Resting-State Brain Connectivity and Risk of Cardiovascular Disease Risk in Successful Agers

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RESTING-STATE BRAIN CONNECTIVITY AND CARDIOVASCULAR DISEASE RISK IN SUCCESSFUL AGERS

By

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RESTING-STATE BRAIN CONNECTIVITY AND CARDIOVASCULAR DISEASE RISK IN SUCCESSFUL AGERS

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Successful Agers (SA) are older adults (aged > 65 years) with cognitive function comparable to healthy adults aged 20-30 years younger. These individuals demonstrate preserved volume of the hippocampus and posterior cingulate cortex (PCC), cortical regions supporting episodic memory, with advancing age. Since fMRI studies reveal lower resting state functional brain connectivity (rsFC) of these structures in individuals with episodic memory loss and cardiovascular disease, it is possible lower connectivity of these episodic memory hubs may be associated with SA status and lowered risk for developing cardiovascular disease. In this study, a seed-to-seed connectivity analysis of rsFC between the left and right of the hippocampus and PCC was performed on a group of 20 SA and 18 age-matched controls in order to determine whether SA status or ten-year risk for developing cardiovascular disease, i.e. Framingham Risk Score (FRS), predict the magnitude of rsFC between these hubs. The second aim was to test the interaction of FRS and SA status on rsFC between these hubs. SA status predicted 16% of the variance in rsFC between the left hippocampus and right PCC $F(2,35) = 3.16, p = 0.05$) after accounting for age. FRS score accounted for 8.8% of the variance in rsFC between the left hippocampus and right PCC $F(2,33) = 3.568, p = 0.05$). Increased
connectivity between the left hippocampus and right PCC was associated with SA status and cardiovascular risk but not by the interaction of these factors, suggesting the effect of SA status on rsFC of these episodic memory hubs is independent of Framingham Risk.
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Chapter 1: Introduction

In the United States, the population of older adults is projected to almost double from 43.1 million in 2012 to 83.7 million by 2050 (Ortman, Velkolt & Hogan, 2014). This poses a daunting challenge for clinicians when considering that global cognitive abilities typically decline with advancing age (Salthouse, 2009). Therefore, it is becoming increasingly important to identify behavioral factors associated with the preservation of cognitive health in older age. Since the mid-1900s, a "successful aging” literature has gradually emerged from the behavioral science literature (Baltes & Baltes, 1990). Early definitions of successful agers (SA) were predominantly based on reports of greater activities of daily living, positive attitudes and high life satisfaction (Havighurst, 1963). In 1987, Rowe & Khan proposed a new model for “successful aging” that incorporated: a) low risk of chronic disease, b) maintenance of high mental and physical health and c) continued engagement with life (Rowe & Kahn, 1987). As the literature evolves on this topic so have the views on how to define successful aging, with cognitive function emerging as a key-defining feature (Nyberg & Pudas, 2018).

The domain of cognitive function that has received the greatest attention in terms of operationalized definition is that of episodic memory. Episodic memory is a past-oriented memory system for events that occurred in an individual’s life that is “late developing” and particularly vulnerable to decline in older adults (Tulving, 2002) as well as individuals diagnosed with Alzheimer’s disease (Estevez-Gonzalez, Kulisevsky, Boltes, Otermin, & Garcia-Sanchez, 2003). Decline of episodic memory is widely regarded to be a normal and common facet of aging (Dixon et al., 2004; Mitchell, Brown, & Murphy, 1990). However, there are older adults that exhibit episodic memory
performance that exceeds that of typically aging adults in their age group. The Northwestern SuperAger Study was among the first to identify individuals who at 70-80 years of age had episodic memory performance comparable to healthy adults 20-30 years younger (Harrison, Weintraub, Mesulam, & Rogalski, 2012). Another research group replicated these findings in a cohort of 60-80 year-old individuals demonstrating cognitive performance akin to adults 18-35 years old (Sun et al., 2016). Given its relevance in cognitive aging and onset of Alzheimer’s disease episodic memory consistently shown to be a characteristic of successful aging. Thus, a better understanding of the neural underpinnings of preserved episodic memory, within older adults, may help elucidate factors contributing to the early onset of cognitive impairment amongst within this population.

**Measuring Cognition in Successful Aging**

As previously mentioned, one way to define SA is to compare their episodic memory performance to normative data of younger adults rather than age-matched controls in order to provide an adequate benchmark for the preservation of cognitive functioning in successful agers (Harrison et al., 2012). The measure of episodic memory most widely used typically requires accurate recall of a verbal list of items, such as those in the Rey Auditory Verbal Learning Test (RAVLT). The RAVLT is an episodic memory measure that plays a significant role in diagnosis of early onset Alzheimer's disease (Estevez-Gonzalez et al.). In terms of the neural correlates of episodic memory, structural and functional imaging studies converge upon cortical thickness and cerebral blood perfusion as factors related to performance on the RAVLT. Recently, it was shown that in healthy adults the structural integrity of the hippocampus, angular gyrus, and the left
insula was associated with higher RAVLT scores (Moradi, Hallikainen, Hanninen, & Tohka, 2017). Furthermore, in individuals with mild cognitive impairment decreased RAVLT scores are associated with decreased cerebral blood flow to the precuneus (Nicholas et al., 2015). Collectively, RAVLT scores relate to structural and functional integrity of subcortical as well as cortical structures involved in memory retrieval.

Initial attempts to operationalize SA status also included several non-memory cognitive domains based upon the hypothesis that loss of non-memory cognitive performance (i.e. executive function) is also common in older age (Harrison et al., 2012). Among a battery of cognitive measures, performance on Part B of the Trail-Making Test (TMT-B) was the only non-memory measure that was greater in SA when compared to older adults (Harrison et al., 2012). This is consistent with findings that compared to healthy older adults deficits in TMT-B performance are typical of Alzheimer’s and are associated with impaired activities of daily living (Baudic et al., 2006; Marshall et al., 2011). The Trail Making Test (TMT) is a popular instrument that has been used to detect neurological disease and neuropsychological impairment; part B of the TMT is thought to measure executive function (Bowie & Harvey, 2006). Performance on the TMT-B is also correlated with differences in brain activation, including the dorsal anterior cingulate cortex (Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002) an area which, in SA, has repeatedly been shown to have preserved cortical thickness and reduced Alzheimer's pathology in SA (Rogalski et al., 2013). Due to importance of the preservation of executive function in older age current definitions of successful aging include performance within 1 SD of age-matched normative performance on the TMT-B.
Cardiovascular Risk and Cognition

Despite the growing knowledge of the neuropsychological underpinnings of SA and the detrimental impact of cardiovascular disease (CVD) on brain function, little is known about cardiovascular factors as they relate to neural underpinnings of SA status. However, general studies of cognitive abilities in older adults converge on risk of conferring CVD as an important factor in cognitive decline. The American Heart Association uses CVD as an umbrella term encompassing many heart and blood vessel diseases (Mozaffarian et al., 2015). In older adult populations, risk of conferring CVD such as atherosclerosis and hypertension is linked to increased risk for cognitive decline (Jefferson et al., 2015; Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011). More recent observations of older adult persons with CVD show associations with specific deficits in episodic memory (Olaya, Bobak, Haro, & Demakakos, 2017), poorer global cognitive function and the onset of dementia (Dregan, Stewart, & Gulliford, 2013). While CVD incidence is clearly associated with cognitive dysfunction, risk for developing cardiovascular disease has not been fully interrogated within the context of SA.

Framingham Risk Score (FRS) is a multifactor risk measure of developing a cardiovascular disease such as heart failure, coronary heart disease, stroke, and death from cardiovascular disease within 10 years (Anderson, Odell, Wilson, & Kannel, 1991). FRS is calculated by age, gender, dyslipidemia, blood pressure and incidence of smoking (D'Agostino et al., 2008). FRS is implicated in lower global cognition, including poorer episodic memory and executive function (Jefferson et al., 2015; Kaffashian et al., 2013; Shipley, Sabia, Kivimaki & Sing-Manoux, 2013). However, the neural correlates of FRS, as they relate to episodic memory, are not fully understood.
Mechanisms Linking Cardiovascular Health to Cognition

Cardiovascular disease risk is a plausible factor for decrement in the neural networks underpinning episodic memory due to the physiological mechanisms underlying the perfusion of blood to cerebrovascular tissue. It is estimated that 12% of cardiac output is dedicated to the cerebrovascular hemodynamic response of the brain at rest (Williams & Leggett, 1989). Decreased cardiac output is a feature of many forms of CVD such as hypertension (Afsar & Elsurer, 2014). Hence, decreased cardiac output in individuals with and without diagnosed CVD is linked to lower brain perfusion (Meng, Hou, Chui, Han, & Gelb, 2015). Importantly, this is consistent with findings of associations between higher total FRS, lower cerebral brain volume and lower performance on the TMT-B (Seshadri et al., 2004). Lower cerebral blood flow has also been associated with lower episodic memory performance measured by the RAVLT (Nicholas et al., 2015).

FRS is made up of many components that have been individually linked to cognitive function. Hypertension and dyslipidemia are associated with greater cognitive decline and altered brain structure (Kalaria, 2010; Leritz et al., 2011). In a study encompassing neuropsychological evaluation and gray matter morphology, the relationship between cortical thickness and cognitive impairment were found to vary by individuals’ FRS factors. They found that hypertension was associated with aberrant memory and executive function, dyslipidemia was linked to impaired processing speed and cholesterol was predictive of cortical atrophy of the precuneous (Gonzales et al., 2017 Cohen, Yang et. al., 2017). Hypertension-related changes also coincide with age-related changes in gray-matter within the hippocampus and prefrontal cortex (Beauchet et
structures which are vulnerable to advanced age (Beauchet et al., 2013). Thus, as an aggregate of factors that lead to poorer cognitive outcomes (i.e. hypertension and dyslipidemia), high FSR is likely to be detrimental to cognitive abilities in older age.

The factors that make up FRS are also linked to alterations in resting-state functional brain networks (RSN), i.e., networks of brain regions that are thought to reflect functional systems supporting core cognitive processes (Cole, Smith, & Beckmann, 2010; Greicius, Supekar, Menon, & Dougherty, 2009). Resting-state functional connectivity (rsFC) is the measure of the strength of connectivity within the RSNs while the brain is at rest and is considered to reflect intrinsic energy demands of neurons that consistently fire together with common functional purpose (Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009). In individuals at elevated risk for Alzheimer’s disease, hypertension relates to rsFC between the anterior cingulate cortex and the posterior cingulate cortex (PCC) (Son et al., 2015). In hypertensive individuals, disrupted patterns of rsFC within frontoparietal structures are correlated with executive function impairment measured by the TMT (Li et al., 2015). Adults with Type 2 Diabetes Mellitus (T2DM), who are subject to dyslipidemia, exhibit global decreases in functional connectivity as well as spontaneous resting state activity (Macpherson, Formica, Harris, & Daly, 2017; Xia, Chen, & Ma, 2017). Decrease of spontaneous rsFC in individuals with T2DM is also associated with lower neurocognitive functioning of visuo-spatial memory and executive function (Macpherson et al., 2017). Factors that are known to lead to cardiovascular risk, including hypertension and dyslipidemia, are associated with lower rsFC. However, there a lack of research in how total cardiovascular risk relates to rsFC. A better understanding
of how rsFC related to cardiovascular risk may help to better understand the effects of these factors on RSN related to cognitive decline in older adults that are at an earlier point of clinical intervention.

**Resting State Functional Connectivity and Typical Aging**

In episodic memory, information is encoded and stored as long-term episodic memories by way of brain regions that include the hippocampus and the PCC (Dickerson & Eichenbaum, 2010). In cognitively healthy older adults, defined as older adults that display performance within normative range of their age group on a neurocognitive battery, greater activation in the PCC and hippocampus at rest were associated with episodic memory performance (Wang et al., 2010). Wang and his colleagues noted that the resulting hippocampal connectivity map had considerable overlap with what is known as the Default Mode Network (DMN) (Buckner, Andrews-Hanna, & Schacter, 2008; Vincent et al., 2006), suggesting that coherence between the hippocampus and the posteromedial regions of the DMN relates to episodic memory among cognitively healthy older adults. Notably, the DMN is an RSN bearing functional nodes in the ventromedial prefrontal cortex, PCC, inferior parietal lobule, lateral temporal cortex, dorsal medial prefrontal cortex and the hippocampus (Buckner et al., 2008). DMN function is associated with memory encoding as well as self-oriented and social cognition (Sridharan, Levitin, & Menon, 2008). The DMN is comprised of brain regions that are less engaged during active states (Binder et al., 1999; Shulman et al., 1997) and that become more engaged during mind-wandering and self-referential processes (Fox & Raichle, 2007). The DMN is also accepted as the intrinsic network most associated with memory function, including episodic memory (Buckner et al., 2008; Buckner & Vincent,
However, there appears to be heterogeneity in the structure and function of the DMN hubs. Posterior structures, such as the PCC and the precuneus, are more associated with episodic memory retrieval (Lou et al., 2004; Lundstrom, Ingvar, & Petersson, 2005) while frontal structures, such as the vmPFC, are more often implicated in self-referential processing (D'Argembeau et al., 2005). This is pertinent to understanding the neural underpinnings of SA status since the most consistent changes associated with aging are shown to occur within nodes of the DMN (Ferreira & Busatto, 2013; Vij, Nomi, Dajani, & Uddin, 2018). Within the DMN, there is typically decreased connectivity between the ventromedial prefrontal cortex and the PCC among older adults (Wu et al., 2011). The PCC, as a hub of the DMN, and the hippocampus are implicated in episodic memory performance. More specifically, connectivity between the PCC and the hippocampus is associated with greater episodic memory recall in older adults, particularly cognitively healthy adults (Wang et al., 2010).

**Successful Aging Brain**

If SA status is protective of brain health, then brain regions underpinning episodic memory are likely areas to observe effects of preserved functioning. Post-mortem histopathological studies comparing older adults, SA and older adult with Alzheimer’s reveal the PCC of SAs exhibit lower Alzheimer's disease pathology, indexed by the presence of neurofibrillary tangles (Gefen et al., 2017). Longitudinal studies of successful agers indicate that their stable episodic memory performance is coupled with lower rates of gray matter atrophy in the hippocampus (Cook, Sridhar, Ohm, & et al., 2017; Gefen et al., 2014). Although studies quantifying fMRI activity associated with SA status are lacking, there is some evidence that the structural brain correlates of SA map
onto that of RAVLT and TMT-B tasks. In histopathological study of the hippocampus in SAs they found neurofibrillary degeneration that is typical with aging but there was significant preservation of healthy neurons (Rogalski et al., 2018). This is consistent with findings from an MRI study on cortical thickness, showing that SA had thicker hippocampal volume in the right hemisphere and greater PCC volume than typically aging older adults. Furthermore, greater hippocampal volume correlated with episodic memory performance, consistent with findings that greater performance on the RAVLT is associated with greater cortical thickness within the hippocampus and the right angular gyrus (Moradi et al., 2017; Sun et al., 2016). Given their resistance to Alzheimer’s symptomatology, it is possible that greater understanding of SA status will yield routes of intervention to prevent cognitive decline in older age.

**Current Study**

The primary aim of the current study is to investigate whether successful aging status, CVD risk or the interaction between them is associated with greater resting-state connectivity between the hippocampus and the PCC. It is hypothesized that SA with lower FRS will show greater rsFC between the hippocampus and the PCC than older adults in the control group. Additionally, it is hypothesized that interaction of SA status and lower FRS will predict greater connectivity between these structures. Meaning, SA that have lower FRS will have greater rsFC between the hippocampus and PCC than those who have SA status but have higher cardiovascular risk.

**Specific Aims**

There are two specific aims in the current study. The first aim is to examine differences between successful agers and typically aging older adults on a measure of rsFC of two
nodes involved in episodic memory: the PCC and the hippocampus. It is hypothesized that SA will have significantly increased connectivity between the hippocampus and the PCC nodes compared to older adults. The second aim is to examine differences in rsFC of the PCC and the hippocampus associated with Framingham risk in an effort to determine if a low cardiovascular risk is predictive of SA status. It is hypothesized that SA with lower cardiovascular risk will show greater rsFC between the hippocampus and the PCC than typically cognitively-aging older adults.
Chapter 2: Methods

Participants

Structural and resting-state functional neuroimaging data of adults 65-85 years old were obtained from the repository of the 8th release of the Nathan Kline Institute’s Rockland Sample. Data were collected for this study as a part of the International Neuroimaging Data-sharing Initiative (INDI). In the lifespan sample, 103 older adults completed physiological and psychological assessments and provided biomarker data. Participants were included if they had completed the RAVLT and TMT-B. Participants were excluded based on self-reported psychopathology (i.e. Depression, Anxiety, PTSD, OCD, etc) or history of Alzheimer’s, brain trauma or loss of consciousness.

Based on previous studies, older adults were required to meet two strict psychometric criteria in order to be designated as an SA (Harrison et al., 2012; Sun et al., 2016). First, they were required to perform at or above the mean gender-adjusted level for young adults (aged 18-35 years) on the Long Delay Free Recall measure of the RAVLT. Second, they were required to perform no lower than 1 SD below the mean for their age group on the TMT-B. Twenty-one older adults met psychometric criteria for successful ager status.

Participants in the older adult control group were required to score within 1 SD of published normative values for the Long Delay Free Recall measure of the RAVLT and the TMT-B on the basis of their age and gender. A total of 20 older adults met criteria and were included in the older adult control group. Sixty-two participants were excluded due to missing data or neurocognitive scores that did not meet criteria. Two older adult
control participants and one SA were subsequently excluded due to excessive motion during the scan.

**Procedure**

**Image Acquisition.**

MRI data was collected on a 3.0 T SIEMENS Trio scanner according to protocols approved by the institutional review board of the Nathan Kline Institute. Each subject completed a 10-min resting state fMRI scan acquired using an echo-planar imaging (EPI) sequence (TR/TE = 2500/30 ms, flip angle = 80°, FOV = 216 mm × 216 mm, matrix = 72 × 72, slices = 38, thickness = 3.0 mm, 260 volumes). High-resolution T1-weighted images were also acquired for each subject using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR/TE = 1900/2.52 ms, FA = 9°, thickness = 1.0 mm, slices = 176, matrix = 250 × 250, FOV = 256 mm x 256mm).

**fMRI Quality Check.**

Prior to analysis, MRI data were visually inspected T1 structural images were rated based on whether or not it was usable for coregistration. fMRI Quality Check T1 structural images and EPI images were visually inspected for wrapping, head coverage, blurring, ringing, striping, ghosting or signal loss. EPI images were also inspected for motion slice artifacts or spiking (http://fcon_1000.projects.nitrc.org/indi/enhanced/qc.html).

**fMRI Preprocessing.**

fMRI data were preprocessed using the DPABI toolbox (Yan et al., 2016) that employs FSL and SPM functions. Preprocessing included removing the first four volumes, realigning the images, co-registering to T1 structural images, and smoothing
using a 4mm Gaussian window. EPI images were band-pass filtered at (0.008-0.08 Hz). Next, using the Data Processing Assistant for Resting-State fMRI program (http://rfmri.org/DPARSF), the Friston 24 motion parameters were then regressed out before further analysis (Friston et al., 1996). Three participants that presented head translation exceeding 2 mm or head rotation exceeding 2 mm degrees were excluded, leaving a final sample of 20 SA and 18 older adults in the control group. T1-weighted 3D images were segmented into modulated normalized parts of nuisance covariates (signals associated with gray matter, white matter and cerebrospinal fluid). The normalized EPI volumes were re-sampled to a voxel size of 3 mm x 3 mm x 3 mm in MNI space, then were spatially smoothed using an isotropic Gaussian filter kernel (4 mm FWHM). Motion parameters between groups were not significantly different (see Table 1).

Measures

Rey Auditory Verbal Learning Test (RAVLT).

The RAVLT is a well-known, reliable and valid measure of episodic memory (Schmidt, 1996). A trained administrator reads 15 words to the participant at a steady rate of 1 word per second. Participants have the words repeated to them before they are asked to name all items on the list. This process is then repeated for a total of five trials. After a 20-minute delay, the participants are asked to freely recall the items from the original list presented to them. The RAVLT produces several outcome measures such as Forgetting, Retention, and Recognition. The outcome measure that is most relevant to SA status is Recall Delay. This measure indexes how many of the words in the list the participants are able to recall following a 20-minute delay. The RAVLT Forgetting Score (the score of
Trial 5 minus score of the delayed recall) was also derived from raw RAVLT scores and included in demographic analysis.

**Trail Making Task (TMT).**

The TMT is a popular instrument for the detection of neurological disease and neuropsychological impairment; it is thought to require recruitment of processing speed, sequencing, mental flexibility and visual-motor skills across the lifespan (Tombaugh, 2004). In Part A, the first section of the test, the participant is instructed to draw a line connecting 25-circled numbers in numerical order as quickly and accurately as possible. The participant is then asked to do the same for a sequence of letters by drawing a line connecting the 25-circled letters as quickly and accurately as possible. In Part B, the participant is instructed to connect 13 circled numbers and 12 circled letters, alternating between numbers and letters as quickly and accurately as possible (Bowie & Harvey, 2006). The TMT shows high reliability in psychometric testing including among those with neurological or psychological diagnosis (Franzen, 1996). There is controversy over whether TMT-B performance also captures cognitive functions other executive function, such as processing speed, therefore a corrected score (TMT-B-A ratio) (Arbuthnott & Frank, 2000).

**The Wechsler Abbreviated Scale of Intelligence (WASI-II).**

The WASI is a general intelligence test formulated to measure cognitive capabilities of children, adolescents and adults (ages 6-89). This abbreviated IQ test has a battery of four subtests: Vocabulary, Block Design, Similarities and Matrix Reasoning. The WASI provides estimates of Verbal and Performance that is consistent with more extensive Wechsler tests. The Vocabulary and Similarities subtests are combined to form
the Verbal Scale and yield a Verbal IQ (VIQ) score, and the Block Design and Matrix Reasoning subtests form the Performance Scale and yield a Performance IQ (PIQ) score. The four subtests yield the Full Scale IQ (FSIQ) (Stano, 2004).

**Older Adult Self Report (OASR).**

The OASR is a self-administered questionnaire designed for older adults (ages 60-90) that examines various aspects of adaptive functioning and problems. Participants are asked to review an itemized list and select the best answer to describe themselves over the past two months on a 3-point scale: 0-Not true, 1-Somewhat or Sometimes True, 2-Very True or Often True. The questionnaire provides scores for the following scales: anxious/depressed, worries, somatic complaints, functional impairment, memory/cognition problems, thought problems, and irritable/disinhibited. The OASR also provides scores for depressive problems, anxiety problems, somatic problems, dementia problems, psychotic problems, and antisocial personality problems. Finally, the questionnaire asks about substance use including tobacco and alcohol (Achenbach & Rescorla, 2000). The OASR is a reliable and valid measure among older adults that are 60 years old or older (Rescorla, 2004)

**Framingham Risk Score.**

The Framingham Risk Score (FRS) is a multivariable risk function that outputs a percentage indicating risk for conferring an acute cardiovascular event or onset of CVD, within ten years independent (Anderson, Odell, et al., 1991). It is a validated measure of CVD risk based on health factors that lead to and strongly predict the incidence of cardiovascular events and onset of cardiovascular disease. The FRS is calculated based on age, systolic blood pressure, hypertension, the ratio of triglycerides to high-density
lipoprotein (HDL) cholesterol and cigarette smoking (see Figure 1 for equation)
(D'Agostino et al., 2008 Wolf, Cobain, Massaro & Kennel, 2008). The FRS was
originally validated for people aged up to 75 years but is used in older populations due to
the absence of an appropriate alternative (Rodondi et al., 2012).
Chapter 3: Analysis

Seed-based, Resting-State Functional Connectivity

Functional connectivity analysis of the hippocampus and the PCC (Brodmann area 31) involved the selection of two spherical seed regions of interest (ROIs) were defined with a radius of 6 mm$^3$ (containing 33 voxels) using the AFNI program 3dmaskave. These ROI coordinates were based on MNI coordinates defined in previous work examining connectivity between the hippocampus and PCC in older adults (Wang et al., 2011). MNI coordinates are reported in Table 2 and depicted in Figure 2. Using the 3dUndump command the ROIs were used to extract an average hemodynamic time-series for each seed location, for each subject, by applying each ROI mask to the preprocessed time-series, and averaging across all voxels within the ROI. Within each subject’s native space we performed a correlation analysis for each ROI using the AFNI program 3dfim. Fisher Z-transformed correlations were computed to quantify functional connectivity between the hippocampus and PCC ROIs extracted from each individual subject’s resting state connectivity map. ROI pairs were analyzed in the following pairwise order: Left Hippocampus connectivity to Left PCC, Left Hippocampus to Right PCC, Right Hippocampus to Right PCC and Right Hippocampus to Left PCC. Figure 4 illustrates the connectivity paths between the ROIs.

Relationship of Seed Connectivity to SA and FRS

A hierarchical multiple regression analysis was conducted in order to test the hypotheses that 1) rsFC between the hippocampus and PCC will differ between SA and non-SA individuals, 2) that these associations will further vary as a function of CV risk, and 3) successful aging status will interact with lower cardiovascular risk in its protective
effects on rsFC between the hippocampal and PCC nodes. The Z-transformed connectivity correlation coefficients were entered as dependent variables in 4 separate models in order to interrogate effect and interaction of SA status and FRS on connectivity patterns within these hubs. Statistical significance was defined at the $p < .05$ level.

**Post-Hoc Analyses**

Additional analysis served to parse apart the effect of independent components of FRS and rsFC between the pre-defined nodes. Based upon findings from Aim 1, i.e., the presence of a main effect for FRS, partial correlations were conducted between the connectivity between the Left hippocampus to Right PCC and the other factors that comprise FRS, while controlling for total FRS. The aim of these exploratory analyses is to disentangle the effects of individual risk factors that make up FRS. Test significance was evaluated at the Bonferroni corrected $p < .008$ level in order to account for multiple tests.
Chapter 4: Results

Descriptives

Descriptive analyses included socio-demographic characteristics collected from surveys administered to the NKI Rockland participants, the full-scale IQ from the Weschler Abbreviated Scale of Intelligence-II and the Functional Impairment Score of the Older Adult Self-Report Questionnaire. Means and standard deviations for demographic variables were calculated using SPSS. Demographic information and mean test scores are presented in Table 3. SA and controls were not significantly different in levels of individual risk factors that make up FRS, including hypertension, age, cholesterol, HDL or smoking status. Additionally, SA did have significantly different IQ scores or self-reported impairment compared to the older adult control group.

ROI-Based Correlational Analyses

Regression results are reported in Table 4. Among the seed pairs, the regression model including SA status predicted 16% of the variance in total intrinsic connectivity between the left hippocampus and right PCC $F(2,35) = 3.16, p = 0.05$) after accounting for effects of age. FRS score accounted for an additional 8.8% of the variance in total intrinsic connectivity between the left hippocampus and right PCC $F(2,33) = 3.568 p = 0.05)$. Whereas a positive association arose between SA status and left hippocampus and right PCC intrinsic connectivity ($\beta = 0.364, p = .03$), a negative association arose between FRS and seed-to-seed connectivity ($\beta = -0.307, p = .05$). The interaction between SA status and FRS was not significant. Models including intrinsic connectivity of the remaining seed pairs were not significant. A graph of the regression results is presented in Figure 5.
There was no significant correlation between the seed pairs and Framingham risk components, (hypertension medication use and systolic blood pressure, cholesterol, HDL, and smoking status) while controlling for overall FRS score revealed none of the FRS components were significantly correlated with connectivity between the left hippocampus and right PCC when statistical significance was set at $p > .05$. Among the FRS components, HDL and Cholesterol scores were significantly correlated ($r = -.724, p<0.001$). The correlations between intrinsic functional connectivity and the other FRS risk factors are listed in Table 5.
Chapter 5: Discussion

A seed-to-seed correlation approach was used to assess differences in functional connectivity of pre-specified ROIs germane to episodic memory, i.e., hippocampus and the posteromedial cortex, as a function of SA status and risk of conferring a cardiovascular event or disease within 10 years. Our results show that SAs demonstrated increased rsFC between the left hippocampus and the right PCC when compared to typically aging controls. In previous studies on cognitively healthy older adults, resting-state connectivity of these contralateral structures was also correlated with episodic memory performance (Wang et al., 2010). Although the hippocampal formation has long been implicated in episodic memory retrieval, the exclusivity of the role of this structure as it relates to the varying facets of memory such as memory retrieval, has been challenged frequently (Squire, 1992; Tulving, 2001). Additionally, evidence from functional task studies support the role of PCC in the remembering process associated with episodic memory (Henson, Rugg, Shallice, Josephs, & Dolan, 1999). However the role that PCC plays in episodic memory is largely uncertain – particularly within the context of task-free imaging paradigms (Wheeler & Buckner, 2004). A study comparing the amplitude of low-frequency fluctuations in healthy adults suggests that a hippocampal-parietal network is essential in episodic memory retrieval, since healthy adults demonstrated greater rsFC between the hippocampus and PCC at rest and better overall episodic memory performance (Vincent et al., 2006). From a comparative anatomical perspective the hippocampal formation and medial parietal cortex share dense interconnections (Parvizi, Van Hoesen, Buckwalter, & Damasio, 2006). Dense lesions to the anatomical analog of this structure in Macaques, i.e., retrosplenial cortex, is
associated with marked memory deficits as well (Kobayashi & Amaral, 2003). In light of these findings the results from the current study highlight the role of the hippocampus and PCC in rsFC of older adults with extraordinary episodic memory.

In this study, SA had significantly greater connectivity than older adults, suggesting that their functional connectivity may be protective of their episodic memory performance. Interestingly, successful agers had greater rsFC between the left hippocampus and the right PCC, one of the contralateral pairs rather than the ipsilateral pairs. This replicates previous findings that contralateral connectivity between the left hippocampus and right PCC is associated with healthy cognitive aging (Wang et al., 2010). Together with findings that the hippocampus in SA have greater neuronal density than older adults (Gefen et al., 2015) and display cortical thickness at the hippocampus and PCC that is comparable to younger adults (Harrison et al., 2012), findings suggest that the hippocampus and PCC play a central role in the episodic memory abilities of successful agers.

Significant functional connectivity between the Left hippocampus and the Right PCC was also associated with FRS. The association between Framingham risk and brain connectivity suggests that decreased cardiovascular risk may help to mitigate episodic memory decline. Factors that aggregate to cardiovascular risk, such as hypertension and dyslipidemia, are known to disrupt functional connectivity and neurocognitive ability independent of age (Li et al., 2015; Macpherson et al., 2017). Protection from early cardiovascular risk factors may also be protective against episodic memory deficits, as evidenced in older adults with CVD (Olaya, Bobak, Haro, & Demakakos, 2017). A potential mechanism behind this relationship which may be further explored is the
The possibility that successful agers have increased cerebral-vascular health. A substantial amount of cardiac output is allocated to the brain and cardiovascular disease is known to decrease cardiac output (Afsar & Elsurer, 2014). Functional connectivity studies measure the fluctuations in BOLD-weighted signal, which represents a combined signal of blood oxygenation, cerebral blood volume, the metabolic rate of oxygen and cerebral blood flow. Lowered cardiac output impairs cerebral bloodflow, which may in turn dampen rsFC (Meng et al., 2015). There is controversy over the mechanistic relationship between cerebrovascular health and cognitive impairment, however there is an established relationship between cerebrovascular health and cognitive impairment in Alzheimer’s disease (O’Brien & Thomas, 2015). Decrements in cerebral blood flow are related to aging, cardiovascular disease and dementia (Shaw et al., 1984). Individuals with mild cognitive impairment present decreased cerebral blood associated related to deficits in episodic memory indexed by the RAVLT (Nicholas et al., 2015). Cerebral blood flow reductions are also associated with severity of dementia (Tachibana et al., 1984). It is possible that an inverse effect among cardiovascular risk and episodic memory and that cerebrovascular blood flow buffers this effect; a relationship which seems to be particularly relevant in older age.

SA demonstrated greater FRS risk than older adults despite the fact that individual risk factors that add up to cardiovascular risk were not independently lower in SA. Lower FSR was also inversely related to rsFC of the hippocampus and PCC, further suggesting that lower FSR is protective of rsFC of episodic memory hubs in a sample of older adults that demonstrate superior episodic memory performance. This highlights the role of lower cardiovascular risk in preserved cognition and rsFC in late life. Finally, the current
study did not find an interaction between SA status and cardiovascular risk. This may be indicative of the protective effects of SA status overlapping with the protective effects of lower cardiovascular risk without having a detectable, additive effect. It is possible that much of what protects SA from decreased episodic memory in late life is attributable to their lowered cardiovascular risk.

**Limitations**

Of note, there were limitations to the current study. Data was compiled from a relatively small group of SA and findings are based on cross-sectional data. However, our strict criteria may have increased the power to detect effects by removing confounds associated with the participant disease comorbidity, movement artifacts via quality control, and a moderately stringent definition for SA status. Future studies would benefit from the inclusion of a second control group made up of younger adults. This would allow comparisons between SA, older adults, and younger adults would better parse out whether or not the rsFC changes observed in SA resemble that of younger adults as their episodic memory abilities do. Additionally, FRS was used to calculate risk of conferring a cardiovascular event or disease even though was originally validated for people aged up to 75 years (Anderson, Wilson, Odell, & Kannel, 1991). FSR has used in older populations due to the absence of an appropriate alternative, however future studies may benefit from a more comprehensive transformation of FSR which has been validated for older adults (Rodondi et al., 2012).

**Clinical Implications**

SA have been found to have lowered frequency of Alzheimer’s disease pathology in post-mortem histopathological analysis of SA (Gefen et al., 2017; Gefen et al., 2015).
The current study further reinforces this theory, as SA were resistant to decrease in DMN connectivity decrease which is typical in Alzheimer’s patients (Greicius, G. Srivastava, A. L. Reiss, & V. Menon, 2004). In individuals with risk of Alzheimer’s disease, hypertension relates to decreased rsFC between the ACC and the PCC (Son et al., 2015), which suggests that lower cardiovascular risk in SA is positively associated with rsFC of brain structures. Given the converging evidence that greater rsFC is critical for preserved memory function, longitudinal fMRI studies are crucial to determine whether greater DMN connectivity during midlife will serve as a predictor episodic memory maintenance in SA over time. Longitudinal data would also yield more conclusive evidence as to whether CVD risk in earlier life is related to achieving SA status in older age.

Conclusion

In summary, the current findings provide further support for the hypothesis that rsFC of cortical and subcortical DMN structures may be relevant to the individual differences in specific cognitive behavior among older adults. Findings support Rowe and Khan's (1987) proposition that not all older adults exhibit lower cognitive ability that is thought to be common with aging and provide support for their theory that SA enjoy a lower risk of conferring disease. Further elucidating the neural correlates of SA status or FRS may reveal causal or preventative factors in the decline of episodic memory. Indeed, aberrant connectivity of the DMN is implicated in Alzheimer’s (Greicius, Srivastava, Reiss, & Menon, 2004) and although greater Tau deposition within DMN structures was demonstrated to not be indicative of aberrant rsFC (Adriaanse et al., 2014) the observed resistance of SA to Alzheimer’s pathology may help inform the mechanism by which episodic memory decline in older age can be buffered. Future interventions could benefit
from incorporating a physical fitness regimen, which in previous studies has increased connectivity of the DMN of older adults (Voss et al., 2010). Even with modest success, interventions that prevent cognitive decline could translate into substantial public health benefits such as reduced reliance on caregivers, lower healthcare cost, and improved quality of life for our aging adult population (Livingston et al., 2017).
References:


Table 1.
*Motion Parameters differences between groups*

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<tr>
<th></th>
<th>t-value (df)</th>
</tr>
</thead>
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<td>-0.998 (35)</td>
</tr>
<tr>
<td>Pitch</td>
<td>0.639 (35)</td>
</tr>
<tr>
<td>Yaw</td>
<td>1.595 (35)</td>
</tr>
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</table>

*p < .05; **p<0.01 and 0.001; ***p<0.10*
Table 2.
Locations of seeds used for correlation analysis

<table>
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<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
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<tr>
<td>Right Hippocampus</td>
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<td>-30</td>
<td>-6</td>
</tr>
<tr>
<td>Left PCC</td>
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<td>39</td>
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<tr>
<td>Right PCC</td>
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<td>-54</td>
<td>39</td>
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Table 3.

Demographics

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<tr>
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<th>Successful Agers M(SD)</th>
<th>Control M(SD)</th>
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<th>df</th>
<th>p-value</th>
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<td>58%</td>
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<td>.508</td>
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<td>100%</td>
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<td>94.5%</td>
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<td>Age</td>
<td>73.3(5.2)</td>
<td>76.1(4.2)</td>
<td>-1.77</td>
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<td>194.2(33.9)</td>
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<td>Smoking</td>
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<td>94%</td>
<td>0.73</td>
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<td>HDL</td>
<td>66.65(18.7)</td>
<td>68.3(23.1)</td>
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<td>Systolic BP</td>
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<td>127.9(15.1)</td>
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<td>.440</td>
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<td>FSR Risk</td>
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<td>.036*</td>
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<td>Highest Grade Completed</td>
<td>16.67(3.0)</td>
<td>17.00(2.5)</td>
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<td>36.7</td>
<td>.618</td>
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<td>RAVLT: Delay Recall Score</td>
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<td>6.55(1.5)</td>
<td>8.37</td>
<td>37</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>RAVLT: Forgetting Score</td>
<td>0.84(2)</td>
<td>4.39(1.5)</td>
<td>-6.116</td>
<td>35</td>
<td>&lt;.001*</td>
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<td>TMT- Part B: Time to Completion</td>
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<td>101.3(35.6)</td>
<td>-2.62</td>
<td>37</td>
<td>&lt;.001*</td>
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<td>2.7(.67)</td>
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<td>TMT B-A</td>
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<td>.181</td>
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<td>OASR</td>
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<td>50.8(1.3)</td>
<td>1.392</td>
<td>35</td>
<td>.173</td>
</tr>
</tbody>
</table>

* p < .05; **p<0.01 and 0.001; ***p<0.10
Table 4.

*Regression models of connectivity predicted by Successful Ager status and Cardiovascular Risk: Left Hippocampus to Left PCC*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>$\Delta F^2$</th>
<th>$\beta$</th>
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<tbody>
<tr>
<td>Step 1:</td>
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<tr>
<td>SA Status</td>
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<tr>
<td>Age</td>
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<tr>
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<tr>
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<td>0.121</td>
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<td>0.000</td>
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<tr>
<td>Interaction between SA status</td>
<td></td>
<td></td>
<td></td>
<td>.007</td>
</tr>
<tr>
<td>and FRS Risk</td>
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* $p < .05$; ** $p < 0.01$ and 0.001; *** $p < 0.10$

*Regression model of connectivity predicted by Successful Ager status and Cardiovascular Risk: Left Hippocampus to Right PCC*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>$\Delta F^2$</th>
<th>$\beta$</th>
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<tbody>
<tr>
<td>Step 1:</td>
<td>0.157</td>
<td>0.157</td>
<td>3.166</td>
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<tr>
<td>SA Status</td>
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<td>Interaction between SA status</td>
<td></td>
<td></td>
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<td>-.145</td>
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<tr>
<td>and FRS Risk</td>
<td></td>
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</table>

* $p < .05$; ** $p < 0.01$ and 0.001; *** $p < 0.10$
Regression models of connectivity predicted by Successful Ager status and Cardiovascular Risk: Right Hippocampus to Right PCC

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>$\Delta F^2$</th>
<th>$\beta$</th>
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<tr>
<td>Step 1:</td>
<td></td>
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<tr>
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<td>Interaction between SA status and FRS Risk</td>
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Ty6
* $p < .05$; **$p<0.01$ and 0.001; ***$p<0.10$

Regression models of connectivity predicted by Successful Ager status and Cardiovascular Risk: Right Hippocampus to Left PCC

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>$\Delta F^2$</th>
<th>$\beta$</th>
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<tbody>
<tr>
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* $p < .05$; **$p<0.01$ and 0.001; ***$p<0.10$
### Table 5.
**Summary of Partial Correlations between connectivity of the Right Hippocampus to Right PCC and individual FRS factors which controlling for total FRS**

<table>
<thead>
<tr>
<th>Measure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
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<td>1. Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Hypertension</td>
<td>.031</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3. Smoking</td>
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<td>-.026</td>
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<td></td>
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</tr>
<tr>
<td>4. Cholesterol</td>
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<td>-.098</td>
<td>.140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. HDL</td>
<td>-.026</td>
<td>.182</td>
<td>-.190</td>
<td>-.724**</td>
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</tr>
<tr>
<td>6. L. Hippocampus to R PCC Connectivity</td>
<td>-.174</td>
<td>-.045</td>
<td>.125</td>
<td>.090</td>
<td>-.259</td>
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</tbody>
</table>

* *p < .05; **p<0.01 and 0.001; ***p<0.10

### Summary of Partial Correlations between connectivity of the Right Hippocampus to Left PCC and individual FRS factors which controlling for total FRS

<table>
<thead>
<tr>
<th>Measure</th>
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<th>2</th>
<th>3</th>
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<th>5</th>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>2. Hypertension</td>
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<tr>
<td>3. Smoking</td>
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<td>4. Cholesterol</td>
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<td>-.098</td>
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<tr>
<td>5. HDL</td>
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<td>.182</td>
<td>-.190</td>
<td>-.724**</td>
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<tr>
<td>6. L. Hippocampus to R PCC Connectivity</td>
<td>-.174</td>
<td>-.045</td>
<td>.125</td>
<td>.090</td>
<td>-.259</td>
</tr>
</tbody>
</table>

* *p < .05; **p<0.01 and 0.001; ***p<0.10

### Summary of Partial Correlations between connectivity of the Left Hippocampus to Left PCC and individual FRS factors which controlling for total FRS

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1. Age</td>
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<tr>
<td>2. Hypertension</td>
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<tr>
<td>3. Smoking</td>
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<td></td>
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</tr>
<tr>
<td>4. Cholesterol</td>
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<tr>
<td>5. HDL</td>
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<td>.163</td>
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<td>.894**</td>
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<td>6. L. Hippocampus to R PCC Connectivity</td>
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<td>-.186</td>
<td>.069</td>
<td>.111</td>
<td>.179</td>
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</table>

* *p < .05; **p<0.01 and 0.001; ***p<0.10
### Summary of Partial Correlations between connectivity of the Right Hippocampus to Left PCC and individual FRS factors which controlling for total FRS

<table>
<thead>
<tr>
<th>Measure</th>
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<th>3</th>
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<th>5</th>
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<tr>
<td>2. Hypertension</td>
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<td>4. Cholesterol</td>
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<td>5. HDL</td>
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<td>.182</td>
<td>-.190</td>
<td>-.724**</td>
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<tr>
<td>6. L. Hippocampus to R PCC Connectivity</td>
<td>-.174</td>
<td>-.045</td>
<td>.125</td>
<td>.090</td>
<td>-.259</td>
</tr>
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</table>

* $p < .05$; **$p<0.01$ and 0.001; ***$p<0.10$

---

### Summary of Partial Correlations between connectivity of the Right Hippocampus to Right PCC and individual FRS factors which controlling for total FRS

<table>
<thead>
<tr>
<th>Measure</th>
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<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>2. Hypertension</td>
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<tr>
<td>3. Smoking</td>
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<td>-.022</td>
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<tr>
<td>4. Cholesterol</td>
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<td>-.069</td>
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<td>5. HDL</td>
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<td>.163</td>
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<td>-.728**</td>
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<td>-.113</td>
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<td>.058</td>
<td>-.015</td>
<td>-.133</td>
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</table>

* $p < .05$; **$p<0.01$ and 0.001; ***$p<0.10$
\[ \hat{p} = 1 - S_0(t)^{\exp(\sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \bar{X}_i)} \]

Figure 1. Framingham Risk Equation, where \( S_0(t) \) is baseline survival at follow-up time \( t \), \( \beta_i \) is the estimated regression coefficient (log hazard ratio), \( X_i \) is the log-transformed value of the \( i \)th risk factor, (if continuous), \( \bar{X}_i \) is the corresponding mean, and \( p \) denotes the number of risk factors.
Figure 2. Seed location for a) Left Hippocampus PCC and b) Right Hippocampus
Figure 3. Seed locations for a) Right PCC and b) Left PCC
Figure 4. Seed-to-seed paths between seed pairs
Figure 5. Association and interaction between L Hippocampus and R PCC connectivity with Framingham Risk.