mental disorders, the TNN and TPN become less and less decoupled. For example, in individuals with Alzheimer's disease (AD), the TNN and TPN are simultaneously activated, and do not exhibit the classic anti-correlation (Andrews-Hanna et al., 2007; Jones et al., 2011; Lustig et al., 2003; Greicius et al., 2004; Wang et al., 2006; Sorg et al., 2007; Celone et al., 2006; Buckner et al., 2009; He et al., 2007; Gili et al., 2011; Zhang et al, 2010; Bai et al., 2009; Zhou et al., 2010; Damoiseaux et al., 2011; Chen et al., 2011; Supekar et al., 2008; Fleisher et al, 2009; Buckner et al, 2005; Sauer et al., 2006; Seeley et al., 2009). Studies of healthy older adults also show that the TNN and TPN are not decoupled as they are in young healthy adults. Steffener et al. found that in older adults, the TNN remains active in conjunction with the TPN, such that the two networks are actually positively correlated rather than negatively correlated (2012). Steffener *et al.* speculates that the TNN and TPN may operate together in order to enhance performance, as a compensatory mechanism for older adults. These findings are based on cross-sectionals studies of older adults, and the field is lacking in longitudinal studies to better determine the effect of aging on inter-TNN-TPN connectivity.

### 5.1.2.1 Plasticity in Older Adults' Functional Connectivity

While the characterization of brain networks is variable, the pattern of increased intra-network connectivity and decreased inter-network connectivity between the TNN and TPN holds in the majority of studies on young healthy adults, and therefore represents a paradigm of healthy functional connectivity. In Aim 3, we compared how a lifestyle activity intervention impacts the functional connectivity of EC participants relative to Controls. While functional connectivity is a relatively new metric of interest in the fMRI literature, emerging studies show that brain networks are not fixed, and can be modulated by targeted interventions. In a longitudinal study of a language learning intervention, Ghazi *et al* found that after participating in a French learning program, native Persian speakers exhibited decreased functional integration between the language and control networks with increased proficiency in the new language (2013). This decreased connectivity suggests that as the participants become more proficient, they rely less on the control network, and more on the language network for automatic processing, as their language fluidity increases (2013). Ghazi *et al.* observed this trend across the age range of their participants from 26-66 years, indicating plasticity in functional connectivity throughout adulthood into older ages.

Another intervention study exploring brain networks in older adults compared patients with aphasia to healthy controls, averaging 70 years old, before and after a language therapy. In this study, Marcotte *et al.* found that patients with Aphasia exhibited reduced anterior-posterior TNN connectivity, and that after the therapy, this intranetwork connectivity increased (2013). However, TNN connectivity remained stable in the Control subjects (Marcotte *et al*, 2013). This finding illustrates the plasticity of the TNN, in the face of pathology, and its stability in healthy aging, in the absence of

pathology. Longitudinal studies in fMRI are limited, and these emerging findings illustrate that brain networks can be potential targets for intervention.

#### 5.1.3 Generativity in Older Adults

The core principle of the Experience Corps (EC) intervention involves volunteering (Carlson *et al.*, 2008; Fried *et al.*, 2004; Glass *et al.*, 2004; Rebok *et al.*, in press). We posit that generativity may serve as a mechanism through which EC may promote improved functional connectivity and cognitive outcomes. Generativity is defined as caring for and making a difference for others (Erikson, 1950). Studies have shown that the health benefits of volunteering are especially strong in older adults (Piliavin *et al.*, 2007). One reason for the proposed more salient benefit of volunteering in older adults versus younger adults is that in many societies, elders are ostracized and left with limited social networks; volunteering helps to integrate these individuals back into society and give them a meaningful social network (Piliavin *et al.*, 2007). Another reason for the potential benefits of generativity in elders is that at this stage in life, individuals have a life's worth of experiences, and with mortality inevitable, they may be more likely to think about how to share their experiences and leave behind a legacy.

The health benefits of senior volunteer service include lower rates of mortality and disability, as well as higher self-assessments of health and improved cognition (Carlson, 2011; Harris and Thoresen, 2005; Lum *et al.*, 2005; Morrow-Howell *et al.*, 2003). A number of studies have established the benefits of volunteering on physical health and subjective measures of well-being. However, the Brain Health Study is the only study to our knowledge that investigates the associations between senior service and

objective measures of brain function. We explored the effect of generativity on both brain network connectivity and cognitive functions.

### 5.2 Methods

This section details the study sample; the Experience Corps intervention; the measurement of functional connectivity and cognitive outcomes; and the statistical analysis employed.

#### 5.2.1 Study Sample

The data are drawn from the BHS, a study nested within the Baltimore Experience Corps Trial (BECT). Details about study participants at baseline are included elsewhere (Aim 1 and Background). The sample in this analysis included participants at the baseline visit as well as the two follow-up visits at 12-month and 24-month intervals. At each visit, participants underwent an fMRI scan, according to the protocol described in Aim 1, as well as a battery of neurocognitive tests outside of the scanner. For the functional connectivity analysis, the study sample at each visit is described in Table 5.1. There were 90 participants at baseline with usable fMRI data, 85 participants at Follow-Up I, and 67 at Follow-Up II. The study sample for the parallel cognitive functions analysis is described in Table 5.6, which included 123 participants at baseline, 108 at Follow-Up I, and 105 at Follow-Up II. The sample sizes are larger for the analysis of the cognitive functions than for the analysis of the fMRI data because (1) not every participant underwent an fMRI scan; (2) not all the fMRI data were usable, due to scanner artifact and quality issues. For both the fMRI measures and the cognitive test measures, there were no differences in those lost to follow-up and those who were not lost to follow-up in intervention status, sex, race, education, income, or MMSE (p's >0.05).

#### 5.2.2 The Baltimore Experience Corps Trial

*Intervention*. Experience Corps is a community-based model of senior service in which older adults volunteer in public schools to help meet the greatest unmet needs of children, and simultaneously benefit from the act of giving back. This model represents a win-win situation for both the older adult participants who are volunteering, and the school children who are receiving. The program was developed by members of the Johns Hopkins Center on Aging and Health together with Civic Ventures, a think tank on baby boomers' societal issues (Freedman *et al.*, 1999). Establishing community partnerships facilitated implementation of the program. A pilot randomized trial of EC took place in Baltimore in 1999-2001, implemented by the Greater Homewood Community Corporation (GHCC), which also took the lead in implementing the subsequent larger trial, the Baltimore Experience Corps Trial (BECT). This randomized controlled trial of EC took place incrementally in 22 Baltimore city public schools from 2006 – 2011 with funding from the National Institute on Aging.

*Structure*. The EC program requires significant commitment from each volunteer and a critical mass of volunteers in each school. These requirements differentiate EC from other types of volunteering. The significant time commitment amounts to 15 hours per week for the full academic year of September – June, with the option of continuing for a second year. The critical mass places teams of 15-20 volunteers per school to integrate EC into the culture of the school and provide networks of social support for the senior volunteers (Fried *et al.*, 2013). This sustained dose coupled with a strong network helps to promote maximal benefit for both the children and the older adults. The

volunteers served in grades Kindergarten  $-3^{rd}$  grade to fulfill unmet needs. These standardized roles for older volunteers include, providing support in literacy, math, library, and computing skills; promoting behavior management, violence prevention, and school attendance; and enhancing the involvement of parents in school activities (Fried *et al.*, 2004; Rebok *et al.*, 2004).

EC Volunteers. Experience Corps training was conducted by the Greater Homewood Community Corporation (GHCC) and includes a number of components for both the older adult volunteers, and staff from the participating schools including teachers and principals. The senior volunteers training spans a five-day period over one week totaling to 30 hours. This EC standardized volunteer training program includes lectures, discussions, exercises, and other activities designed to orient the older adults to the school; teach skills in working with children; provide an overview of volunteer roles; and promote a sense of community among the volunteers (Fried *et al.*, 2013). After the summer break, returning volunteers also participated in a refresher training session conducted at the beginning of the school year which is designed to review the protocol and remind volunteers of their roles (Fried et al., 2013). Throughout the school year, school-based teams meet bi-weekly to discuss, problem-solve, and continuously refresh training and strengthen community among the teams of volunteers. Additionally, the principal and teacher training programs consist of a 1-hour orientation session that occurs prior to the placement of volunteers in the school. The purpose of these trainings was to explain the EC program; describe the roles of the volunteers; and provide methods for solving problems that may arise (Fried *et al.*, 2013).
*Control*. Participants who were randomized to the Control arm are connected with the Baltimore City Commission on Aging and Retirement Education (CARE), and given the option to serve in ordinary volunteer activities, aside from EC. These types of opportunities do not have the sustained dosage of EC or the comprehensive social network of EC, and instead tend to represent more typical options, such as daylong activities at health fairs or senior events (Fried *et al.*, 2013).

Table 5.1 Flow Chart of fMRI Enrollment



#### 5.2.3 Brain Network Connectivity

Functional connectivity was assessed by first applying the Region of Interest (ROI) method on the preprocessed fMRI brain images to extract the brain networks, followed by a correlation analysis, as described in Section 3.2.6. The ROI method resulted in 6 TNN sub-networks and 6 TPN sub-networks, using 6-mm a priori seeds from Yeo *et al*, as listed in Table 5.2 (2011).

## **Table 5.2 Definitions of Networks**

Task Negative Network (TNN)
A. Prefrontal cortex (PFC)
B. Inferior parietal lobule (IPL)
C. Lateral temporal cortex (LTC)
D. Dorsal medial prefrontal cortex (dMFC)
E. Parahippocampal cortex (PHC)
F. Posterior cingulate/retrospenial cortex (PCC/Rsp)

Task Positive Network (TPN)

- A. Anterior control network
- B. Medial control network
- C. Lateral control network
- D. Dorsal attention network
- E. Premotor Cortex
- F. Superior parietal cortex

The correlation analysis resulted in a 12 x 12 connectivity matrix with the Pearson correlation coefficients between each of sub-network pairs for each participant. The matrix included 15 coefficients of intra-TNN connectivity, 15 coefficients of intra-TPN connectivity, and 24 coefficients of inter-TNN-TPN connectivity. This correlation coefficient represents a measure of functional connectivity, and an identical analysis is carried out at each of the three time points: baseline, follow-up I, and follow-up II. The trajectory of each connectivity score was investigated longitudinally to assess changes in intra-network and inter-network connectivity. Prior to performing the longitudinal analysis on the connectivity scores for each subject, these scores were averaged across subjects, and we present the average connectivity matrix at each time point. This group

level average helps to identify general trends in brain network connectivity from baseline through the two years of follow-up, and help to calibrate expectations for the subsequent longitudinal data analysis.

### 5.2.4 Cognitive Outcomes

The cognitive outcomes measured are described in Section 4.2.3. At each visit participants completed the same battery of behavioral tests to assess changes in the domains of executive function and memory over the two-year time period.

### 5.2.4.1 Executive Function

We developed the executive function (EF) score by normalizing and aggregating two tests that involve psychomotor speed, task switching, attention, mental flexibility, working memory, and processing: the Trail Making Test (TMT) Part B and the Digit Span Test (DST) Backward (Seeley *et al.*, 2007; Groeger *et al.*, 1999; Lezak, 1995). Details are described in Section 4.2.3.1. The normalized score was calibrated such that a higher score indicates better cognitive performance.

### 5.2.4.2 Memory

We developed the memory score by normalizing and aggregating the five trials of the Rey Auditory Verbal Learning Test (RAVLT), which assesses immediate recall and long-term memory (Rey, 1958; Spreen & Straus, 1991). The score was normalized similarly to the EF score such that higher scores represent better performance, as detailed in Section 0.

### 5.2.5 Statistical Methods

We modeled the longitudinal changes in functional connectivity and in cognitive outcomes using generalized estimating equations (GEEs). GEEs allowed us to estimate the parameters of a generalized linear model, factoring in the correlation between the

outcomes. One benefit of using GEEs is that under mild regularity conditions, the parameter estimates remain consistent even if the covariance structure is miss-specified. This quality makes GEEs ideal for addressing questions in functional connectivity and cognitive outcomes, in which little is known about the correlation from one time point to the next. GEEs regression parameters represent population averaged effects, which will provide convenient summaries for the EC and control groups.

All models included the standard covariates: age at baseline, education, and sex, in addition to the variables of interest, intervention status and visit. We chose to model age as a continuous variable because the vast literature on cognitive aging demonstrates that cognitive outcomes decline linearly with age. The models have the following basic structure, as outlined in Equation 1:

$$Y = \beta_0 + \beta_1 I_{EC} + \beta_2 X_{educ} + \beta_3 I_{sex} + \beta_4 X_{age} + \beta_5 X_{visit} + \epsilon \quad (1)$$

The indicators are labeled with an "I," in equation 1. The indicator for EC indicates assignment to EC. The indicator for sex indicates being male. Education, age, and visit are modeled as continuous variables representing years of schooling, years since birth, and year in the study respectively. We selected an exchangeable structure for the covariance matrix. All analyses were performed using an intention-to-treat (ITT) design. We performed the analyses using R (*www.r-project.org/*).

#### 5.2.5.1 Functional Connectivity Models

In the functional connectivity models, the connectivity score served as the outcome. There were 66 connectivity scores, representing intra-TPN, intra-TNN, and inter-network connectivity. Therefore, 66 GEEs were run according to the structure in

equation (1). The goal was to assess the trajectory of functional connectivity over the study period, and to determine how the EC intervention may moderate that trajectory. Therefore, the two variables of interest are the variable for visit and the indicator for EC. First, a main effects model was run for each of the connectivity scores to assess the impact of visit and EC. We noted the P-values for these variables of interest. If these two variables were significant, then we re-ran the model including an interaction term to investigate how the intervention moderates the trajectory of the connectivity score throughout the study period. We present parameter estimates and provide model predictions to illustrate group level trends in functional connectivity.

#### 5.2.5.2 Cognitive Outcome Models

In the cognitive outcome models, the Executive Function (EF) score and Memory score served as the outcome. The remainder of the model maintained the same structure as that in Equation 1. The analytic procedure to investigate the trajectory of EF and Memory also followed the sequence for that of assessing functional connectivity. First, the main effects models were run to determine if visit and EC intervention status were significant, and if so, the corresponding interaction term was incorporated.

## 5.3 Results

In this section, we describe the results from the GEEs for the functional connectivity and cognitive score models respectively. Exploratory data analysis is also provided.

## 5.3.1 The Effect of EC on Brain Connectivity

The association between EC and functional connectivity varied according to the sub-networks selected within each network. The majority of the network pairs exhibited consistent connectivity patterns at each time point, suggesting that the functional

connectivity was not changing over the two-year period. Figure 5.1 shows the average connectivity matrices, across subjects, at each time point. The connectivity matrix is symmetric along the diagonal, with the correlation values displayed as percentages in the lower triangle and corresponding circles representative of the sign and degree of correlation in the upper triangle. For the majority of the sub-network pairs, the averages are remarkably stable over repeated visits. For instance, the average correlation between the inter-network pair (1,12) representing Control A and Default F is -0.21 at Baseline,

-0.23 at Follow-Up I, and -0.21 at Follow-Up II, indicating that the average trajectory of this connectivity score is unchanged. Other sub-network pairs exhibit increases or decreases in connectivity. The intra-network correlation between Default E and Default F, indicated by pair (11,12) in Figure 5.1 increases steadily at each time point—at Baseline, the correlation is 0.41, at Follow-Up I, it is 0.53, and at Follow-Up II, it is 0.57. Other sub-network pairs demonstrate steady declines in connectivity. The inter-network pair (4,11), representing Control D and Default E has an average correlation coefficient of -0.41 at Baseline, -0.43 at Follow-Up I, and -0.46 at Follow-Up II, indicating that these networks become more anti-correlated over the study period. Figure 5.1 provided an average global view of the data, and in order to extrapolate the effect of EC on functional connectivity, we took another look at the data that considers individual trajectories stratified by intervention group.

## Baseline

Follow-Up I

Follow-Up II



#### Figure 5.1 Average Connectivity Patterns

This figure shows the results of the average correlations across at each time point, from left to right: Baseline, Follow-Up I and Follow-Up II. The correlations are calculated using the ROI method, and the averages include 90 participants at Baseline, 85 at Follow-Up I and 69 at Follow-Up II.

Figure 5.2 shows spaghetti plots of select connectivity scores stratified by intervention status and color-coded by sex (red indicates female, and blue indicates male). The plots included in Figure 5.2 represent those scores that exhibited the most significant changes in trajectories over time. The majority of connectivity scores did not exhibit significant changes over time, as suggested by the average connectivity scores shown in Figure 5.1. Therefore, we focused attention on the inter and intra-network correlation coefficients that appear to be most susceptible to longitudinal change. In Figure 5.2, the values of the connectivity scores are jittered to facilitate viewing. The y-axes range from (-1,1) in the plots of connectivity scores V17 and V20; the y-axis for V25 spans the range from (-0.5,1) because these scores are not as widespread as the others. However, overall, each plot exhibits substantial variability both within subject and between subject. The blue line indicates the fitted line along with a transparent gray 95% confidence band, which helps in viewing trends in the data given the large amount of variability. The blue line also helps to view the nature of the connectivity scores over

time. The changes in connectivity are not linear, and exhibit increases followed by decreases, of vice versa over the three time points presented.

The upper left panel of Figure 5.2 shows a select longitudinal intra-TPN connectivity trajectory, V17, as listed in Table 5.2. V17 represents the intra-network correlation between Control B and Control D. Both the EC and Control groups exhibit average negative correlations and demonstrate a gradual decline in connectivity.

The remaining spaghetti plots in Figure 5.2 exhibit select inter-network correlations, V20 and V25, which are described in Table 5.2. The upper right panel shows the trajectory of V20, the inter-network correlation between Control B and Default A. Both the Control and EC groups showed negative connectivity scores for V20 at baseline, and both became more negative over the follow-ups. Lastly, the lower left panel of Figure 5.2, shows the trajectory of V25, representing the connectivity between Control B and Default F. Both the EC and Control groups exhibited increases in V25 connectivity; however the Control group appears to start with a higher connectivity score at baseline. Additionally, the V25 connectivity score increased at a faster rate for the EC group.

## Table 5.3 Listing of select connectivity scores

Connectivity Score	Network Pair	Interpretation
V17	Control B, Control D	Intra TPN: Medial and dorsal control
V20	Default A, Control B	Inter Network: PFC and Medial Control
V25	Default F, Control B	Inter Network: PCC/Rsp and Medial Control



To investigate which connectivity pairs are the most likely targets for intervention, we applied a data-driven approach, which involved running 66 GEE models, as described in equation (1) using the connectivity score as the outcome of each. Figure 5.3 displays the resulting P-values for the coefficients corresponding to visit and EC, respectively. The probabilities have been converted to percentages for display purposes. Smaller circles indicate smaller probabilities, and thus more statistically significant results. The left panel of Figure 5.3 shows the P-Values corresponding with EC. At the 0.05 level, EC achieves significance in 14 of the 66 connectivity scores, indicating that at baseline the EC and control groups are comparable for the majority of the network pairs investigated. The right panel of Figure 5.3 displays the P-Values corresponding with visit. At the significance level of 0.05, five coefficients for visit are statistically significant, indicating that on average the majority of the network pairs do not change significantly over the study period.

Main Effects Models. In order to study how EC moderates functional connectivity over time, we selected the connectivity scores that exhibited the largest statistical differences from one visit to the next, and those that exhibited the largest differences between the EC and control groups. Using a P-Value threshold of 0.05 yielded three common connectivity scores with both significant coefficients for EC and for visit: V17, V20, and V25, which are displayed in Figure 5.3. The results from the main effects models for these connectivity scores are exhibited in Table 5.4. The coefficient estimates confirmed the trends inferred from the spaghetti plots in Figure 5.2. The coefficient for visit was negative for V17 and V20, indicating that on average there was a longitudinal reduction in connectivity between the network pairs that each of these scores represents. The coefficient for visit was positive for V25, indicating that on average, the connectivity between Control B and Default F increased over the study period. The EC coefficients also confirm the trends from the exploratory data analysis: although all of these estimates

hover close to one tenth of zero, the value is positive in V17, and V20, and it is negative in V25.

1	•	•					•				
3	2	•		•					•		
5	5	3	•	•		-			•		
46	0	4	4								
97	4	5	52	5							
38	81	28	36	23	6						
62	1	2	20	73	81	7					
	27	15	13		9	48	8				
46	32	93	19	40	55	60	26	9			
13	2	7	4	63	12	39	6	26	10		•
60	21	88	38	11	49	52	88	44	32	11	
21	0	2	6	74	94	18	7	16			12

## **EC P-Values**

Visit P-Values

# Figure 5.3 Summary of GEE P-values

This figure shows the P-values from the main effects GEE models corresponding with the Experience Corps (EC) variable on the left, and those corresponding to the Visit variable on the right. The P-values are probabilities ranging from 0-1, and have been converted to percentages for presentation purposes. The lower triangle of each image indicates the value and the upper diagonal indicates a graphic representation, in which the larger the circle, the closer the probability is to 1.

	V17 Estimate	Robust S.E.	P-Value			
Intercept	-0.734	0.305	0.016			
Visit	-0.058	0.029	0.050			
EC	0.156	0.046	0.0006			
	V20	Robust		V25	Robust	
	V20 Estimate	Robust S.E.	P-Value	V25 Estimate	Robust S.E.	P-Value
Intercept	<b>V20</b> Estimate -0.654	Robust S.E. 0.287	P-Value 0.023	V25 Estimate 0.847	Robust S.E. 0.196	P-Value 1.55E-05
Intercept Visit	<b>V20</b> Estimate -0.654 -0.074	Robust S.E. 0.287 0.027	P-Value 0.023 0.007	V25 Estimate 0.847 0.042	Robust S.E. 0.196 0.019	P-Value 1.55E-05 0.025
Intercept Visit EC	<b>V20</b> Estimate -0.654 -0.074 0.111	Robust S.E. 0.287 0.027 0.043	P-Value 0.023 0.007 0.011	V25 Estimate 0.847 0.042 -0.121	Robust S.E. 0.196 0.019 0.032	P-Value 1.55E-05 0.025 0.0001

## **Table 5.4 Main Effect Model GEEs**

This Table shows the results of the GEE regression on the indicated Connectivity Score adjusting for Visit, Intervention Status, Age, Sex, and Education. The top left panel shows the regression results for the Connectivity Score V17, and the lower panels from left to right show the results for V20 and V25, respectively. These connectivity scores each have significant visit and EC intervention coefficients at the Pvalue = 0.05.

	V17	Robust	D. V. I			
	Estimate	S.E.	P-Value			
Intercept	-0.726	0.310	0.019*			
Visit	-0.063	0.042	0.137			
EC	0.135	0.121	0.267			
Visit*EC	0.011	0.058	0.851			
	V20	Robust		V25	Robust	
	V20 Estimate	Robust S.E.	P-Value	V25 Estimate	Robust S.E.	P-Value
Intercept	<b>V20</b> Estimate -0.647	Robust S.E. 0.288	P-Value 0.025*	V25 Estimate 0.882	Robust S.E. 0.195	P-Value 6.12E-06*
Intercept Visit	<b>V20</b> Estimate -0.647 -0.078	Robust S.E. 0.288 0.039	P-Value 0.025* 0.044*	V25 Estimate 0.882 0.019	Robust S.E. 0.195 0.025	P-Value 6.12E-06* 0.448
Intercept Visit EC	<b>V20</b> Estimate -0.647 -0.078 0.095	Robust S.E. 0.288 0.039 0.115	P-Value 0.025* 0.044* 0.407	V25 Estimate 0.882 0.019 -0.205	Robust S.E. 0.195 0.025 0.083	P-Value 6.12E-06* 0.448 0.013*
Intercept Visit EC Visit*EC	<b>V20</b> Estimate -0.647 -0.078 0.095 0.008	Robust S.E. 0.288 0.039 0.115 0.054	P-Value 0.025* 0.044* 0.407 0.877	V25 Estimate 0.882 0.019 -0.205 0.043	Robust S.E. 0.195 0.025 0.083 0.038	P-Value 6.12E-06* 0.448 0.013* 0.247

**Table 5.5 Interaction Model GEEs** 

This Table shows the GEE regression results of the models above, with the addition of an interaction term between Visit and the EC Intervention Status for the connectivity scores V17, V20, and V25. Coefficients that achieve significance at the 0.05 level are marked with an asterisk, \*. All models included the covariates age, education, and sex.

Interaction Models of EC vs. Control by Follow-Up. The main effects models were important for establishing which connectivity scores are subject to change over the study period, and the most sensitive to the intervention. However, interaction models were required to investigate how EC moderates the trajectory of change. Table 5.5 presents the interaction models. The interaction term coefficient estimate, Visit\*EC, was positive in all of the models, including both the intra and inter-network connectivity models. However, this term did not attain statistical significance in any of the models. The coefficient associated with visit maintained its statistical significance in the internetwork connectivity models, V20, and it did not achieve statistical significance in the other models.



**Figure 5.4 Predicted Trajectories from Interaction Model** 

This figure shows the predicted values of connectivity scores for V17, V20, and V25, based on the interaction models for an individual with the average age of 67.39 years and education level of 14.2 years. The dashed line represents the expected trajectories for the Experience Corps (EC) group, and the solid line represents the trajectories for the Control Group. The estimated trajectories for males and females are also indicated separately in blue and red, respectively.

Graphic displays of the parameter estimates from Table 5.5 for predicted group level data are displayed in Figure 5.4. The dashed line indicates the estimated trajectory for the EC group and the solid line indicates the corresponding trajectory of functional connectivity for the Control Group, for an individual with the average age of 67.39 years and education level of 14.2 years. The estimated trajectories for males and females are also indicated separately in blue and red, respectively. In the Intra-TPN connectivity model of V17, between Control B and Control D, both the EC and control groups exhibit longitudinal declines with similar slopes. The two inter-network connectivity models also exhibit opposite trends: in V20, the connectivity decreased for both the EC and Control groups, while for V25, the connectivity increased longitudinally for both groups. In V25, the slope is larger for the EC group compared to the control group, indicating a faster increase in connectivity.

### 5.3.2 The Effect of EC on Cognitive Outcomes

This section describes the results of performance on the cognitive tests administered outside of the scanner. Table 5.6 provides tabulations of the sample size at each time point.

### **Table 5.6 Tabulations by Visit**

Visit	Experience Corps N	Control N	Total N
Baseline	65	58	123
Follow-Up I	57	51	108
Follow-Up II	56	49	105

Table 5.7 provides summaries of performance on the neuropsychological tests that are used for the formation of the Executive Function (EF) and Memory Scores. This table .indicates performance on the test, prior to normalization of the data. The unit of each test is also listed. T-tests were performed to detect differences between performance for the EC and Control groups at each time point, and to assess whether there are overall longitudinal differences in the data. The EC group performed significantly better than the Control group in DST Forward and in TMT Part A at Follow-Up II; however both of these tests were conducted for calibration purposes and are not factored into the calculation for the EF score. TMT Part B, a component of the EF score, was significantly different for the EC and Control groups at Follow-Up II with averages of 99.09  $\pm$  57.96 seconds and 146.06  $\pm$  77.560 seconds, respectively. In the memory tests, there were no significant differences between the EC and Control groups. Overall, the means exhibited increases from Baseline –2-year Follow-Up in each of the memory tests, indicating improvement.

The parallel summary statistics for the EF and Memory scores are provided in Table 5.7. For the EF score, the EC participants demonstrated improved performance at Follow-Up II, with a score of  $0.27 \pm 0.79$  compared with the Control group, which has an average EF score of  $-0.20 \pm 0.86$ . Consistent with the component-wise results, the memory score is not statistically different for the EC and Control Groups, while it does increase longitudinally across the two groups. The normalized and aggregated cognitive scores summarized in Table 5.7 serve as the outcomes of interest in the GEE models.

Score	Formulation	Visit	Experience Corps	Control	Total
Executive	Digit Span	Baseline	$0.01\pm0.85$	$-0.11 \pm 0.84$	$-0.05 \pm 0.84$
Function	Backwards & (-1)*Trails B	Follow Up I	$0.09\pm0.83$	$\textbf{-}0.08\pm0.87$	$0.01\pm0.85$
		Follow Up II	$0.27\pm0.79\texttt{*}$	$-0.20 \pm 0.86*$	$0.05\pm0.85$
Memory	RAVLT learn, short delay, &	Baseline	$-0.23 \pm 0.87$	$-0.26 \pm 0.81$	$-0.25 \pm 0.84^{+1}$
		Follow Up I	$0.11\pm0.88$	$-0.11 \pm 0.77$	$0.0 \pm 0.83^{+1}$
	long delay	Follow Up II	$0.40\pm0.97$	$0.17 \pm 1.13$	$0.29 \pm 1.05^{+1}$

Table 5.7 Memory and Executive Function Scores (Mean ± SD)

\*Significant difference between the intervention and control at the  $\alpha = 0.05$  level.

<sup>1</sup> Significant difference between the indicated time points.

The longitudinal trajectories of the EF and Memory scores are displayed in Figure 5.5. As suggested in the summary statistics from Table 5.7, the executive function score, in the right panel of Figure 5.5, appears to increase more over the study period for the EC intervention group than for the control group. The memory score, exhibited on the right panel of Figure 5.5, increased for both the EC and Control groups. The spaghetti plots are color-coded by sex, although it is difficult to observe sex-specific trends due to the large amount of variability in the performance of both males and females.



**Figure 5.5 Trajectories of Cognitive Outcomes** 

This figure exhibits the longitudinal trajectories of the Executive Function (EF) and Memory scores, stratified by the Experience Corps (EC) and Control groups. Women are indicated in red and men in blue.

The results of the GEEs are exhibited in Table 5.8 for the EF and Memory Score models. The coefficient corresponding with EC is not significant in either model. In the EF model, the two significant predictors were age and education. As expected, increasing age was negatively associated with the EF score, and increasing education was positively associated with the EF score.

The right panel of Table 5.8 exhibits the results of the memory model. The significant predictors of performance were visit, sex (indicator for male), and education. Visit is positively associated with performance; being male was negatively associated with performance; and lastly, education was positively associated with the memory score.

	EF	Robust		Mem		
	Estimate	S.E.	P-Value	Estimate	Robust S.E.	P-Value
Intercept	0.088	0.773	0.910	-0.477	0.829	0.565
Visit	0.015	0.025	0.549	0.232	0.036	1.04E-10*
EC	0.112	0.138	0.386	0.023	0.140	0.872
Sex	-0.236	0.156	0.130	-0.487	0.156	0.002*
Age	-0.021	0.012	0.073*	-0.018	0.011	0.119
Education	0.089	0.021	0.00002*	0.094	0.019	1.20E-06*
Correlation	0.815			0.686		

**Table 5.8 GEEs with Cognitive Outcomes** 

\*Indicates significance at the 0.05 level.

The left panel of this Table shows the results of the GEE regression on the Executive Function Score, adjusting for visit, intervention status, sex, age, and education. The right panel shows the results for the parallel analysis on the Memory Score.

The interaction models were not run for cognitive outcomes since visit and EC are not significant together in either model.

### 5.4 Discussion

The results demonstrated that the longitudinal trends in functional connectivity and cognitive functions in older adults from the BHS are complex. The majority of subnetwork pairs exhibited robustness in connectivity, remaining stable throughout the twoyear study period, which yielded null results in our attempt to observe interventionrelated change over time. The sub-network pairs that changed longitudinally did not do so in predictable ways, and the ways in which they were moderated by the intervention were subtle. Similarly, the cognitive results tell a story more complex than the literature would suggest. Rather than observing cognitive declines in each domain, the Executive Function (EF) score on average remained the same, while the Memory score improved. The effects of the EC intervention on performance on the neuropsychological tests appear subtle. The following subsections synthesize these findings.

#### 5.4.1 Brain Connectivity

The subset of connectivity scores that exhibited significant changes over time and significant associations with the intervention are listed in Table 5.3. The literature suggests that for intra-networks, the correlation should be high, and that a loss of correlation is associated with aging or pathology. The connectivity score V17 represents the intra-network connectivity measure that achieves significance in the main effects models. The differences between the EC and Control groups did not achieve statistical significance, and the graphical trends from both the model results in Figure 5.4 and the spaghetti plot of the data in Figure 5.2 confirmed this result, showing that the intranetwork connectivity of V4 declined at the same rate for both the Control and EC groups. The result for V17 showed that the connectivity scores between the medial and dorsal regions of the TPN decreased for both the EC and Control groups. Both showed declines in connectivity that are close to parallel. In the main effects model, this loss in intranetwork connectivity from one visit to the next is statistically significant (P-Value = (0.050), as detailed in Table 5.4, suggesting that the correlations between these two networks are on average decreasing. This decline in intra-TPN connectivity could be due to aging.

Inter-network, the literature suggests that negative correlations between the TNN and TPN represent healthier functional connectivity. V20, representing the inter-network connectivity between the PFC and Medial Control Networks, exhibited a decline in connectivity, as expected, illustrated in the lower left panel of Figure 5.4. Both the EC and Control groups exhibited this trend at similar rates. V25, the inter-network connectivity score representing the correlations between the PCC/Rsp and the Medial Control Network is illustrated in the lower left panel of Figure 5.4. This inter-network

connectivity score increased longitudinally for both the EC and control groups. The increase in V25 connectivity was steeper for the EC group than in the Control group. This increase in positive correlations for the EC group is contrary to what we expect, given that the literature suggests that the TNN and TPN are anti-correlated in young healthy adults. However, in older adults, this relation is not the same as that in younger populations, and other studies have also observed positive correlations between internetwork TNN and TPN pairs (Steffener *et al.*, 2012). It may be that the connectivity between the PCC/Rsp and Medial Control Network increases as a compensatory mechanism as suggested by Steffener *et al* (2012). In this case, an increase in connectivity is neuro-protective, and EC may confer improved functional connectivity.

Figure 5.4 also shows differences between the intervention and Control groups at baseline. This difference was only observed in functional connectivity, and not in cognitive performance at baseline. The randomized controlled trial design should mitigate concerns about selection bias.

### 5.4.2 Cognitive Outcomes

The results of the Executive Function (EF) and Memory models are listed in Table 5.8, and the data are displayed in Figure 5.5. Although EC was not significantly associated with improved performance on the neuropsychological tests, the longitudinal trajectories displayed in Figure 5.5 show beneficial trajectories for the EC group compared to the Control group. For both EF and Memory, the differences between Baseline and Follow-Up I were modest; and the larger differences were seen at Follow-Up II. In fact, when cross-sectionally comparing the EF score of EC and Control

Participants at Follow-Up II, the EC group performed better at a level that achieves statistical significance. In order to detect this trend longitudinally in the GEE model, additional follow-up visits may be necessary.

The EF score and Memory score trajectories exhibited qualitatively different patterns. The EF score improved for the EC group and remained stable for the Control group, while the Memory score improved for both groups. The longitudinal increase in the Memory score may represent practice effects. During each visit, the participants learn the same words on the RAVLT, and may begin to commit the words to their long-term memory. Therefore, perhaps, memory is not an ideal target domain in studies of cognitive aging. The domain of executive function appears more sensitive and reliable to study because it is less susceptible to practice effects.

Although the memory score is susceptible to practice effects, if the EC intervention were to be associated with improvements in memory, the increase would be steeper for the EC group compared to the control group. However the trajectories are both qualitatively similar and not statistically different. Perhaps the memory score is less prone to change than the EF score as a result of EC because memory is not an explicit target of intervention for Experience Corps. While the senior volunteers surely used working memory in the classroom, the nature of their tasks changed daily, requiring higher executive functions to plan, task-switch, and make decisions on the spot. Therefore, in light of the nature of the intervention, it makes sense that the EF score is more sensitive to exhibit intervention-related changes. An additional follow-up measure could confirm this trend, and the sensitivity of EF over Memory as a target domain for this intervention.

The GEE results in Table 5.8 confirm what studies in cognitive aging have repeatedly shown: increased age is associated with cognitive decline while education is associated with improved cognitive outcomes. This result is statistically significant for both the EF and Memory scores. It is helpful to view this result as a validation of our study design and methods. For practical applications, however, these results cannot help an older adult today. Since time moves only forward, it is not helpful for one who has already attained old age to find that the education that one acquired from childhood through early adulthood is protective against cognitive decline. However, this is one of the most consistent findings in the cognitive aging literature, so it would be wise to promote education for all youth and young adults as a public health intervention to preserve cognition in later life.

## 5.4.3 Men vs. Women

The longitudinal stability in the functional connectivity findings existed throughout the BHS population, including in both men and women. Exploratory data analysis exhibited few differences in the functional connectivity between men and women. Figure 5.6 shows the longitudinal trajectories of the intra-network connectivity score, V17, and the inter-network connectivity score, V25, stratified by sex with women on the left and men on the right of each plot. The intra-network connectivity score displayed decreases for both men and women, although one can observe differences in the trajectories. While V17 increased and then decreased for women, from Follow-Up I to Follow-Up II, for men, it decreased, and then remained stable. Another follow-up measurement would help to determine if both trajectories would continue along the same trajectory of gradual decline. The inter-network connectivity score, V25, on the right panel of Figure 5.6, increased for both men and women, with both exhibiting approximately parallel trajectories. In the formal models that we conducted, Figure 5.4, also showed that the functional connectivity trajectories of both men and women is similar, and sex was not statistically significant. The robustness of functional connectivity within sub-groups of the study sample provided further support for the findings in the overall sample.

### Figure 5.6 Functional Connectivity Stratified by Sex

This figure shows longitudinal functional connectivity trajectories stratified by sex, with women on the left and men on the right of each plots. The left panel represents the intra-network connectivity score, V17 and the right panel represents the inter-network connectivity score, V25.



### 5.4.4 The Overall EC Effect

While the longitudinal differences between the EC and control groups were modest, and in most cases not statistically significant, the overall trends showed that in both the brain and cognitive measures, EC was associated with maintenance of or improved outcomes. EC was associated with decreased inter-network connectivity for V20, which supports the literature that links higher intra-network connectivity and lower inter-network connectivity with better brain health. On the other hand, EC was also associated with increased inter-network connectivity for V25, which could serve as a compensatory mechanism for the aging brain (Steffener *et al*, 2012). In the behavioral results, EC appears to have no impact on memory, although it was associated with better cognitive performance for executive function at Follow-Up II.

### 5.4.5 Strengths & Limitations

## 5.4.5.1 Strengths

The longitudinal study design of the Brain Health Study represents a key strength of this investigation. The cognitive performance and fMRI brain image data are collected at each time point. This longitudinal study design makes it possible to investigate changes in brain structure and function over a period of two years. Few studies have explored the longitudinal trajectories of functional activity, making these fMRI data novel.

The pool of participants included in the BHS data also distinguishes this investigation. While most fMRI studies of older adults consist of white, highly educated, and upper-middle class individuals, this sample consisted primarily of black, variably educated, and lower income individuals. This sample represents an under-served target population, the at-risk community- dwelling older urban denizen. Results therefore have major implications for this socio-demographically vulnerable group of individuals.

Lastly, the novel functional connectivity analysis was conducted within a randomized intervention trial. Therefore, the results grouped by intervention status help to illuminate mechanisms through which the intervention impacted brain connectivity. Differences between the volunteer group and the low-activity control group in functional connectivity and in cognitive outcomes help to suggest brain pathways and cognitive domains through which the intervention is acting. These results help to inform future preventative recommendations to preserve healthy brain network function and cognition.

### 5.4.5.2 Limitations

There are a number of limitations in this investigation that may have impeded our ability to detect differences between the intervention and control groups. While the behavioral measurement for executive function appeared sensitive to change, the memory score was highly susceptible to practice effects. This score is based on the RAVLT, in which participants are aurally presented with the same set of 15 words in each visit, which lends itself well to long-term memory storage. A more sensitive memory test may present a different set of words in each session. This strategy would reduce practice effects, although it would break from the standard in the field, which is to use the RAVLT as it is.

The biological measure of interest in the brain that we used, functional connectivity scores, remained stable throughout the study period. This lack of change impeded our ability to investigate the effect of an intervention on longitudinal change trajectories. Therefore, perhaps it would be valuable to investigate a different fMRI marker that may exhibit larger changes, such as brain activity in response to a task or brain volume. The fMRI marker that we selected is more complex than usual measures because each score involves a pair of regions, and represents the interactions between networks. Nevertheless, the fact that the complex measures that we used exhibited a lack of change demonstrated that these connectivity scores are robust. The fMRI world suffers from a lack of reliability and consistency due to the tremendous amount of noise relative to the signal. Therefore, the functional connectivity scores that we developed posit a reliable metric for use in future studies. Furthermore, although it is not what we had intended to find, the fact that the functional connectivity scores remained unchanging over a two- year period provided a result that is biologically interesting, and methodologically useful.

Another limitation that makes it difficult to detect differences may be that the intervention acted on a number of pathways, and the selected targets, the TNN and TPN are among the most generally represented in the brain. Unlike a language task that acts on the language network, the EC intervention is multi-modal, and in this study we sought to determine the ways in which it acts on networks that modulate the activity of the entire brain. While this question is more difficult to answer, it may be more reflective of the integrationist nature of brain network function. Also, while it may be more difficult to deconstruct the mechanisms of action of a multi-modal intervention like EC, the multiple modalities through which this intervention works is also more reflective of the complexities of brain network activity. Perhaps generativity exists not just in one place in the brain, but throughout multiple networks. This investigation lays the foundation for measuring the effect of a highly complex multi-modal program on the health of brain networks, a collection of regions working together and modulating each other in ways

that are even more highly complex than a manmade program. In asking big questions, we lay the groundwork to help answer them.

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Neuropsych Exam	Unit	Visit	Experience Corps	Control	Total
Digit Span	# correct	Baseline	8 ± 1.72	$7.45 \pm 1.7$	$7.74 \pm 1.72$
(Forward)		Follow-Up I	$7.58 \pm 2$	$7.11 \pm 2.09$	$7.36\pm2.05$
		Follow-Up II	$8.2 \pm 2.15^{*}$	$7.25 \pm 1.79*$	$7.76\pm2.04$
Digit Span	# correct	Baseline	5.39 ± 2.35	4.86 ± 2.31	$5.14 \pm 2.34$
(Backward)		Follow-Up I	$5.19 \pm 2.61$	$5 \pm 2.27$	$5.1 \pm 2.45$
		Follow-Up II	$5.58 \pm 2.64$	$4.91 \pm 2.09$	$5.27 \pm 2.41$
Trail Making A	Time in seconds	Baseline	45.89 ± 15.66	44.94 ± 15.71	$45.44 \pm 15.63^{11}$
		Follow-Up I	$39.95 \pm 14.24$	$40.88 \pm 15.66$	$40.38 \pm 14.84^{t}$
		Follow-Up II	38.61 ± 12.07*	46.56 ± 22.57*	42.33 ± 18.22
Trail Making B	Time in seconds	Baseline	131.34 ± 76.82	$132.31 \pm 73$	131.8 ± 74.72
		Follow-Up I	114.73 ± 61.06	131.69 ± 76.61	122.53 ± 68.82
		Follow-Up II	99.09 ± 57.96*	146.06 ± 77.56*	121.08 ± 71.46
RAVLT	# Correct	Baseline	39.12 ± 7.74	39.34 ± 7.65	$39.23 \pm 7.67$
(learn)		Follow-Up I	$41.69 \pm 8.14$	$39.62\pm7.27$	$40.7 \pm 7.77^{11}$
		Follow-Up II	$44.82\pm8.62$	$42.49 \pm 9.63$	$43.7 \pm 9.15^{+1}$
RAVLT	# correct	Baseline	$4.42 \pm 1.48$	$4.53 \pm 1.51$	4.47 ± 1.49
(Interference)		Follow-Up I	$4 \pm 1.57$	$4.22 \pm 1.43$	$4.11 \pm 1.5^{+1}$
		Follow-Up II	$4.82 \pm 1.52$	$4.44 \pm 1.66$	$4.64 \pm 1.59^{11}$
RAVLT (Short Delay)	# correct	Baseline	6.74 ± 2.93	6.5 ± 2.61	$6.63 \pm 2.77^{+}$
		Follow-Up I	$7.98 \pm 2.7$	$7.2 \pm 2.38$	$7.61 \pm 2.57^{+1}$
		Follow-Up II	$8.51 \pm 2.94$	$8.07\pm3.36$	$8.3 \pm 3.14$
RAVLT (Long Delay)	# correct	Baseline	6.54 ± 2.97	6.38 ± 2.73	$6.46 \pm 2.85^{++}$
		Follow-Up I	$7.41 \pm 2.69$	$7.07\pm2.63$	$7.25 \pm 2.65^{+1}$
		Follow-Up II	$8.12 \pm 3.22$	$7.98 \pm 3.33$	$8.05\pm3.26$

5.6 Appendix Table 5.9 Behavioral Data for Intervention and Control Groups (Mean ± SD)

\*Significant difference between the intervention and control at the  $\alpha = 0.05$  level.

<sup>1</sup> Significant difference between the indicated time points.

6 Chapter 6. Conclusions

### 6.1 Summaries

We have conducted a rigorous investigation of two fundamental networks in the brain: the Task Positive Network (TPN) and Task Negative Network (TNN). In Aim 1, we found that, compared to the literature based on young healthy adults, the TPN and TNN exhibit similar patterns of functional intra-network connectivity, and differences in inter-network connectivity, suggesting biological changes with aging. We then took the functional connectivity scores that we developed in Aim 1, and investigated the association between this score and dementia-linked cognitive functions in Aim 2. We found important associations that both confirmed and challenged our hypotheses. Lastly, in Aim 3, we studied the one-year longitudinal intervention effect on these associations. We quantified the ways in which Experience Corps may affect both functional connectivity and cognitive functions. In this investigation, each aim built upon the next, and together, they helped to develop a more comprehensive understanding of functional connectivity in older adults, its relations to cognitive functions, and how these outcomes can be modified by a lifestyle-based intervention of senior service. Details for the specific aims are summarized below and related to the original hypotheses, as stated in Chapter 1.

#### 6.1.1 Aim 1. Functional Connectivity

In Aim 1, we assessed functional connectivity between and within each of the Task Positive (TPN) and Task Negative Networks (TNN) in the brain images of Brain Health Study participants using three methods:

 The Region of Interest (ROI) Method, an approach that defines the networks based on a priori seeds.

- 2. Independent Component Analysis (ICA), a method that searches for the networks using the data.
- 3. Seed Analysis, an approach that uses a priori seeds and searches across the whole brain for correlations and anti-correlations.

In the ROI results, each network showed substantial intra-network functional connectivity, supporting the hypothesis that each network ought to be highly connected with itself. The connectivity inter-network included both positive and negative correlations; the negative correlations support the decoupling hypothesis and the positive correlations challenge our hypothesis.

In the ICA results, the TPN was highly correlated with itself while the TNN was less correlated with itself, providing overall support for the hypothesis for intra-network connectivity. Inter-network ICA results exhibited both positive and negative correlations, as in the ROI method results.

Results of the seed analysis showed that each network was correlated with itself, supporting the hypothesis for intra-network connectivity. However, no anti-correlations between the TNN and TPN survived the P-value threshold, which challenges the hypothesis that these networks should be negatively correlated.

Across all methods, *intra*-network pairs exhibited high functional connectivity with one another. This result is especially robust within the TPN, and it is more variable in the TNN. *Inter*-network, functional connectivity manifested itself as both positive and negative correlations between the TNN and TPN using both ROI and ICA methods. The seed analysis yielded no anti-correlations between the networks.

### 6.1.2 Aim 2. The Brain-Behavior Link

Aim 2 investigated the baseline relationship between inter and intra-network functional connectivity and cognitive functions. The cognitive functions were selected due to their relevance to independent functions and dementia risk: memory and executive functions. To assess each cognitive domain of interest, we developed standardized cognitive outcome scores. The Memory Score consists of an aggregate of performance on the Rey Auditory Verbal Learning Test, and the Executive Function Score consists of a normalized aggregate of the Trail Making Test, Part B and the Digit Span Test, Backwards, in which higher scores indicate better performance.

We ran linear models to test the associations between functional connectivity and cognitive scores. In the *inter*-network models, we found that the majority of functional connectivity scores that survive the significance threshold (p = 0.05) are inversely correlated with cognitive scores. These results support the hypothesis that inter-network connectivity ought to be inversely correlated with cognitive functions. In the *intra*-network models, we found primarily positive associations between connectivity scores and cognitive outcomes, as expected. However, none of the connectivity score coefficients survived the significance threshold (p = 0.05). Nevertheless, the nature of this result supports the hypothesis that intra-network connectivity is positively associated with cognitive functions.

When comparing the brain-behavior results by cognitive domain, we found that the memory and executive function outcomes were associated differently with functional connectivity. In the inter-network connectivity model with memory, both positive and negative connectivity score coefficients achieved significance. However, in the inter-

network model with executive function as an outcome, the only connectivity score coefficient that achieved significance is negative. In both cases, the inter-network models were more strongly associated with cognitive functions than the intra-network models. These results suggest that functional connectivity between networks may have a more important role in cognitive functions than intra-network connectivity, and therefore represent better markers of cognitive aging in the brain.

### 6.1.3 Aim 3. The effect of Experience Corps

In Aim 3, we investigated the effect of Experience Corps (EC) on the longitudinal trajectory of (1) inter and intra TNN and TPN functional connectivity patterns; and (2) cognitive functions in the domains of memory and executive functions, for baseline and two follow-up visits. The longitudinal trajectories capture annual changes over a two-year period, and we investigated the effects of aging, and how EC moderates aging.

### 6.1.3.1 Functional Connectivity

Over the two-year study period, the connectivity between the majority of network pairs remains stable, neither increasing nor decreasing. Of the connectivity scores that do change, some exhibit age-associated deterioration in the expected direction (increased inter-network correlation and decreased intra-network correlation). In these cases, the intervention effect does not achieve statistical significance in the models with an interaction term.

#### 6.1.3.2 Cognitive Functions

The longitudinal trajectories of cognitive functions differed. The memory score improved over the two-year study period for both the EC and control groups. The executive function score stayed constant for the control group, and further improved for the EC group. While this result was statistically significant at Follow-Up II, using cross-sectional

T-tests, the longitudinal modeling using GEEs did not detect statistically significant differences between the EC and control groups in executive function.

#### 6.2 6.2 Connections

In this section, we draw connections from each of the three aims, and relate them to neurologic mechanisms, making inferences beyond the hypotheses.

## 6.2.1 Functional Connectivity

The data demonstrated that while each network is correlated with itself, as expected, the two networks are not homogenously anti-correlated. This lack of uniform negative correlations between the TNN and TPN shows that in older adults, these networks are not anti-correlated, as they are in younger adults. These results provide biological insight into the functional connectivity of the aging brain.

In addition to the biological conclusions from Aim 1, our results also provide methodological contributions. The concordance of findings across methodology provides further evidence in support of the biological finding, and demonstrates that the different methods help to answer the same question. Because the ROI method is the simplest and the easiest to standardize across studies, this approach is used in the investigations for Aims 2 and 3.

#### 6.2.2 Functional Connectivity and Cognitive Functions

The models linking functional connectivity and dementia-linked cognitive functions provide support for the integrationist model of brain function and help to suggest which domains would serve as more sensitive targets of intervention. The internetwork models better explained the variability in the data and exhibited more statistically significant results, which supports the integrationist model of brain function.

The intra-network models include either only the TNN or only the TPN and the activities of each with itself, which restricts the regions being investigated to a more localized model of brain function. The activities of the two networks with each other provide a more global measure that takes into account how the divergent networks modulate one another.

The brain-behavior models between functional connectivity and memory produce heterogeneous results compared to the models with executive function scores as an outcome. The heterogeneity in the memory models may be due to the fact that memory utilizes regions in the brain from both the TNN and the TPN. Executive function, on the other hand, requires the TPN in the absence of the TNN. The positive and negative coefficients for the connectivity scores in the inter-network model for memory reflects this biology. This result also suggests that executive function would be a more sensitive domain to target.

### 6.2.3 Experience Corps and Functional Connectivity

The longitudinal changes in functional connectivity are subtle for most network pairs. EC appeared neuro-protective for particular inter-network and intra-network connectivity scores of interest. However, the heterogeneity in the overall results suggests that it is difficult to measure the neuro-protective benefit of the intervention using global measures of brain connectivity. Since the overall connectivity scores remained stable over the follow-up period, it may be that there was not enough variability in the data to detect statistically significant differences between the EC and control groups. Nevertheless, the lack of change also represents a methodological advantage: the functional connectivity scores are a stable measure with minimal noise, which can be used to evaluate changes in brain function.

### 6.2.4 Experience Corps and Cognitive Function

The analysis on the longitudinal effects of EC on cognitive functions demonstrated differences between the executive function and memory domains. While executive function improvements were detected in the EC group compared with the control group at Follow-Up II; the memory score improves for both groups similarly. Therefore, this analysis provides further support that executive function may be the more sensitive domain to target for interventions.

#### 6.2.5 Strengths and Limitations

Attributes of the study design, intervention, and methods used in the analysis carry both strengths and limitations. We discuss these attributes below.

A methodological choice that we made is to use the results from the ROI analysis from Aim 1 to answer the questions posed in Aims 2 and 3. We used the ROI results to relate functional connectivity with cognitive functions, and to investigate the longitudinal intervention effect, in order to keep the method simple. As the conceptual problem became more complex, and we sought to answer more challenging questions, using a simple methodology provides a source of strength. The ROI methodology relies on a priori seeds from the literature, and this reliance on previously validated studies allows us to place our novel results answering new questions in the landscape of what has already been discovered. The ROI methodology is also the easiest to standardize, which would help to make our results more generalizable. However, using this method for Aims 2 and 3 also presents potential trade-offs. The ROI method depends on seeds from the literature, which were developed on populations of young healthy adults, and therefore may not be appropriate for the BHS sample of older adults. The ICA method is datadriven, and therefore can be better calibrated for our sample, which would present a strength over the ROI method. However, because ICA is data-driven, it would be more difficult to standardize the results. Therefore, ultimately, the ROI method represented a sound methodological decision for our analyses. However, to improve the ROI method, seeds should be developed that are based on populations of older adults rather than relying on young healthy adults as the standard.

The entire fMRI investigation utilized a standard preprocessing protocol that researchers originally developed using samples of young healthy adults. The normalization step involves warping the brains onto a standard MNI template, which is larger than the brain images from the BHS sample and its ventricles are smaller. Warping the BHS brain images onto the MNI template brain may result in changes that alter the biological inference from each image. Section 5.1.2 discussed how the brains of older adults are more heterogeneous than the brains of younger adults; therefore, the same structures from the MNI template may not necessarily map to the brain images from the BHS sample. A template that allows for more subject-specific variability would provide a more accurate standard for the BHS data. However, no such template exists for older adults, and investigations that do use their own template do so as the primary purpose of their studies. The purpose of this study extends beyond normalization, and seeks to establish brain-behavior relations. Therefore, we decided to use the standard template in the field in order to make the results generalizable to other trials, and instead we have

developed methodological advancements relevant to the questions that we have directly addressed.

A potential limitation of the neuropsychological tests administered is that they are all susceptible to practice effects. This is a weakness of administering the same behavioral test at multiple points. In our investigation, the tests resulting from the memory score exhibited practice effects, and we treated the fact that the scores improved longitudinally in our interpretation as a nuisance because it became more difficult to gauge the effects of aging. However, perhaps the very existence of practice effects in samples of older adults is something to celebrate—it demonstrates that older adults can continue to learn and improve, challenging some theories of cognitive aging, and providing hope in developing interventions to promote growth and community involvement for older adults.

The longitudinal study design represents one of the key strengths of this investigation. Few longitudinal fMRI RCTs exist in older adults. The longitudinal aim also exhibits the smallest effects, compared to Aims 1 and 2, and a number of the differences surface only at Follow-Up II. Therefore, this investigation may show stronger effects with additional follow-up visits. It may take more than two years to detect biologically meaningful changes.

The multi-modal nature of the intervention has been raised as a potential weakness due to the difficulty in detecting which aspects of the intervention may be most beneficial for functional connectivity and cognitive functions. What about Experience Corps should confer the benefits in brain network connectivity and in cognitive abilities?

Is it the generativity? Is it the expanded social networks? Is it the physical activity from traveling to the schools? To parse out which aspect is associated with the most benefit, novel technological devices are necessary to measure each aspect separately. Perhaps an accelerator could be incorporated to measure the physical activity; a GPS to measure and estimate social networks; and a smart device to measure feelings of generativity throughout the day. Trials incorporating these types of gadgets are under development in the BHS; and in the meantime, the study presented as it is also presents a strength because the multimodal nature of EC is more representative of real-life interactions. It may be that the benefits cannot be partitioned because it is neither generativity nor physical activity alone that improves brain health and neurocognitive functions. Perhaps it is the synergy between being generative and active that yields benefit. Such synergy would not be captured by separate analyses of each individual modality. The multimodal nature of EC also serves as a better intervention in the effort to prevent dementia, which has multifactorial origins, and therefore requires interventions that address multiple domains. Designing multi-domain interventions is a great challenge, and few such interventions exist in randomized controlled trials for older adults; therefore EC presents a paradigm that can be replicated.

## 6.3 Future Directions

This investigation provides a foundation for the understanding of functional connectivity, its relation to cognitive functions in older adults, and how these brain and behavioral measures are modified by Experience Corps. The data come from a community-based sample of socio-economically diverse older adults, which is unlike most fMRI studies, and makes the results more generalizable. One avenue that future studies could take is to develop the connectivity scores into clinically meaningful

measures with predictive utility for cognitive decline. Aim 2 showed that select cognitive scores are associated with better performance on neuropsychological tests. Thresholds could be selected based on these results and tested on new populations in order to further refine the connectivity score into a metric that could one day be used in clinic. This metric could help detect changes in cognitive functions before they become clinically meaningful, far before the onset of dementia, while there is still time to intervene.

# **CURRICULUM VITAE**

## Sarah A. Khasawinah

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### **EDUCATION**

2009-2014	<ul> <li>Ph.D., Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; Advisor: Michelle C. Carlson, PhD</li> <li>MHS, Department of Biostatistics, Johns Hopkins Bloomberg School of</li> </ul>
	Public Health, Baltimore, MD; Advisor: Brian Caffo, PhD
2005-2009	Joint MA and BA in Mathematics and BA in English, both with Honors,
	Bryn Mawr College, Bryn Mawr, PA, <i>Summa Cum Laude</i>
2001-2005	International Baccalaureate Diploma, JEB Stuart High School, Falls Church, VA, Valedictorian

### SKILLS

- Computer: Proficient in Microsoft Office Suite (Word, Excel, and PowerPoint), R/S-Plus, STATA, LaTex, Mac OS X, Microsoft Windows 7/Vista/XP/2000, MRICRON, Adobe Photoshop CSS, SPM, FSL, and Mipav; intermediate in SAS, WinBUGS, and MPLUS
- Languages: English (Native); Arabic (fluent in spoken); and Spanish (proficient)

# **TEACHING & WORK EXPERIENCE**

Spring 2013 & 2014	<b>Lead TA</b> , 280.375 Cultural Factors in Public Health (undergraduate), Johns Hopkins University. Developed syllabus; taught select classes; wrote and graded homework assignments, quizzes, papers, and presentations; led discussion sections; held office hours; managed course website; and addressed student needs.
Spring 2013	<b>Lead TA</b> , 330.623 Brain and Behavior (graduate), Johns Hopkins Bloomberg School of Public Health. Graded essays and exams, gave a lecture, held office hours.
2011-2012	<b>TA</b> , 140.621-2 Statistical Methods in Public Health I-IV (graduate), Johns Hopkins School of Public Health. Conducted lab, graded assignments and exams.
2010-2011	<b>TA</b> , 140.651-3 Methods of Biostatistics I-IV (graduate), Johns Hopkins School of Public Health. Conducted lab, graded assignments and exams.
Summer 2010	<b>TA</b> , 140.613-4 Data Analysis Workshop I-II (graduate), Johns Hopkins School of Public Health. Conducted STATA lab.
2007-2009	<b>Peer Led Instructor</b> , Calculus I, II, and III (undergraduate), Bryn Mawr College. Carried out weekly review sessions, facilitated group learning, graded assignments.
2006-2009	<b>Head Supervisor</b> , Haffner, Bryn Mawr College Dining Services, Bryn Mawr, PA
	Hired 65 student workers annually; recruited and hired 3-6 supervisors
	annually; scheduled student workers regularly; worked with cooks and
	manager to improve procedures; planned social events for student workers;
	trained student workers; introduced improved sanitary practices and
	nearmer rood options campus while.

2006-2009	Peer Mentor, Resident Dorm, Bryn Mawr College, Bryn Mawr, PA
	Helped students excel by advising on time and stress management and
	course planning.

Winter 2005 **Researcher/Analyst**, Telogical LLC, McLean, VA Researched competitive marketing intelligence for Telecom service providers; Prepared extensive report comparing digital video recorders' features.

- Summer 2004 Intern, Supervisor Penny Gross, Mason District Government Center, Fairfax, VA
- & 2005 Participated in zoning meetings, worked with Department of Motor Vehicles to fix roads; drafted articles for The Civic Associations Newsletter; edited weekly newsletter, wrote scripts for television show, *Mason Matters;* met with constituents.

### HONORS

Summer 2014	Best New Investigator Poster Research Presentation. International Society
	For Pharmacoeconomics and Outcomes Research
Spring 2014	2nd Place Poster Prize. JHSPH Gerontology Interest Group
Summer 2013	National Science Foundation Scholar awarded by the American Chemical
	Society Green Chemistry Institute
2009-Present	National Science Foundation Graduate Student Research Fellowship
2009-Present	Sommer Scholar. Honors JHSPH students for leadership
Summer 2009	Enhancing Diversity in Graduate Education Scholar
Spring 2009	Charlotte Angas Scott Prize for excellence in mathematics
2007-2009	Clare Boothe Luce Scholar. Honor for excellence in mathematics and
	leadership record
2007-2009	Mellon Mays Undergraduate Fellow. Awards commitment to higher
	education
Summer 2007	International Summer Internship Award, Bryn Mawr College
Summer 2006	Green Grant, Bryn Mawr College Alumna
Spring 2005	Princeton University Prize in Race Relations
Spring 2005	National Conference for Community and Justice Brotherhood Sisterhood
	Youth Award
Spring 2005	The Honorable Thurgood Marshall Scholarship

## LEADERSHIP

2010-Present	Founder, President, Johns Hopkins Apiary Association
	Installed a honeybee hive on campus, raise awareness on importance of
	pollination; organize Earth Week annually.
2011-Present	Mentor, Hopkins Honeybees at Homewood, Johns Hopkins University
	Helped to found the club, established the beehive, and trained students in
	beekeeping.
2010-2013	President, Johns Hopkins Graduate Muslim Students Association.
	Organized weekly prayer service for students, faculty, staff, and patients.
	Served as liaison between Johns Hopkins Medical Institution international
	Muslim patients and Chaplain's office; and between the Johns Hopkins
	Bloomberg School of Public Health Muslim students and the Dean's office.
	Organized annual events, including the Ramadan Banquet, Eid celebrations,
	lecture series, and multi-faith conversations.

Spring 2012	<b>Campus Coordinator</b> , Bike to Work Day, Johns Hopkins University Increased participation by 300%, planned safety and sustainability biking workshops.
Spring 2008	<b>President</b> , Self Government Association of Bryn Mawr College, Bryn Mawr Reformed election system to facilitate voting, developed initiatives to review and revise constitution and Honor Code, increased participation in SGA by 50%.
2007-2009	<b>Founder</b> , National Solidarity Project, Pennsylvania-Wide Collaborated with 33 colleges and universities in Pennsylvania to raise \$47,000 towards scholarship funds in memories of the Virginia Tech School Shooting Victims.
2007-2009	<b>Founder</b> , <b>Instructor</b> , Multi-Faith Running Initiative, Bryn Mawr College Developed course for Physical Education credit; Organized weekly runs, discussions, and dinners; All 13 members participated in Philadelphia Marathon.
2006-2009	Founder, President, Bryn Mawr College Apiary Association.
2005-2006	Delegate, Model United Nations, Bryn Mawr College.
2004-2005	<b>President</b> , Student Government Association, JEB Stuart High School, Falls Church, VA

### **PUBLIC SERVICE**

- Summer 2007 **Social Worker and Teacher**, Jordanian Women's Union, Irbid, Jordan. Founded a school to teach Iraqi refugees ages 5-17; taught English and Math; worked with Iraqi mothers to obtain housing and healthcare; wrote grants.
- Summer 2006 **Volunteer Intern**, Office of Pesticides Program, US EPA, Washington D.C. Assisted in policy-making on pesticide regulations and health effects; Drafted speeches for EPA Administrator, OPPTS Director and Deputy Director; Drafted piece on 10 year milestone accomplishments of "Food Quality Protection Act."
- Summer 2006 **Volunteer Intern**. Congressman James P. Moran, 8<sup>th</sup> District, VA. Developed 10-year plan to make America oil-free; prepared memo about foreign held federal debt and a report about US involvement in Israel; responded to constituents.
- 2008-2009 **Senior Representative**, Mathematics Department, Bryn Mawr College, Bryn Mawr, PA

Attended meetings with faculty, planned social department activities. 2006-2008 **Photographer**, Mathematical Association of America, Bryn Mawr College

### **RESEARCH EXPERIENCE**

- Summer 2013 Summer Program on Neuroimaging Data Analysis, Statistical and Applied Mathematical Sciences Institute, Research Triangle Park, NC, USA
   Summer 2011 Industrial Mathematical and Statistical Modeling Workshop, North Carolina State University, Raleigh, NC, USA
   Experimental Design and Inverse Problems in Plant Biological Modeling
- 2008-2009 **MA Dissertation**, Bryn Mawr College, Bryn Mawr, PA, USA On the Boundedness of Oscillatory Integral Operators in Harmonic Analysis

- 2008-2009 **Honors English Thesis**, Bryn Mawr College, Bryn Mawr, PA, USA A Detached Path to the Sacred: The prose & poetry of Wallace Stevens & Annie Dillard
- Summer 2008 **US-Hong Kong Undergraduate Research Experience**, sponsored by National Science Foundation, Hong Kong City University, Kowloon, HK Evaluation of Hypersingular Integrals Utilizing Quadrature Rules

### PRESENTATIONS

Summer 2014	<b>International Society For Pharmacoeconomics and Outcomes Research</b> <b>19th Annual International Meeting</b> , Montreal, QC, Canada Provision of Cultural Competency Training in the National Home and
Spring 2014	<b>Department of Mental Health Seminar</b> , Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
	Functional Connectivity in fMRI Brain Images of Older Adults from the Baltimore Experience Corps Trial
Spring 2014	<b>7th Annual Research on Aging Showcase</b> , Johns Hopkins University, Baltimore, MD. Functional Connectivity in fMRI Brain Images of Older Adults from the Baltimore Experience Corps Trial
Fall 2013	<b>Gerontological Society of America 66th Annual Scientific Meeting</b> , New Orleans, LA Changes in The Default Mode Network of Older Adults from Experience Corps
Summer 2011	<b>Statistical Methods for Very Large Datasets Conference</b> , Baltimore, MD Sample, Model, and Analyze with Regression Trees (SMART) for Very Large Datasets: A Case Study of the Hearst Magazines Challenge
Fall 2008	<b>Eastern Mathematical Association of America Regional Conference</b> , Ursinus College, Collegeville, PA Evaluation of Hypersingular Integrals Using Numerical Methods
Winter 2008	<b>Mellon Mays Regional Conference</b> , Bryn Mawr College, Bryn Mawr, PA Convergence of Hyperharmonic Series Using Residue Theory
Winter 2008	Nebraska Conference for Undergraduate Women, University of Nebraska, Lincoln, NE Convergence of Hyperharmonic Series Using Residue Theory

## **PROFESSIONAL MEMBERSHIPS**

Gerontological Society of America International Society For Pharmacoeconomics and Outcomes Research

### **ADDITIONAL INFORMATION**

Birth date and place: September 1987 in Chicago, Illinois Citizenship: United States of America