

IMPACT OF DEFAULT MODE NETWORK FUNCTIONAL CONNECTIVITY, BLOOD  
GLUCOSE, AND RACE ON THE RELATIONSHIP BETWEEN AGE AND VERBAL  
EPISODIC MEMORY IN AN OLDER ADULT SAMPLE

by

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(Under the Direction of Lawrence H. Sweet)

ABSTRACT

Black older adults are more likely to develop dementia, and at a younger age, than White older adults, and cognitive performance differs between race as a function of age. Default mode network (DMN) function has been linked to normal and abnormal aging and may represent a mechanistic neuromarker of these effects. The current study evaluated the impact of age, DMN functional connectivity (FC), blood glucose (HbA1C), and race (proxy for social determinants of health) on verbal episodic memory task (Rey Auditory Verbal Learning Task – RAVLT) in a matched sample of Black and White older adults. We predicted that the RAVLT performance would be inversely associated with age and HbA1C, and positively associated with DMN FC. Finally, Black older adults were also expected to perform more poorly on the RAVLT. Participants included a subsample of the Human Connectome Project – Aging (HPC-A) sample. Fifty Black adults over age 50 were matched to 50 White participants on age, education, and sex. Fourteen participants and their matched pair were excluded during rigorous functional MRI (fMRI) quality control, reducing the sample 72. Per HPC-A protocol, demographic, serum,

fMRI, and cognitive assessments were completed in one visit. FMRI data processing included *a priori* seed region FC of the DMN (i.e., mPFC, IPL, PCC, hippocampus). Analyses were performed with the full sample of 72 participants and a subsample of 50 with complete blood glucose data (i.e., *blood glucose sample*, n=50). A three-step hierarchical linear regression was conducted on the full sample with age, DMN FC, and race as independent variables and RAVLT total score as the dependent variable. None of these models significantly predicted RAVLT performance. A four-step hierarchical linear regression was performed in the blood glucose sample using age, HbA1C, DMN FC, and race as independent variables and RAVLT total score as the dependent variable. The first step of the regression with age as a predictor was significant; however, steps two, three, and four did not yield further significantly predictive utility. While results did not support *a priori* hypotheses, they provide a unique matched sample approach incorporating brain, health, and social factors into a single study.

INDEX WORDS: Cognitive Aging, Default Mode Network Functional Connectivity, Verbal Episodic Memory, Social Determinants Of Health

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## CHAPTER 1

### INTRODUCTION

Black older adults are more likely to develop Alzheimer's disease (AD), and at a younger age, than White older adults (Díaz-Venegas et al., 2016; Matthews et al., 2019; Weuve et al., 2018). Racial differences are also apparent on test performance in cognitive domains, such as verbal memory, with marked age-associated decline. Specifically, several studies have found differences between Black and White participants (Díaz-Venegas et al., 2016; Zahodne et al., 2017) and some of them have suggested this difference can be explained by health factors, including social determinants of health (SDoH; Early et al., 2013; Matthews et al., 2019; Schwartz et al., 2004). Therefore, a growing research priority has been the use of multi-measure assessments to determine what underlying differences there may be in cognitive aging across races and what social and neurobiological factors are contributing to these effects.

In recent years, neuroimaging has been used in conjunction with behavioral assessments to better understand the relationship between cognitive performance and brain function across the lifespan. However, there is limited research on the social determinants of known neurobiological risk factors associated with cognitive aging. These biomarkers of cognitive decline include integrity of neural networks underlying cognition and general health conditions associated with aging that impact neurocognitive functions. Specifically, the default mode network (DMN), a well-characterized brain system (discussed below), has been linked to both normal and abnormal aging (Eyler et al., 2019). Additionally, the DMN is associated with metabolic processes associated with aging, including deficits in glucose uptake that can result

from type II diabetes, a health problem that is more prevalent in Black adults (Cheng et al., 2019). Given racial disparities in cognitive aging and assessments related to cognition and memory, it is important to take an integrative approach that considers these neurobiological markers to better understand how cognitive aging may impact races differently via SDoH.

### **Functional Connectivity and Resting-state fMRI**

Functional magnetic resonance imaging (fMRI) is a non-invasive neuroimaging technique used to evaluate brain function in real-time by examining the changes in blood oxygen level-dependent (BOLD) signal that result from neural metabolic demand (Fox & Greicius, 2010). This technique has been widely used since its inception in the early 1990s to quantify brain responses to carefully designed stimulus manipulations presented in the scanner (Bandettini et al., 1993; Kwong et al., 1992; Ogawa et al., 1992). The initial focus of fMRI on such task-based designs has changed drastically, especially in recent years, to include resting-state experiments.

Resting-state functional connectivity (FC), defined as observed synchrony in BOLD signal between spatially distinct brain regions (Biswal et al., 1995), has become a valuable technique to quantify patterns of spontaneous neural activity that were initially interpreted as signal noise (Leonardi et al., 2013). Seed region FC is a frequently used approach to reveal network synchrony. This involves averaging the BOLD signal intensity over time in a seed region, typically a known core node of the network of interest, and calculating the cross-correlation of this time series with the BOLD signal over time in other target regions in the rest of the brain (Joel et al., 2011). While other approaches are available, such as exploratory independent component analysis (ICA), seed region FC is advantageous when the network and its nodes are known *a priori* and study hypotheses pertain to the specific network.

The utility of resting-state FC to infer functional integrity of the examined network when it is actively engaged was initially supported by Biswal and colleagues (1995). They demonstrated that spontaneous activation fluctuations in motor areas during rest were correlated in a similar way to their relationship while performing a motor task. It is now well established that resting-state FC is associated with the brain's functional organization and reflects the integrity of the networks examined, which supports its use in evaluating distinct cognitive networks (Fox & Greicius, 2010; Leonardi et al., 2013).

### **Default Mode Network**

The default mode network (DMN) is one of the most commonly studied neural networks using the resting-state FC approach. It is a group of brain regions characterized by increased activity during resting states compared to when a person actively participates in externally demanding cognitive tasks (Buckner et al., 2008; Mevel et al., 2011). The degree of DMN resting-state synchrony has been associated with the level of performance of several different higher-order cognitive functions including memory (e.g., autobiographical, semantic, episodic), social cognition, and imagining events (Smallwood et al., 2021; Ward et al., 2015). One prominent theory suggests that variations in resting-state FC in the DMN reflect memory consolidation and may, therefore, serve as an index of ability to retain and later retrieve previously learned and encoded information (Mohan et al., 2016).

The DMN spans several regions and includes core bilateral nodes in the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), inferior parietal lobule (IPL), and hippocampal structures (Anderson et al., 2011; Di & Biswal, 2014; Miao et al., 2011; Sharaev et al., 2016). Functional and structural connectivity studies have demonstrated the significant relationship between the PCC and mPFC (Greicius et al., 2009; Tang et al., 2017), as well as the

PCC and the rest of the DMN (Fransson & Marrelec, 2008). Although the cognitive functions mediated by this system remain under investigation, the anterior DMN - centered on the bilateral mPFC - has been associated with prospective executive functioning and the posterior DMN - including the bilateral PCC hub and hippocampal nodes - has been associated with retrospective memory (Andrews-Hanna et al., 2010; Buckner & Vincent, 2007; Raichle, 2015).

Although other nodes, such as the hippocampus, may be used as seed regions to center the DMN, the PCC is the most robust of the DMN nodes, and it has, therefore, been used most frequently as a reliable seed region in resting-state FC neuroimaging studies of the DMN (Jovicich et al., 2016; Miao et al., 2011). When integrated, hippocampal and thalamic seed maps are able to fully explain DMN maps seeded using the PCC. This notable overlap provides further evidence that the hippocampus and PCC are significantly interrelated (Lee & Xue, 2018). There is also evidence of interactive effects with the PCC and hippocampus when evaluating the role of the DMN in memory function (Dunn et al., 2014). This overlap of the DMN, hippocampus, and memory function indicates the multiple domains and networks that are integral to understanding memory outcomes in older adults.

Not only does the hippocampus appear to play a major role in DMN FC, but hippocampal connectivity has been associated with performance on tasks measuring episodic memory. Briefly, episodic memory is a memory system associated with semantic memory, which is long-term memory of declarative information such as words and dates (Squire, 2009; Squire et al., 1993; Tulving, 2002). Episodic memory is distinct from semantic memory in that it allows individuals to recall autobiographical memories and mentally project themselves back to these events (Tulving, 2002). High FC between the hippocampi and the left dentate-left lingual gyrus have both been found to be associated with poorer performance on measures of verbal episodic

memory (Salami et al., 2014; Smagula et al., 2018). Free recall of recently learned information has also been predicted by the level of interhemispheric FC of the hippocampi (Wang et al., 2010). In young adults with the APOE e4 genotype, there has been reported changes in FC over time from the left middle hippocampus and lateral temporal lobe to the left posterior hippocampus. Furthermore, these changes were related to altered memory performance (Zheng et al., 2021). Finally, recent research literature has also reported that resting-state FC in the hippocampus predicts episodic memory performance in healthy young adults. Specifically, using relevance vector regression researchers were able to utilize whole brain FC in relation to the anterior hippocampus to predict participants' episodic memory performance (Persson et al., 2018). Taken together, this body of research illustrates the importance of the DMN in understanding memory and the strong FC link between the DMN and the hippocampus. Evaluation of the posterior DMN and hippocampus in aging and cognition in the context of race is an important addition to this ongoing field of research.

### ***Effects of Neurological Conditions on DMN Function***

Interest in changes to the DMN in abnormal cognitive aging has increased significantly in recent years given previous research indicating the DMN role in memory. Compared to younger adults, healthy older adults exhibit higher DMN FC. Similarly, when compared to healthy older adults, AD patients demonstrate higher connectivity in the anterior DMN, which is thought to be evidence of additional compensatory activation in those with more severe changes to FC in the posterior DMN. Comparison studies between cognitively normal older adults and patients with mild cognitive impairment (MCI) and AD provide additional evidence of decreased FC in cognitively impaired groups (Lee et al., 2016; Qi et al., 2010; Zhang et al., 2009). In particular change in the posterior DMN is thought to be an early neuromarker of MCI and AD (Wang et al.,

2013). Common areas of decreased intranetwork FC in MCI, compared to age and education matched control participants, include the PCC, left hippocampus, and bilateral IPL (Cha et al., 2013; De Vogelaere et al., 2012; Wu et al., 2011). Additionally, evidence suggests the amyloid deposition in AD is detected initially, and most prominently, in brain regions within the DMN (Ferreira & Busatto, 2013; Jin et al., 2012). Given the saliency in these changes between healthy controls and those with AD, it is important to attempt to identify other factors that may be able to distinguish healthy controls prior to the onset of MCI and AD.

Default mode network FC has also been associated with cognitive performance in other patient groups that have cognitive impairment, including people diagnosed with stroke, temporal epilepsy, and Parkinson's disease. For instance, in a stroke sample, decreased FC within the PCC/precuneus was associated with performance on the Montreal Cognitive Assessment (MoCA) 10 days after stroke and predictive of MoCA scores at a 3-month follow-up. Additionally, a subsample who reported with post-stroke cognitive problems, FC in the mPFC and left hippocampus were significantly lower than a subsample without post-stroke cognitive problems (Ding et al., 2014). Among a sample with temporal epilepsy, memory retention scores on a verbal memory test (California Verbal Learning Test – 2<sup>nd</sup> Edition, CVLT-II) were positively associated with increased FC between right sided precuneus and IPL to the left hippocampus, indicating a possible compensatory connectivity pathway (Holmes et al., 2014). Finally, in a sample of participants with Parkinson's disease, lower FC in the DMN was found to be correlated with lower verbal and visual memory performances (Lucas-Jiménez et al., 2016). Similar patterns of association between DMN FC and cognitive performance among both healthy aging samples and those with known neurological diagnoses supports the idea that the utilization

of both neuroimaging and cognitive assessment in research is necessary to better understand the underlying neuronal mechanisms that may be driving cognitive aging.

### ***Impact of Metabolic Risk Factors Associated with Neurodegenerative Processes on DMN FC***

Type II diabetes is a known risk factor of AD, MCI, and other neurodegenerative processes and has been shown to impact FC in the DMN, including a significant association between Hemoglobin A1C (HbA1C) and FC in the DMN (Ishibashi et al., 2018; Rashid et al., 2019). Furthermore, research has shown blood glucose levels can impact DMN FC across the lifespan. Within healthy young adults, increased plasma glucose was associated with decreased resting neuronal activity in the PCC/precuneus (Ishibashi et al., 2018). In middle aged adults at risk for pre-diabetes, alterations in FC density were found in the precuneus and left medial orbitofrontal cortex, particularly among the female participants who had a high insulin resistance (Lopez-Vilaret et al., 2022). Among older adults, when comparing those with and without type II diabetes, there is decreased intra-regional FC between the hippocampus and several regions of the brain including the precuneus, IPL, and posterior cingulate gyrus in those with type II diabetes (Zhou et al., 2010). The impact of insulin has also been further supported with noted increases in FC between the hippocampal regions and mPFC in a group of older adults with type II diabetes who received intranasal insulin prior to imaging (Zhang et al., 2014). Taken together this research supports that more elevated blood glucose, regardless of diabetes diagnosis, can impact DMN FC across the adult lifespan.

Given the previously established relationship between blood glucose and cognition, researchers have also assessed for the relationship between DMN FC and cognition while accounting for blood glucose (Cui et al., 2015). Compared to healthy older adults, older adults with type II diabetes have shown worse performance on verbal memory tasks related to HbA1C

level (Zhou et al., 2010). However, several other studies have found more support for impacts on executive functioning as opposed to memory performance. In middle aged adults, executive functioning performance has been predicted by the interactive effects of known symptoms of metabolic syndrome and the FC in the DMN, though notably, the association with memory performance was not significant (Foret et al., 2021). Similarly, in post-menopausal women at risk for AD, those with higher insulin levels were found to exhibit reduced FC between the hippocampus and mPFC, and mPFC and parahippocampal regions, which were also related to executive function but not memory performance (Kenna et al., 2013). The relationship between metabolic uptake of glucose has also been shown to mediate the decrease in FC in relation to age. Subsequently, in this study FC in the DMN was found to mediate executive functioning deficits (Xu et al., 2023). Given mixed results regarding the relationship between blood glucose, DMN FC, and memory performance it is important to continue to evaluate this relationship while including other factors such as SDoH that may further explain this relationship.

### ***Healthy Cognitive Aging and the DMN***

While a large body of research has been dedicated to FC in the DMN and its relation to AD and MCI, decreased FC in the DMN is often conceptualized as a normal part of healthy cognitive aging as well (De Marco et al., 2019; Klaassens et al., 2017; Malagurski et al., 2022; Mevel et al., 2011; Salami et al., 2014). Specifically, FC between the anterior and posterior nodes of the DMN decreases as a result of aging including in the PCC, superior and middle frontal gyrus, and superior parietal region (Hafkemeijer et al., 2012). While several cross-sectional studies have shown declines in FC in the DMN over time in healthy adult samples (Li et al., 2016), there is some evidence that FC of the DMN is more stable across time among those who deny subjective cognitive decline (Beason-Held et al., 2009; Persson et al., 2014).

Nevertheless, the preponderance of evidence suggests that cognitive decline, and particularly memory changes over time, appear to be associated with declines in FC (Persson et al., 2014). In addition to this pattern of decreased FC, there have also been reports of increased areas of deactivation during a task relative to rest in more frontal areas of the DMN including the anterior cingulate, medial prefrontal, and superior frontal gyrus. This increase in deactivation is thought to be a compensatory mechanism in which more cognitive effort is diverted to other brain regions to perform a tasks (Duda & Sweet, 2020; Mevel et al., 2011).

There is growing evidence that two well-known AD risk factors, subjective cognitive complaints and biological risk factors (e.g., diabetes, APOE status), may be detected at the neurobiological level using FC. Regarding subjective memory complaints, older adults who present with a normal cognitive profile but report subjective memory complaints appear to be objectively at an elevated risk for neurocognitive impairment. This group tends to exhibit decreased FC when compared to control participants without subjective complaints, but still exhibit higher FC than those with confirmed MCI or AD (Wang et al., 2013), though some studies have reported this pattern was not found in the DMN in their samples (Kawagoe et al., 2019). Furthermore, decreased FC in those with subjective cognitive complaints has been linked to greater decline in performance on cognitive control and attention assessments (Zajac et al., 2020).

An association has also been found between APOE genetic status in healthy older adults and poorer performance on word list recognition and cued recall. This decrease in performance was also related to changes in FC in the left medial temporal gyrus (Matura et al., 2014). Older adults with cognitively normal neuropsychological profiles, but at biological risk for developing AD (e.g., APOE4 genetic carriers, individuals with preclinical amyloid deposition), exhibit FC

patterns similar to AD patients. Specifically, it has been reported that both groups exhibit weaker FC between DMN nodes, including the precuneus, hippocampus, and anterior cingulate cortex compared to healthy controls (Hafkemeijer et al., 2012; Sheline et al., 2010). Both of these findings support the concept that FC changes in the DMN may precede detectable changes in cognitive performance in those who will go on to develop AD (Hafkemeijer et al., 2012; Sheline et al., 2010).

### ***DMN and Memory***

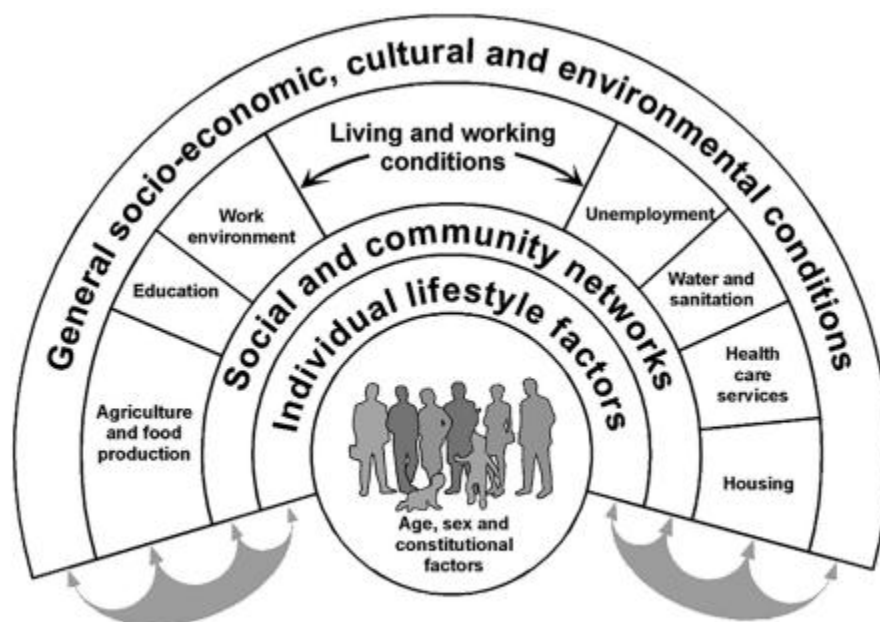
In addition to indirect evidence, there is direct evidence that FC may parallel cognitive function, and particularly episodic memory. Specifically, among healthy older adults, decreases in DMN FC have been found to be associated with decreased performance on tasks of episodic memory (Mevel et al., 2013; Staffaroni et al., 2018). Performance on immediate and delayed episodic memory recall on auditory verbal learning tasks has been significantly and positively associated with regional homogeneity of the DMN in the parahippocampal gyrus, PCC, precuneus, IPL, and mPFC (Huo et al., 2018). Similarly, positive associations have been reported between DMN FC and performance on verbal memory scores from the CVLT-II and Weschler Memory Scale (WMS; Jin et al., 2012; Li et al., 2017). While the limited extant literature supports the notion that FC changes with age and interacts with cognitive performance, there needs to be more focus on healthy older adults FC. Specifically, what factors within this group may impact FC to help determine which healthy older adults may still become susceptible to subsequent MCI and conversely what factors may contribute to further healthy aging.

Another line of direct evidence that DMN FC reflects episodic memory function employs transcranial magnetic stimulation (TMS) and task-based fMRI. In one study, a group of healthy older adults increased their performance on a verbal episodic learning and memory measure

following TMS and this coincided with and increased in DMN FC including the precuneus (Cui et al., 2022). Similarly, older adults who exhibited increased FC in the DMN following intermittent theta burst stimulation, a form of TMS, over the left IPL performed better on learning and memory assessments at baseline as well as at a 3 year follow-up, compared to older adults who did not exhibit increased FC following the stimulation (Abellana-Pérez et al., 2019). Using a similar pre-post design to predict long-term outcome, Oren and colleagues (2019) reported that age-related decreases in left intra-hippocampal RSFC after a visual memory fMRI task also predicted worse episodic memory performance two years later.

### **Social Determinants of Health**

The Center for Disease Control (CDC) defines SDoH as “nonmedical factors that influence health outcomes” which include “the conditions in which people are born, grow, work, live, worship, and age” (Hacker, 2022). A common model used to illustrate SDoH by Dahlgren and Whitehead (2021) is colloquially referred to as the “rainbow model”. This model demonstrates how various elements from the macro to the micro level all interact with each other and can in turn impact the individual (see Figure 1).



Source: adapted from Dahlgren and Whitehead, 1991

**Figure 1**

*Rainbow Model of SDoH*

SDoH greatly impact healthcare outcomes the United States (US) in regards to mortality rates, quality of life, and lifespan (Braveman & Gottlieb, 2014; Chen et al., 2022; Ding et al., 2024; Javed et al., 2022). Many deaths within the US healthcare system have behavioral causes and these health-related behaviors are formed by social factors, including income, education, and employment (Braveman & Gottlieb, 2014). There is evidence to support a stepwise increase in overall health as social position rises due to increased income, education, or employment position (Braveman & Gottlieb, 2014). In older adults, there has been evidence that SDoH are associated with glucose intolerance, metabolic syndrome, cognition function, and multiple morbidity (i.e., having two or more chronic health conditions; Brunner, 2005; Jester et al., 2023; Northwood et al., 2018).

SDoH also have indirect effects on health outcomes via chronic stress and allostatic load and these outcomes impact minority populations more significantly than White populations (Braveman & Gottlieb, 2014). The Weathering Hypothesis states that the exposure to social and economic disadvantage across the lifespan may accelerate the normal aging process and lead to earlier neurodegenerative symptoms and diseases in Black adults when compared to White adults (Chen et al., 2022). Additionally, cumulative stress can partially account for variance in performances on tasks of executive functioning and episodic memory in Black older adults when compared to White older adults (Chen et al., 2022).

These known SDoH factors impacting health lends itself to dismantling previous research conclusions suggesting that race itself explains discrepancies in health outcomes between Black and White groups, as there are well-known differences in socioeconomic status, educational achievement and other SDoH between races. This is further supported by research findings that racial differences in health outcomes significantly decrease once the effects of SDoH variables have been accounted for (Braveman & Gottlieb, 2014). In recent years some models of SDoH have expanded to incorporate how structural racism leads to inequalities and racial disparities (Egede et al., 2023). The World Health Organization (WHO) defines SDoH to include social class, gender, ethnicity/race, education, occupation, and income. However, the current model followed by the US government does not include race, ethnicity, or racism as part of the model of SDoH, despite research supporting how structural racism impacts clinical outcomes such as blood pressure, HbA1c, self-care behaviors, standards of care, and mortality (Egede et al., 2023; Hill-Briggs et al., 2021). Additional research supports that lifetime discrimination is associated with dementia incidence (Joshi & Tampi, 2024) and poorer episodic memory in middle-aged adults

(Seblova et al., 2022). This research provides strong support for the recognition and integration of race and discrimination when evaluating SDoH and associated health outcomes.

While the current study does not have direct access to specific SDoH variables outside of education, and given the evidence reported above, the use of race as a variable of interest should be seen as a proxy to reflect various SDoH components that impact Black adults more significantly. When determining differences in performance within the current study, race will not be viewed as an inherent “biological difference” to explain cognitive performance differences, but rather lends itself to indicate there are other underlying factors within the realm of SDoH that should be considered. Previous research has inaccurately attempted to portray race as explaining biological differences in cognitive aging; therefore, it is important to continue to examine SDoH that likely explain these differences (Owens et al., 2024; Ramanan et al., 2023). Simultaneously, it is important to recognize how structural racism and discrimination within the US leads to macro-level legislation and economic decisions that can impact SDoH and lead to an increase in health disparities in minority populations (Tsai et al., 2021; Yearby, 2020). While interventions to reduce health disparities is well beyond the scope of the current research, gaining depth and understanding of the relationships that lead to these health disparities can be utilized in the healthcare systems in providing better prevention and intervention strategies.

### **Neurocognitive Aging among Black Older Adults**

It was been well established there are racial disparities in cognitive aging and the prevalence of health conditions that increase risk for cognitive decline. Additionally, it has been demonstrated that FC of the DMN is useful in better understanding and more accurately assessing mechanisms of cognitive aging. Despite this, DMN FC has not yet been employed to examine racial disparities in cognitive aging. As previously mentioned, Black older adults have

the highest rate of AD and other dementias by race in the US (Matthews et al., 2019). Further, one of the leading risk factors for poor cognitive aging, diabetes, is nearly twice as prevalent among Black Americans compared to their White peers. Between 2011 and 2016 the overall estimated prevalence of diabetes was 12.1% for White adults and 20.4% for Black adults (Cheng et al., 2019), who also exhibit worse diabetes control along with higher rates of complications (Peek et al., 2007). These differences have been replicated in other studies, although results have been mixed when controlling factors that may underlie the race effects. Specifically, some have found this racial disparity effect in diabetes prevalence decreases to a non-significant level when controlling for age, sex, socioeconomic status, and health variables (Link & McKinlay, 2009). However, other studies have found that the disparity continues to persist in older adults even when controlling for these variables (Blazer et al., 2002). Taken together, measuring diabetes is an important biological factor to consider, given its links to changes in cognition, impact on FC in the DMN, and disproportionate prevalence in Black Americans.

Currently one study has found that in healthy older adults, Black participants exhibited lower FC compared to White participants in the DMN, particularly between the precuneus, ventrolateral temporal cortex, IPL, and parahippocampal gyrus. Additionally, race was found to modify the relationship between DMN FC and cognitive performance (Misiura et al., 2020). However, no further studies have replicated these findings. Given the evidence that even in healthy aging there may be changes in FC that relate to cognitive outcomes, this should be further evaluated.

### **Current Study**

Given the importance of FC in the DMN in relation to aging and the known disparities in cognitive aging outcomes in Black older adults with higher SDoH profiles, it is important to

further evaluate psychosocial and biological factors influencing FC in the DMN, DMN FC itself, and cognitive outcomes associated with FC in the DMN in the context of race. Past literature has established racial disparities in the prevalence of type II diabetes, and performance on cognitive measures of verbal memory. To date, there has been little research evaluating how race and associated SDoH may impact the known relationship between the DMN FC, cognitive assessment outcomes, and aging.

The current study intends to evaluate the cognitive performance of a matched sample of Black and White older adults while evaluating the impact of DMN FC, blood glucose, and race (as a proxy for SDoH) on verbal episodic memory. As past research has established, we predict there will be a negative relationship between age and performance on a verbal episodic memory task. HbA1C will then be added to the model with the expectation that higher HbA1C will be associated with poorer episodic memory. When added as an additional independent variable, DMN FC will also impact episodic memory, with lower FC being predictive of poorer episodic memory. Finally, race will be added as a variable to serve as a proxy for SDoH and it is predicted that Black older adults will perform more poorly on the verbal episodic memory task, even when all other variables (i.e., age, DMN FC, HbA1C) have already been included in the model.

We also predict additional correlations between several variables. First, age will be significantly negatively correlated with DMN FC and significantly positively correlated with blood glucose. Finally, we predict that there will be a significant negative relationship between DMN FC and glucose, and a significant positive relationship between DMN FC and episodic verbal memory.

## CHAPTER 2

### METHODS

#### **Participants**

Participants included in this study are a subsample of the Human Connectome Project – Aging (HCP-A) sample. Recruitment occurred at multiple sites across the US (Washington University, St. Louis; University of Minnesota, Twin Cities; Massachusetts General Hospital; and University of California, Los Angeles) beginning in 2017. Recruitment was accomplished using public advertisements, announcements at workshops on aging, and outreach while visiting senior living centers. A detailed description of HCP-A recruitment has been previously published (Bookheimer et al., 2019). Briefly, participants were recruited in three age cohorts: Mature (34-64), Old (65-79), and Oldest Old (80 and above). The sample was intended to reflect the overall US population using the 2015 Census Bureau’s projections to determine the race, ethnicity, and sex distributions within each age group. Race, ethnicity, and sex were determined via self-report. Individuals were excluded by the HCP-A research group if they had been diagnosed with a major psychiatric disorder, neurologic disorder, or had a history of a severe depressive episode that required more than 12 months of treatment. Individuals over the age of 60 were also excluded if they received a score of less than 30 on the Telephone Interview for Cognitive Status modified (TICS-M; Bookheimer et al., 2019).

In total the HCP-A study (2.0 Release, Released on 02/26/2021) included 101 Black adults ranging in age from 36 to 100 years old. A subset of 50 older Black adults over the age of 50 were selected to evaluate cognitive aging in the present study. Given the study aims regarding

SDoH reflected in racial disparities between Black and White older adults, all Black participants over the age of 50 in the HCP-A dataset were matched to one of 406 White participants using the characteristics of age, education, and sex. The matching process was done using R Studio's (2020) package "MatchIt" using the "optimal" method to facilitate replicability and ensure each matched pair were as similar as possible. Each pair was determined to be a "good" match based on standard mean difference, variability ratio, and an empirical cumulative distribution function (eCDF) mean. Distance is defined through a propensity score and sex was evenly distributed across groups (Table 1). During fMRI data processing (see Functional MRI section below), eight participants were excluded due to excessive motion, two were excluded due to corrupted data files, and four were excluded due to poor MRI alignment. Given the matched nature of this study, this resulted in these 14 participants and their matched partner to be excluded from the final sample, leaving the total sample to be 72 (see Table 2).

Analyses for this study were performed with the full sample of 72 participants and a subsample of the participants with complete blood glucose data, hereafter referred to as the "*blood glucose sample*." Eleven participants without blood glucose data and their matched pair were excluded from the blood glucose sample, resulting in a subsample size of 50 (see Table 3). To preserve statistical power, individuals without blood glucose data were not excluded from the full sample. It was noted that there was a higher proportion missing blood glucose data among Black (11%) than White (4%) participants. T-tests were performed to determine if there were significant differences between the means of sample characteristics of Black and White groups within the full sample and blood glucose sample. Other than the proportion of missing blood glucose data, there were no significant differences between these groups, indicating removal of participants to create the subsample did not significantly alter the makeup of the sample based on

these variables. However, there was a significant difference on MoCA scores between Black and White participants in both the full sample and blood glucose sample (see Tables 2 and Table 3). Additionally, participants were separated by sex to determine if there were any sex differences in DMN FC or RAVLT performance within either sample (see Table 5). In the full sample and blood glucose sample, there were no significant differences between male and female participants regarding RAVLT total score or for any DMN FC ROI.

**Table 1**

*Summary of balance matched variables before and after individual matching*

	Standard Mean Difference	Variability Ratio	eCDF mean
Un-Matched Data			
Distance	1.11	0.35	0.22
Education	0.56	0.81	0.10
Age	0.60	1.34	0.19
Matched Data			
Distance	0.09	0.75	<0.01
Education	-0.07	1.13	0.05
Age	0.09	1.16	0.05

**Table 2***Full sample characteristics by race after individually matching age, sex, and education*

	Black Older Adults (n=36)	White Older Adults (n=36)	t-Value	Significance ( <i>p</i> )
Frequency Male (%)	13 (36.11)	13 (36.11)	--	--
Mean Age (SD)	60.71 (8.97)	61.71 (9.26)	-0.46	.65
Mean Education (SD)	16.03 (2.16)	16.17 (2.57)	-0.25	.81
Mean MoCA scores (SD)	24.53 (2.48)	26.86 (2.24)	<b>-4.19</b>	<b>&lt;.01</b>
Mean HbA1c % (SD)	5.47 (0.51)	5.51 (1.19)	-0.17	.86
RAVLT Total Score Trials 1-5 (SD)	39.69 (10.07)	43.56 (10.93)	-1.56	.12

*Note.* MoCA = Montreal Cognitive Assessment, RAVLT = Rey Auditory Verbal Learning Task\* Differences between groups are based on two-tailed significance ( $p < 0.05$ )**Table 3***Blood glucose sample characteristics by race after individually matching age, sex, and education*

	Black Older Adults (n=25)	White Older Adults (n=25)	t-Value	Significance ( <i>p</i> )
Frequency Male (%)	11 (44.00)	11 (44.00)	--	--
Mean Age (SD)	59.77 (7.77)	61.20 (8.92)	-0.56	.58
Mean Education (SD)	15.68 (2.32)	15.88 (2.82)	-0.27	.79
Mean MoCA scores (SD)	25.00 (2.18)	26.72 (2.46)	<b>-2.61</b>	<b>.01</b>
Mean HbA1c % (SD)	5.47 (0.53)	5.64 (1.36)	-0.56	.58
RAVLT Total Score Trials 1-5 (SD)	41.16 (11.04)	43.36 (10.43)	-0.72	.47

*Note.* MoCA = Montreal Cognitive Assessment, RAVLT = Rey Auditory Verbal Learning Task\* Differences between groups are based on two-tailed significance ( $p < 0.05$ )

**Table 4***T values of mean differences between full sample and blood glucose sample*

		Full Sample	Blood Glucose	t-Value	Significance ( <i>p</i> )
Mean Age (SD)	Black Older Adults	60.71 (8.97)	59.77 (7.77)	0.42	.67
	White Older Adults	61.71 (9.26)	61.20 (8.92)	0.21	.83
	All Older Adults	61.21 (9.07)	60.43 (8.31)	0.48	.63
Mean Education (SD)	Black Older Adults	16.03 (2.16)	15.68 (2.32)	0.60	.54
	White Older Adults	16.17 (2.57)	15.88 (2.82)	0.42	.68
	All Older Adults	16.10 (2.36)	15.87 (2.56)	0.51	.61
Mean MoCA scores (SD)	Black Older Adults	24.53 (2.48)	25.00 (2.18)	0.76	.45
	White Older Adults	26.86 (2.24)	26.72 (2.46)	0.23	.82
	All Older Adults	25.69 (2.63)	25.86 (2.46)	0.36	.72
Mean HbA1c % (SD)	Black Older Adults	5.47 (0.51)	5.47 (0.53)	<.01	.99
	White Older Adults	5.51 (1.19)	5.64 (1.36)	0.40	.69
	All Older Adults	5.49 (0.95)	5.55 (1.03)	0.33	.74
RAVLT Total Trials 1-5 (SD)	Black Older Adults	39.69 (10.07)	41.16 (11.04)	0.54	.59
	White Older Adults	43.56 (10.93)	43.36 (10.43)	0.07	.94
	All Older Adults	41.63 (10.61)	42.26 (10.69)	0.32	.75

*Note.* MoCA = Montreal Cognitive Assessment, RAVLT = Rey Auditory Verbal Learning Task

**Table 5**

*T values of mean differences between male and female participants in full sample and blood glucose sample*

		Male	Female	t-Value	Significance ( <i>p</i> )
RAVLT Total	Full Sample	40.38	42.47	-0.82	.42
Score Trials 1-5 (SD)		(11.45)	(10.05)		
	Blood Glucose Sample	41.09 (11.84)	43.26 (9.71)	-0.71	.48
DMN FC Hippocampus (SD)	Full Sample	0.058 (0.03)	0.057 (0.04)	0.04	.97
	Blood Glucose Sample	0.055 (0.03)	0.057 (0.04)	-0.12	.91
DMN FC IPL (SD)	Full Sample	0.162 (0.12)	0.135 (0.10)	0.99	.33
	Blood Glucose Sample	0.184 (0.12)	0.143 (0.10)	1.33	.19
DMN FC mPFC (SD)	Full Sample	0.036 (0.04)	0.024 (0.04)	1.32	.19
	Blood Glucose Sample	0.035 (0.04)	0.027 (0.04)	0.64	.53

*Note.* MoCA = RAVLT = Rey Auditory Verbal Learning Task, IPL = Internal Parietal Lobule, mPFC = Medial Prefrontal Cortex

## Procedures

Per HCP-A protocol, an initial phone screening was performed to determine whether participants experienced any major health conditions that would warrant exclusion from the study. Adults over 60 also completed the Telephone Interview for Cognitive Status Modified (TICS-M) to determine whether cognitive impairment was present. Eligible participants provided informed written consent prior to participation in the HCP-A study and then completed the Montreal Cognitive Assessment (MoCA), as well as an MRI contraindication questionnaire. All data was collected in one day during an 8-10-hour baseline visit, which included the MRI, serum, cognitive, and self-report assessments used in this study. The order of testing during this assessment is shown in Table 6 (Bookheimer et al., 2019). Research sites were provided “standard operating procedure manuals” and study-based trainings to ensure consistency in data collection (Harms et al., 2018). A complete list of procedures and measures can be found elsewhere (Bookheimer et al., 2019).

**Table 6**

*Outline of study procedures in order of completion (Bookheimer et al., 2019)*

Baseline visit (8-10 hours)
Informed Consent
MoCA (Montreal Cognitive Assessment)
RedCap assessment of current medications
Vitals (e.g., blood pressure, height, weight)
Biological Samples (e.g., blood draw, saliva swab, drug screening)
First Neuroimaging Scan (45 minutes)
RedCap Block 1 (e.g., demographic and self-report questionnaires)

NIH Toolbox

Second Neuroimaging Scan (45 minutes)

Cognitive Testing (e.g., RAVLT, Picture Memory)

RedCap Block 2 (e.g., demographic and self-report questionnaires)

Satisfaction Survey

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## **Measures**

Participants provided self-reported demographics (e.g., years of education, age in months, sex), had their blood drawn, completed cognitive assessments, and participated in neuroimaging. These occurred on the same day during an 8- to –10-hour baseline assessment.

### ***Self-Report***

Self-reported demographics were collected during a structured interview. Measures used in the present analyses were years of education, age in months, race, and sex.

### ***Blood Draw***

Blood samples were collected preferably after an 8-hour fasting period, but blood was still collected and included in analyses from participants who did not fast. Within the current study sample, only 4 participants reported not fasting prior to their blood draw. A fasting metabolic panel was performed which included serum glucose, hemoglobin A1c (HbA1C), and insulin. Glucose was measured in milligrams per deciliter (mg/dL), normal levels of glucose are typically between 70 and 100 mg/dL. HbA1c is measured as a percentage with the normal range being between 4 and 5.6%. Insulin was measured in millionths per milliliter (uU/mL) with a normal range being below 17 uU/mL.

### ***Cognitive Assessment***

Episodic memory was measured using standardized administration of the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) which has consistently been shown to have good reliability and validity (Boone et al., 2005; Magalhães et al., 2012). The RAVLT is a 15-item word list task where a series of words is presented to the participant verbally five times. Following each reading of the list, the participant is asked to recall all the words they learned to establish a learning curve. They are then administered a second list, which operates as a distractor, and asked to recall them, followed by a query to report the initial list again. The commonly administered 20-minute delayed recall was not administered to reduce the length of the overall test battery (Bookheimer et al., 2019).

### ***Functional MRI***

MRI data were collected using Siemens 3T Prisma scanners across HCP-A research facilities. Whole-brain, high-resolution multi-echo MPRAGE (FOV = 224 mm; matrix = 320 mm; TR = 2400 ms, TE = 2.14 ms, 0.8mm-thick sagittal slices) and whole-brain echoplanar imaging (EPI) series were acquired. EPI acquisition parameters (FOV = 208 mm x 180 mm, matrix = 104 x 90, MB 8, TR/TE = 800/37 ms, flip angle = 52 degrees) resulted in 2.0 mm isotropic voxels covering the whole brain in 72 oblique-axial slices (Glasser et al., 2013; Harms et al., 2018). During four 5.6-minute resting-state EPI scans, participants viewed a white fixation crosshair on a black background. They were instructed to stay still and awake and blink normally.

fMRI data processing and analysis were conducted in the UGA CNS Lab using Analysis of Functional Neuroimages software (AFNI; Cox, 1996) using the `afni_proc.py` processing stream (see example 11b: [https://afni.nimh.nih.gov/pub/dist/doc/program\\_help/afni\\_proc.py.htm](https://afni.nimh.nih.gov/pub/dist/doc/program_help/afni_proc.py.htm),

retrieved fall 2023) to extract residual activity following removal of known confounding signal sources (e.g., movement). Functional data sets were slice-time corrected, despiked, aligned to T1 data sets, volume registered, and scaled to percent signal change from mean signal intensity. Data were spatially smoothed using a 3-dimensional 4-mm full width half maximum Gaussian filter and transformed into standard stereotaxic space (Talairach & Tournoux, 1988). The first two volumes of each run were removed to avoid T1 saturation artifact. Volumes with intervolumetric movement greater than 0.20 mm along any axis were censored from further analysis. Although 202 participants were recruited for the study, 14 were excluded following stringent quality control steps. Twelve were excluded due to excessive intervolumetric movement (>2mm across >25% of volumes) during EPI scans and two were excluded due to data corruption which made data processing not possible.

A seed region FC analysis was conducted to quantify the strength of DMN synchrony. Specifically, a DMN seed region of interest (ROI) was created using 5mm radius spheres surrounding the left and right PCC center of mass coordinates reported in previous literature (Anderson et al., 2011). A mean EPI signal time series was extracted across the bilateral PCC for each participant for use as a predictor in voxel-wise cross-correlations. Cross-correlations were performed at the individual level to quantify synchronicity over time between seed ROI time series and the time course each voxel of the brain using the AFNI program 3dTcorr (Cox, 1996). Resulting Pearson's correlation coefficients reflecting each voxel's EPI association with the seed region over time were converted to normally distributed z-scores using a Fishers r to z transformation.

Target ROIs were determined *a priori* based on past literature and include the most frequently reported nodes of the default mode network (i.e., bilateral mPFC, IPL, PCC and

hippocampus) (Buckner et al., 2009; Robinson et al., 2015), see Table 7 below for RAI atlas coordinates of these ROIs in Talairach space. One DMN FC measure was calculated for each target ROI by averaging the z-values of all of its voxels. These mean z-values, representing the strength of synchrony of intrinsic brain activity between each target ROI and the PCC seed ROI for each participant, were averaged and used as independent variables in tests of hypotheses including DMN FC.

**Table 7**

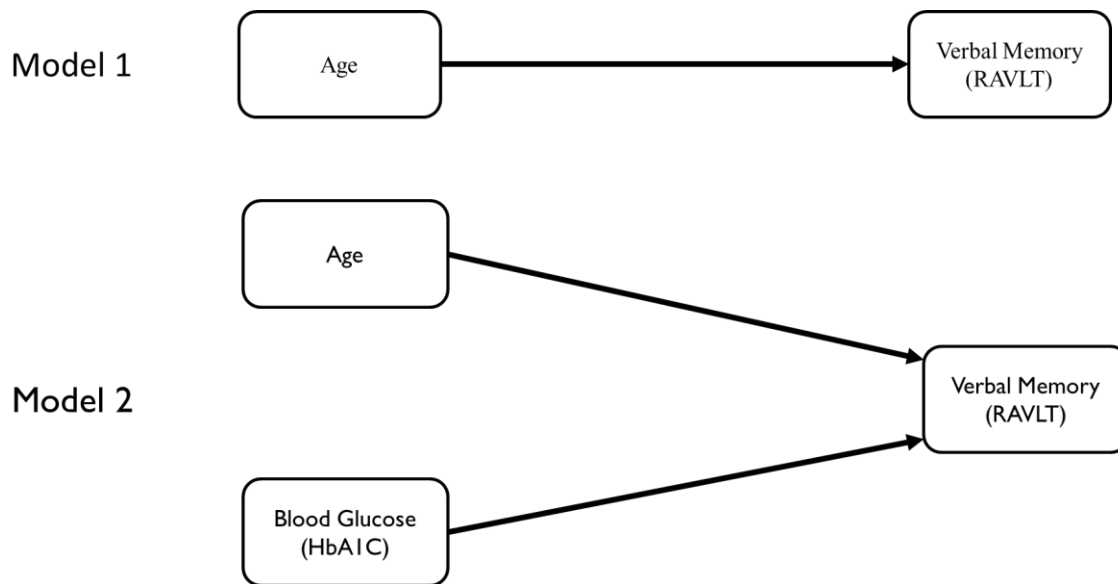
*Coordinates for seed and target ROIs in Talairach space*

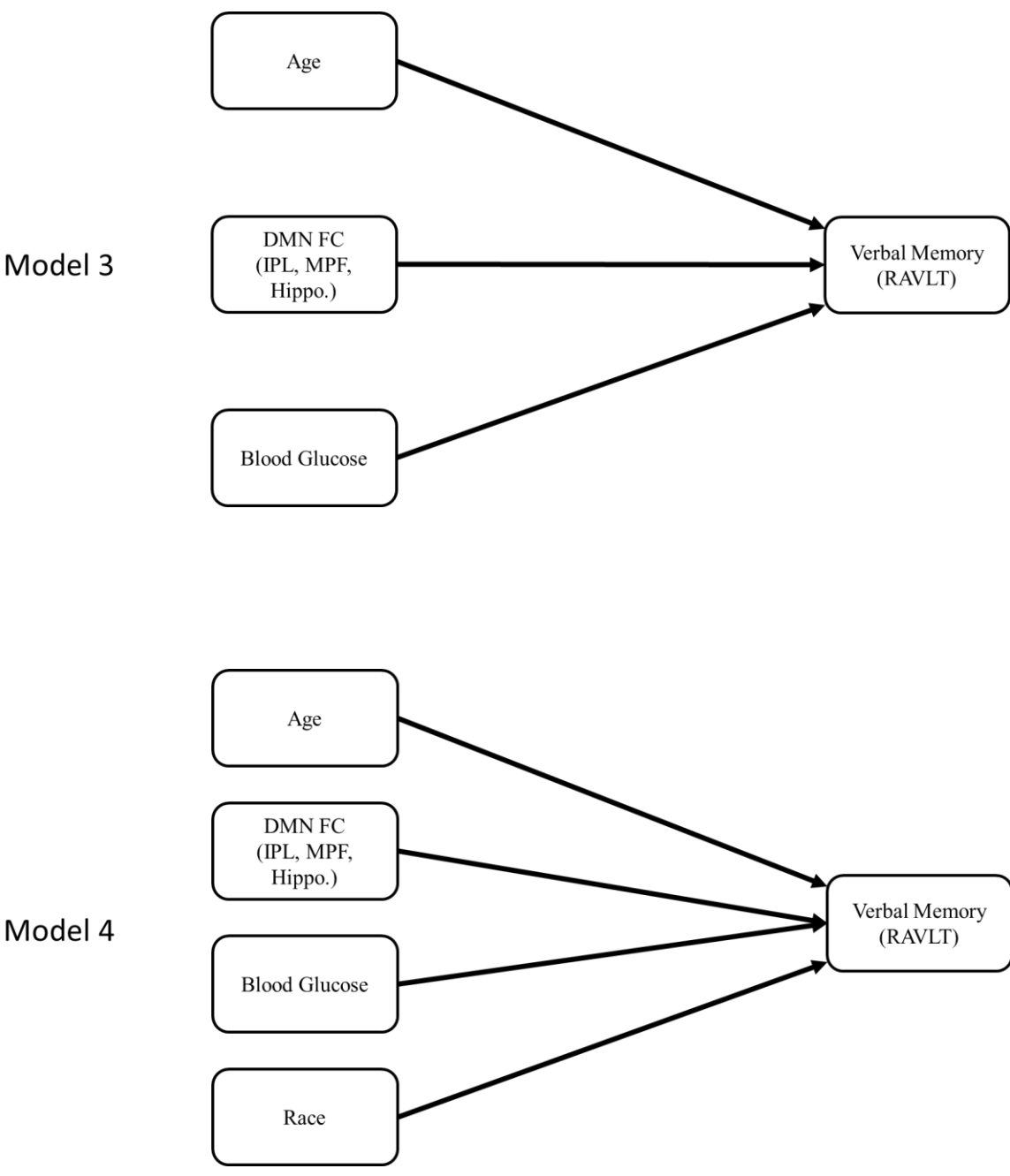
Name of Seed and Target Regions	Atlas Coordinates (x, y, z)
Left Inferior Parietal Lobule (I IPL)	42, 61, 48
Right Inferior Parietal Lobule (rIPL)	-47, 58, 47
Left Medial Frontal Cortex (lMFC)	5, -52, -9
Right Medial Frontal Cortex (rMFC)	-4, -52, -9
Left Posterior Cingulate Cortex (lPCC)	4, 47, 34
Right Posterior Cingulate Cortex (rPCC)	-5, 47, 34
Left Hippocampus	25, 20, -11
Right Hippocampus	-27, 20, -10

### **Data Analyses**

Hypotheses were tested using the Statistical Package for Social Sciences (SPSS; Version 26) using one-tailed significance criteria of  $p < .05$ , as they are directional. Hypotheses were tested using Pearson correlations and step-wise linear regressions to determine the magnitude of

expected effect of age and other independent variables on RAVLT performance. Three steps were modeled in the full sample to predict RAVLT scores. The first included only age, the second added FC measures (i.e., FC of hippocampus, IPL, and mPFC targets with PCC seed), and the third added race. For the blood glucose sample, the first two steps were identical. Blood HbA1C level was added in the third step (Model 3) followed by adding race in the fourth step (Model 4; see Figure 2). Bivariate correlations among all these variables were examined, and contrasts of race were conducted for each of the other measures.





**Figure 2.** Stepwise hierarchical linear regression models used to test hypotheses in the blood glucose sample

## Observed Power

Initial proposed analyses of the current study included a sample of 100 participants. However missing data, rigorous quality control of the fMRI data, and losing pairs of participants due to the matched pair design, resulted in significantly smaller sample sizes. As such the power within both samples is significantly lower than what was expected.

Power analyses were conducted using Jamovi Cloud from the Jamovi Project version 2.6 (2025). Within the full sample of 72, Model 1 of the linear regression was able to detect medium to large effects when holding power at 0.80 and using a one-tail alpha of 0.05. The linear regression models 2 and 4 (without HbA1C) were able to detect large effects when holding power at 0.80 and using a one-tail alpha of 0.05 (See Table 8).

**Table 8**

*A Priori Power Analysis for Full Sample*

	N	Effect Size ( $\eta^2$ )	$f^2$	Power	DF	DF (res.)	$\alpha$
Model 1	72	0.10	0.11	0.80	1	70	0.05
Model 2	72	0.15	0.18	0.80	4	67	0.05
Model 4 (w/o HbA1C)	72	0.16	0.19	0.80	5	66	0.05

Power analyses for the blood glucose sample regressions were also conducted. Within the blood glucose sample of 72, Models 1, 2, 3 and 4 of the linear regression were able to detect large effects when holding power at 0.80 and using a one-tail alpha of 0.05 (See Table 9).

**Table 9**

*A Priori Power Analysis for Blood Glucose Sample*

	N	Effect Size ( $\eta^2$ )	$f^2$	Power	DF	DF (res.)	$\alpha$
Model 1	50	0.14	0.16	0.80	1	48	0.05
Model 2	50	0.21	0.27	0.80	4	45	0.05
Model 3	50	0.23	0.29	0.80	5	44	0.05
Model 4	50	0.24	0.31	0.80	6	43	0.05

## CHAPTER 3

### RESULTS

Primary measures were assessed for distribution normality and outliers. Age, education, Montreal Cognitive Assessment (MoCA) scores, Rey Auditory Verbal Learning Task (RAVLT) performance, and neuroimaging data were normally distributed with skew and kurtosis both below |2|. Regarding the FC data for both the full and blood-glucose sample, outliers beyond two standard deviations were winsorized to either the fifth or ninety-fifth percentile. Within each ROI there were between one and four outliers. Following winsorization, paired sample t-tests were performed to ensure that this process did not significantly change the means of these variables. For the full sample, the winsorized means, hippocampus ( $t(71) = .32, p = .75$ ), IPL ( $t(71) = 1.19, p = .24$ ), and mPFC ( $t(71) = 1.67, p = .10$ ) ROIs were not significantly different from means prior to winsorizing and there were no longer any outliers. Similarly, in the blood-glucose sample winsorized means of hippocampus ( $t(49) = .06, p = .95$ ), IPL ( $t(49) = 0.13, p = .90$ ), and mPFC ( $t(49) = 0.27, p = .79$ ) ROI FC were not significantly different from the means prior to winsorizing and there were no longer any outliers.

The ROIs used in the seed-target approach were determined *a priori*; therefore, *t*-test vs. 0 were conducted on the mean FC effect per target ROI to confirm whether they were significantly related to the PCC seed region. The hippocampus ( $t(71) = 16.67, p < 0.01$ ), IPL ( $t(71) = 11.58, p < 0.01$ ), and mPFC ( $t(71) = 6.97, p < 0.01$ ) were all found to be significantly related to the PCC in the full sample, and these effects were stronger in the subsample with blood glucose data available ( $t's(49) > 16.67, p's < .01$ ).

Bivariate zero-order correlations between all variables were examined to evaluate Hypothesis 1, to confirm expected relationships (i.e., validity checks), and to screen for potential errors.

Age was not significantly correlated with RAVLT total scores in the full sample; however, marginal one-tailed significance level in the predicted direction ( $r(70)=-.182, p=.063$ ) suggest that Hypothesis 1 cannot be rejected without concern for type 2 error. While not a variable within our proposed models, MoCA scores were found to be positively correlated to RAVLT performance as well as race (see Table 10). The correlation between race and MoCA score is consistent with t-test findings indicating White participants performed significantly higher than Black participants (see Table 2). The positive relationship between the MoCA and RAVLT also provides support for the validity of performance on the RAVLT as it should coincide with higher general cognitive functioning on the MoCA, which also includes verbal episodic memory. No other significant correlations were found (see Table 10). This lack of significance also held true when the age – RAVLT score correlations were calculated separately by race. The expected inverse correlations were not significant in Black ( $r(34)=-.112, p=.517$ ) or White ( $r(34)=-.270, p=.111$ ) groups.

Hypothesis 1 was supported in the blood glucose sample, as age was found to be significantly and negatively correlated with RAVLT total score ( $r(48)=-.290, p=.041$ ). Additionally positive correlations between MoCA scores and race and RAVLT scores were again found. No other significant correlations among the study variables were found (see Table 11). When separated by race, White participants showed a significant negative correlation with a large effect between age and RAVLT scores ( $r(23)=-.491, p=.006$ ) but Black participants did not ( $r(23)=-.097, p=.323$ ). None of the intranetwork functional connectivity associations were

significant, but all were in the positive direction, except the mPFC association with the hippocampus.

In the full sample, Black and White participants did not differ significantly on RAVLT score ( $t(70)=1.56, p=.12$ ), age ( $t(70)=0.46, p=.65$ ), hippocampus FC ( $t(70)=0.54, p=.59$ ), IPL FC ( $t(70)=0.97, p=.34$ ), or mPFC FC ( $t(70)=0.11, p=.91$ ). Likewise, in the blood glucose sample, Black and White participants did not differ significantly on RAVLT score ( $t(48)=0.72, p=.47$ ), age ( $t(48)=0.56, p=.58$ ), HbA1C ( $t(48)=0.56, p=.57$ ), hippocampus FC ( $t(48)=-.10, p=.92$ ), IPL FC ( $t(48)=0.44, p=.66$ ), or mPFC FC ( $t(48)=0.04, p=.97$ ).

**Table 10**

*Pearson's correlations between independent and dependent variables in full sample (n=72)*

	RAVLT Score	Age	MoCA	Hippocampus	IPL	MPFC	Race
RAVLT Score	1.00	-.18	.45**	.03	.08	-.01	-.18
Age	-.18	1.00	-.16	-.003	.13	-.22	-.06
MoCA	.45**	-.16	1.00	.17	.09	-.07	.45**
Hippocampus	.03	-.003	.17	1.00	.12	-.02	-.06
IPL	.08	.13	.09	.12	1.00	.07	-.12
MPFC	-.01	-.22	-.07	-.02	.07	1.00	-.01
Race	-.18	-.06	.45**	-.06	-.12	-.01	1.00

Note.

\*  $p < .05$

\*\* $p < .01$

**Table 11**

*Pearson's correlations between independent and dependent variables in blood glucose sample (n=50)*

	RAVLT Score	Age	MoCA	HbA1c	Hippocampus	IPL	MPFC	Race
RAVLT Score	1.00	-.29*	.40**	-.10	-.07	.002	-.10	-.10
Age	-.29*	1.00	-.01	-.07	.10	.06	-.23	-.08
MoCA	.40**	-.01	1.00	.21	.16	.16	-.21	.36*
HbA1c	-.10	-.07	.21	1.00	.02	-.01	-.06	-.08
Hippocampus	-.07	.10	.16	.02	1.00	.19	-.05	.02
IPL	.002	.06	.16	-.01	.19	1.00	.04	-.06
MPFC	-.10	-.22	-.21	-.06	-.05	.04	1.00	-.01
Race	-.10	-.08	.36*	-.08	-.02	-.06	-.01	1.00

Note.

\* p<.05

\*\*p<.01

A three-step hierarchical linear regression was conducted on the full sample with age, DMN regions FC, and race as independent variables and RAVLT total score as the dependent variable (see Table 12). Following the proposed model, age was entered first, then all 3 regions of the DMN, and then race. As noted above, blood glucose level was not included in this model due to missing data. The first step of the regression analysis included only age as a predictor. As expected based on the bivariate correlation ( $r(70)=-.182, p<.05$ ), this model did not significantly predict RAVLT total score ( $R^2=.039, F(1,68)=2.775, p=.10$ ). In the second step, FC of the three regions of the DMN were added to the model (mPFC, IPL, and hippocampus). This model also

did not significantly predict RAVLT scores ( $R^2=.055$ ,  $F(4,65)=.955$ ,  $p=.44$ ). Finally, race was added into the model as a proxy for SDoH. Again, this model did not significantly predict RAVLT total score ( $R^2=.083$ ,  $F(5,64)=1.155$ ,  $p=.34$ ).

**Table 12**

*Hierarchical linear regression of all participants on RAVLT total score*

Variable	Model 1			Model 2			Model 3		
	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	$\beta$
Age	-.23	.14	-.20	-.26	.15	-.22	-.26	.15	-.23
Hippo				10.40	38.30	.03	6.72	38.13	.02
IPL				11.39	11.75	.20	9.53	11.75	.10
mPFC				-8.51	34.69	-.03	-10.82	34.49	-.04
Race							-3.55	2.57	-.17
R <sup>2</sup>		.04			.05			.08	
F		2.78			.96			1.16	

*Note.*

\*  $p < .05$

Next, a four-step hierarchical linear regression was performed in a similar fashion on the blood glucose sample using age, blood glucose, DMN regions, and race as independent variables and RAVLT total score as the dependent variable (see Table 13). The first step of the regression only included age as a predictor and, consistent with the bivariate correlation ( $r(48)=-.290$ ,  $p < .05$ ), was significant ( $R^2 = .101$ ,  $F(1,46)=5.141$ ,  $p=.028$ ), confirming age as a significant

predictor of RAVLT performance ( $\beta=-.317, p=.28$ ). The second step of the regression included age and blood glucose and was not significant ( $R^2=.117, F(2,45)=2.983, p=.06$ ), with age continuing to exhibit a significant effect ( $\beta=-.326, p=.03$ ), while blood glucose did not significantly contribute to predicting RAVLT total score. In the third step of the regression the FC of three regions of the DMN were included in addition to age and blood glucose. This model did not significantly predict RAVLT total score ( $R^2=.140, F(5,62)=1.368, p=.26$ ); however the effect of age remained significant ( $\beta=-.357, p=.02$ ). Similarly, in the fourth step race was added to the model; this model was also not significant ( $R^2=.155, F(6,41)=1.250, p=.301$ ) and age remained a significant predictor ( $\beta=-.365, p=.02$ ). Together this regression analysis supports age as the sole significant predictor of RAVLT performance among the primary study variables.

**Table 13**

*Hierarchical linear regression of RAVLT total score in 50 participants with blood glucose data*

Variable	Model 1			Model 2			Model 3			Model 4		
	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	B
Age	-.41	.18	-.32*	-.42	.18	-.33*	-.46	.19	-.36*	-.47	.19	-.37*
HbA1C				-1.33	1.45	-.13	-1.44	1.49	-.14	-1.56	1.50	-.151
Hippo							-8.61	46.18	-.03	-8.14	46.34	-.03
IPL							4.75	14.04	.05	3.81	14.13	.04
MPFC							-39.04	38.39	-.15	-41.18	38.61	-.16
Race										-2.61	3.10	-.12
R <sup>2</sup>		.10			.12			.14			.16	
F		5.14*			2.98			1.37			1.25	

*Note.*

\*  $p<.05$

Since age remained a significant predictor across all models in the blood glucose sample, exploratory analyses assessing the interaction between age and the other independent variables were conducted. However, there were no interactive effects between age and race, blood glucose, or FC in DMN regions that significantly ( $p > .01$ ) predicted RAVLT score.

Finally, exploratory analyses were conducted to determine if there were unilateral effects of the ROIs on RAVLT performance. As such, regressions were rerun including only the left and right ROIs. In the full sample neither left (Table 14) or right (Table 15) ROIs were shown to significantly predict RAVLT scores within the models. Similarly, in the blood glucose sample, neither left (Table 16) or right (Table 17) ROIs were shown to significantly predict RAVLT scores.

**Table 14**

*Hierarchical linear regression of full sample on RAVLT total score with left hemisphere ROIs*

Variable	Model 1			Model 2			Model 3		
	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	$\beta$
Age	-.23	.14	-.20	-.24	.14	-.20	-.24	.14	-.21
lHippo				1.86	35.97	.006	-2.12	35.68	-.007
lIPL				6.42	11.08	.07	4.89	11.01	.06
lmpPFC				-14.00	34.39	-.05	-11.06	34.09	-.04
Race							3.93	2.52	.19
R <sup>2</sup>		.04			.04			.08	
F		2.78			.71			1.07	

*Note.*

\*  $p < .05$

**Table 15***Hierarchical linear regression of full sample on RAVLT total score with right hemisphere ROIs*

Variable	Model 1			Model 2			Model 3		
	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	$\beta$
Age	-.23	.14	-.20	-.25	.15	-.21	-.26	.14	-.22
rHippo				9.67	35.28	.03	8.51	34.88	.03
rIPL				10.55	10.23	.13	9.32	10.14	.11
rmPFC				-16.50	29.35	-.07	-20.23	29.10	-.09
Race							4.03	2.50	.19
R <sup>2</sup>		.04			.05			.09	
F		2.78			.91			1.26	

*Note.*\*  $p < .05$ **Table 16***Hierarchical linear regression of RAVLT total score in 50 participants with blood glucose data with left hemisphere ROIs*

Variable	Model 1			Model 2			Model 3			Model 4		
	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	B
Age	-.41	.18	-.32*	-.42	.18	-.33*	-.43	.19	-.34*	-.44	.19	-.34*
HbA1C				-1.33	1.45	-.13	-1.47	1.48	-.14	-1.57	1.49	-.15
lHippo							-13.93	41.63	-.05	-13.82	41.71	-.05
lIPL							2.91	13.57	.03	1.46	13.69	.02
lmPFC							-48.10	39.48	-.18	-45.98	39.62	-.17
Race										2.77	3.03	.13
R <sup>2</sup>		.10			.12			.14			.16	

F 5.14\* 2.98 1.37 1.25

*Note.*

\*  $p < .05$

**Table 17**

*Hierarchical linear regression of RAVLT total score in 50 participants with blood glucose data with left hemisphere ROIs*

Variable	Model 1			Model 2			Model 3			Model 4		
	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	$\beta$	B	SE B	B
Age	-.41	.18	-.32*	-.42	.18	-.33*	-.43	.19	-.33*	-.45	.19	-.35*
HbA1C				-1.33	1.45	-.13	-1.34	1.48	-.13	-1.49	1.48	-.14
lHippo							3.76	12.13	.04	3.94	12.10	.05
lIPL							-38.01	30.88	-.18	-41.32	30.96	-.19
lmPFC										3.30	3.02	.16
Race												
R <sup>2</sup>		.10			.12			.13			.16	
F		5.14*			2.98			1.33			1.31	

*Note.*

\*  $p < .05$

## CHAPTER 4

### DISCUSSION

As the size and relative proportion of the US population of older adults continues to grow, it is becoming increasingly necessary to better understand the impact of health factors and social determinants of health (SDoH) on cognitive aging. Within existing research literature, there are few publications from studies that have evaluated the interactive effects of health factors and SDoH on aging and cognition. The current study evaluated the known relationship between age and verbal episodic memory, measured via the Rey Auditory Verbal Learning Test (RAVLT), and included variables of blood glucose level, Default Mode Network functional connectivity (DMN FC), and SDoH as possible modifiers of this relationship. As this study utilized previously obtained data via the Human Connectome Project (HCP), and more specific SDoH variables (e.g., income socioeconomic status) were not available, race was used as a proxy. The individually matched sample design of the current study was novel. Black and White participants were matched on variables of age, sex, and education, to improve internal validity and statistical power, and to ensure equal representation of both races, rather than over-representation of White participants. Analyses were conducted with the full sample and a subsample of participants whose blood glucose metrics were reported in the HCP database (*blood glucose sample*). It was predicted based on test norms that older age would be associated with poorer RAVLT performance (Schmidt, 1996; Hypothesis 1). When added to the model, lower DMN FC (Hypothesis 2) and higher HbA1C (Hypothesis 3) were expected to predict poorer RAVLT performance. Finally, it was predicted that race, added as a proxy for SDoH, would

account for significant variance in RAVLT performance with Black participants scoring lower on the RAVLT (Hypothesis 4).

Within the full sample, there were no significant correlations between any of the study variables. The expected negative correlation between age and RAVLT performance was evident as a small effect (Cohen, 2016), but contrary to past research, it was only nearly significant. Additional inverse correlations representing this relationship within Black and White groups were also not significant, although a nearly significant medium effect (Cohen, 2016) was observed in the White sample. In the blood glucose subsample, the inverse association between age and RAVLT scores was confirmed with a significant correlation corresponding to a medium effect size. However, when correlations were computed separately in Black and White groups, Black participants exhibited a very small and nonsignificant effect, while White participants demonstrated a significant negative correlation with a large effect size. There were no additional significant correlations between any of the other study variables. Taken together, confirmation of significant inverse associations between age and RAVLT performance were found only in the blood glucose subsample and driven by a large effect in the White sample. None of the other hypotheses were supported. Specifically, FC of the DMN, blood glucose health, and the race proxy of SDoH did not account for significant variance in RAVLT scores in the full sample or the subsample with blood glucose data available.

While the results of the current study did not support the advanced *a priori* hypotheses, they contribute to the current research literature, as they provide a unique matched sample approach that incorporates brain, health, and social factors into a single study. Consideration of several factors that could explain limited significant main or interactive effects across both samples may inform future investigation of this topic. These include assessments of memory,

blood glucose, DMN, and SDoH, and their complicated associations with race. While results of the current study lack significant effects, the observed patterns of effect sizes may prove valuable for future studies.

### **RAVLT Measurement**

Age and RAVLT scores were not significantly associated in the full sample, but they were nearly significant, and in the expected direction. Consistent with Hypothesis 1, this association did reach significance in the smaller blood glucose subsample. There are several possible reasons for this limited replication of prior research literature. Because the full sample and blood glucose subsample did not differ in demographic characteristics or any of the study measures (Table 4), the significant relationship between age and RAVLT scores only in the smaller blood glucose subsample (with lower statistical power) may indicate a systematic confound or greater variance of key variables in the full sample. For example, although age and RAVLT scores did not differ between full and blood glucose samples and variance was similar, variance in age was unexpectedly larger in the full sample group ( $SD=9.12$  vs  $8.35$ ,  $d = 0.14$ ). It is possible that limited confirmation of Hypothesis 1 is attributable to main or interacting effects of a confounding variable that was not formally analyzed or due to chance via sampling error. For instance, RAVLT measurement approach and their interactions with other factors could have obscured the hypothesized effects.

It was noted that the associations between age and RAVLT were stronger in the White than the Black group, and these racial differences were much stronger in the smaller glucose subsample than the full sample. Therefore, the omission of blood glucose data in 11% of the Black sample and 4% of the White sample may have been associated with another variable that systematically interacted with race and increased confounding variance in the full sample.

Importantly, this speculation, intended to inform future research, is based on qualitative interpretation of gradients in effect sizes rather than statistical significance.

Additionally, these age-RAVLT association differences in significance between full sample and subsample may be due to validity of the assessment technique or measurement error. There are multiple strategies when deciding which scores derived from the RAVLT should be utilized to represent learning and memory performance. In the current study, the total of words learned across trials one through five was utilized. While total learning scores have been well-established in predicting later progression of cognitive decline (de Sousa Magalhães et al., 2012), it may be that the RAVLT scores of total learning are less sensitive to variation in other variables such as age, race, and DMN FC at rest.

A previous study investigating cortical atrophy within the DMN, dorsal attention network, frontal-parietal network, and language network indicated that early learning (RAVLT trials one and two) was most strongly correlated with the cortical thickness within the dorsal attention network; meanwhile late learning (trials four and five) along with delayed recall was associated with DMN cortical thickness (Putchá et al., 2019). Additionally, there is recent evidence that when assessing initial learning, the utilization of trials four and five alone may allow for differentiation of cognitive status between those with dementia, mild cognitive impairment (MCI), subjective cognitive impairment, and cognitively normal healthy controls (Almkvist et al., 2024). The current study utilized secondary data from the HCP-Aging repository, which provided scores only for trials 1 and 5. Therefore, further examination of how late learning trials may have impacted results is not feasible.

In addition to utilizing total scores, there is evidence that integration of intra-individual variability through lost access (no longer recalling words previously recalled) and gained access

(recalling words that were not previously recalled) across learning trials may provide additional insights into likelihood of later cognitive decline. Specifically, higher rates of lost and gained access at baseline were associated with increased risk of cognitive decline at an 18-month follow-up in a sample of cognitively intact older adults. These results were indicative of predictability above and beyond what was predicted with total words learned across trials (Sugarman et al., 2014).

Utilizing additional RAVLT measurement techniques may provide further insights into how different components of the RAVLT interact directly with the current studies variables of interest. In particular, initial learning through trials four and five may have a stronger relationship with DMN FC. Though importantly, utilization of fewer trials of data increases the likelihood of floor or ceiling effects. Future researchers may want to explore evaluating different RAVLT measurement techniques in a single study to determine the interaction between DMS FC and learning performance.

Another factor to consider is, while participants were matched by sex, the distribution of male and female participants was not equal, including more female than male participants. There is evidence to indicate gender differences in default mode network functional connectivity (Ficek-Tani et al., 2023). There is also some evidence that there may also be sex differences in performance on the RAVLT, with researchers finding that older women outperform men across variables of the total words learned, delayed recall, and recognition (Gale et al., 2007). As previously stated, participants within this study were matched by sex, though additional analyses examining performance of Black male and female participants and White male and female participants separately was not done given low sample size. As such, it is possible that sex confounded the relationship between age and RAVLT scores. Given limited sample size,

participants were not separated by both sex and race, however when looking at sex alone, there was no significant difference in RAVLT total score in male and female participants.

### **Default Mode Network Functional Connectivity**

In both the full sample and the blood glucose subsample DMN FC was not a significant predictor of episodic memory performance, which does not support Hypothesis 2, that lower DMC FC would be associated with poorer RAVLT scores. In addition to limited statistical power, this null finding might be attributable to confounding variance associated with sex or age, or their interactions with other study measures.

Similar to the RAVLT, known sex differences in the DMN FC may be important in better understanding changes over time in older adults. Past research has shown that women exhibit higher interhemispheric structural (Ingahalikar et al., 2013) and functional (Sacher et al., 2013) connectivity than men, and specifically in the posterior DMN as they age, particularly around the decades of menopause (Ficek-Tani et al., 2023). Ficek-Tani and colleagues (2023) also reported differential directions of effects among the nodes of the DMN and that higher connectivity among the women in the posterior cingulate cortex to angular gyrus was positively correlated with measures of declarative memory. While sex was matched between race groups in both full and subsamples, variance associated with sex was not controlled. Without controlling for sex in this study these effects could not be taken into account, though independent sample t-tests were conducted on male and female participants, with results indicating there were no significant differences in DMN FC in any of the current study ROIs.

The research literature applying DMN FC to clinical research questions is still emerging and remains varied regarding FC changes during the aging process. While there is evidence to support the direction of the hypothesized DMN FC changes with age (Hafkemeijer et al., 2012;

Li et al., 2016; Persson et al., 2014), some past research has also reported that DMN FC remains stable over time in healthy older adults. Furthermore, it is possible that these stable levels of FC are the result of concurrent increases and decreases in connectivity across different areas of the DMN. This possibility is supported by a recent study of healthy older adults over the age of 64 that found longitudinal stability in the strength of the DMN FC over seven years, yet the different nodes of the DMN showed both increases and decreases in FC strength across time. Specifically, while global DMN strength remained stable, longitudinal FC changes were observed between the right temporal cortex and right precuneus/PCC and between the left parietal and left prefrontal cortex (Malagurski et al., 2022).

Although it is not possible to examine such longitudinal effects in the current study, FC of bilateral network nodes exhibited different associations with age, albeit nonsignificant, in terms of direction and strength. Therefore, exploratory analyses evaluating the associations between left and right hemisphere nodes (ROIs) of the DMN and RAVLT performance were conducted separately to determine if unilateral results may have been masked by combining hemispheres. Results were similar to bilateral analyses, with no significant effects of right or left hemisphere DMN FC ROIs on RAVLT performance.

There has also been evidence of nonlinear changes in DMN FC over the lifespan (i.e., both increasing and decreasing FC), and specifically, different trajectories among middle aged and older adults that may have obscured hypothesized effects. One study reported increasing DMN FC between the ages of 50 and 66 and then significantly accelerated declines in FC after the age of 74 that were associated with episodic memory changes (Staffaroni et al., 2018). Given that the current study included participants spanning both of these age ranges, null findings may reflect changes across age that when aggregated together, yield non-significant findings.

Nonlinear associations between age and DMN FC should be examined in future research.

However, given the relatively small sample size of this study, it would not be prudent to utilize nonlinear regression models, as results would be significantly under powered. Additionally, the overall sample in the current study skews significantly to the younger side of this age range, with only eight of the original 72 participants over the age of 74.

Additionally, the current study sample - with ages ranging from 50 to 87 - were all considered to be healthy with normal cognitive function. While a majority of the sample is currently too young to be considered “super agers” (i.e., individuals over the age of 80 with cognitive abilities expected of individuals three decades younger, Sun et al., 2016), it is important to consider the possibility that some participants may, as they age, be considered “super agers”. Indirect evidence for this notion has been reported by a morphometry study of super agers. Cortical thickness of regions associated with the DMN (i.e., MPF, anterior temporal cortex, anterior mid cingulate cortex) were positively correlated with memory performance (Sun et al., 2016). However, other research on super agers has found that, when compared with normal agers, there was no differences in DMN FC and no significant correlation between FC and memory performance (Keenan et al., 2024).

Given these past mixed findings regarding age effects, older adults may have significant intra-individual variability in DMN FC that precluded detection of group effects in the current study. Given the limited cognitive testing available in the present dataset, the younger age range of participants, and the relatively low sample size, it would not be possible to make this determination in our sample. Overall, the present findings coupled with prior research supports the need for longitudinal analysis of DMN FC in older adults, as a single time point may not

accurately reflect fluctuations in FC over time. While the current study was cross-sectional, the HCP-A study is currently collecting longitudinal data which could be used in future analyses.

Lack of expected DMN FC associations with episodic memory performance could also be related to confounding variance associated with blood glucose levels. While past research has shown that blood glucose levels are associated with changes in DMN FC, which was not evident in the current study (Chen et al., 2016; Ishibashi et al., 2018; Lopez-Vilaret et al., 2022). However, the direct nature of this relationship is still unclear. In a recent study, researchers found that there was an incremental increase in negative DMN FC from samples without diabetes, compared to those with prediabetes and those with diabetes for less than ten years. This increase in negative connectivity was not found in samples with a history of diabetes for more than ten years. When evaluating positive DMN FC there was no significant difference between groups without diabetes, those with prediabetes, and those with early-stage diabetes. Though there was a significant difference between those who had diabetes for less than ten years compared to those who had diabetes for more than ten years (Liu et al., 2019). The current study did not directly evaluate diabetes diagnosis and included one data point for HbA1C. However, longitudinal data is currently being collected via the Human Connectome project and following changes in blood glucose over time, which may allow for additional exploration of blood glucose.

### **Blood Glucose**

Within the subsample of participants who had HbA1C data available, this blood glucose measure was not significantly correlated with other variables, including RAVLT performance, which is contrary to Hypothesis 3 (higher HbA1C would predict poorer RAVLT performance). The relationship between type II diabetes and impaired verbal memory in older adults has been well established (Yau et al., 2014; Zhou et al., 2010). Participants in this study did not have a

history of type II diabetes; however, prior research findings suggest that blood glucose levels at the higher end of normal limits is associated with more cognitive difficulties than blood glucose levels at the lower end of the normal limits. Specifically, older adults with lower HbA1c performed better on RAVLT measures of delayed recall, learning ability, and memory consolidation (Mortby et al., 2013; Sims et al., 2015). These prior results indicate that lower glucose levels are beneficial in maintaining healthy cognitive aging; higher blood glucose levels, even within the normal range, may impact verbal episodic memory (Kerti et al., 2013). It is not clear why the results of the current study are not consistent with these prior research findings. Notable differences between past studies and the current studies include an older average age of the sample, more stringent procedures to ensure fasting blood glucose measures, oral measurement compared to a blood draw, and multiple blood draws over time (Kerti et al., 2013; Mortby et al, 2013; Sims et al., 2015). Additional potential confounding factors to consider include whether the current study participants fasted prior to their blood glucose draw and the relatively limited range in HbA1C levels.

### **Social Determinants of Health and Race**

When discussing the results of the current study, it is imperative that measurement of SDoH be taken into account. In both the full sample and blood glucose sample, the SDoH proxy of race was not found to be a predictor of RAVLT performance, contrary to Hypothesis 4 that Black participants' mean performance on the RAVLT would be lower than that of White participants. However, there were significant relationships between RAVLT performance and MoCA scores and between MoCA scores and race with White participants scoring higher than Black participants in both full and blood glucose samples.

This unexpected lack of support for Hypothesis 4 may indicate that there was some independent confounding variable that impacted race and RAVLT score or that SDoH factors associated with race were not sufficiently captured in the current study. While there could actually be no association between race and RAVLT scores, unexpected low power due to missing data and rigorous quality control of the data make it challenging to determine if the null finding is accurate. The current study was also limited in its capacity to explore variables of SDoH, as data was acquired through the Human Connectome Project, which did not include many measures of SDoH. This made it challenging to evaluate the relationship between SDoH and the proxy of race used in this study.

SDoH are likely to have interactive effects with biological and health factors as the environment individuals live and learn in often can impact physical health (Bambra et al., 2010 ; Braveman, & Gottlieb, 2014; Javed et al., 2022). For example, when considering factors including blood glucose, it is important to recognize that often multiple comorbidities exist in individuals with higher blood glucose or diabetes. Within the research evaluating multiple comorbidities among older adults, variables such as ethnicity, socioeconomic status, and other SDoH are not often emphasized as variables of interest (Northwood et al., 2017). This subsequently leads to a general lack of knowledge of how SDoH variables impact older adults with multiple comorbidities and subsequently makes it challenging to understand how race and SDoH may be related to these health factors. While there has been evidence that there is an interaction of worsening glucose control over time to poor SDoH, aging and cognition has not been integrated in those studies (Walker et al., 2020).

Other potential sources of unaccounted variance are known interactions among SDoH measures. There is specific evidence that there are interactive effects between race and other

measures of SDoH. Level of education and occupational complexity have been identified as mediators of the relationship between race and level of performance on measures of memory including the RAVLT (Rahamani et al., 2022; Schwartz et al., 2004; Zahdone et al., 2017). One study showed that 11% of the association between race and memory were accounted for by the indirect effects of the combination of education and occupational complexity (Owens et al., 2024). While matching the sample on these factors may help to create a matched sample that is demographically similar, it is possible that matching for education may have removed some of the variance that could have been captured by race.

While this study attempted to create a sample that was matched on key characteristics known to impact cognitive aging including age, sex, and education, this method only ensured equivalence of these variables between Black and White participants. Therefore, it limited the range and variance to that of the Black sample and did not account for the full range and variability of each of these characteristics. Specifically, there is long substantiated evidence that educational attainment influences onset and severity of cognitive aging in older adults (Stern et al., 1999). Education was not statistically controlled in the present study, as it was a measure used to match the sample.

Beyond how race may relate to SDoH, it is also important to consider how race can lead to important consequences such as discrimination and increased stress throughout an individual's lifetime. The weathering hypothesis posits that exposure to cumulative social and economic disadvantages across the life course leads to further acceleration of the aging processes and earlier onset of diseases in Black Americans compared with White Americans (Besser et al., 2024; Egede et al., 2023). Due to racism and residential segregation, Black Americans are more likely to live in areas where unemployment, pollution, and violence are disproportionately

concentrated (Ding et al., 2024), leading to more experiences of psychological and social stressors in the form of material deprivation, neighborhood disorder, discrimination, and other adversities both in childhood and adulthood (Gordon et al., 2020; Hooten et al., 2022; Macias-Konstantopoulous et al., 2023). This has been supported in prior research literature, with Black participants experiencing higher exposure to distressing situations, higher overall cumulative stress exposure, and lower executive functioning and episodic memory scores compared with White participants (Chen et al., 2022; Joshi & Tampi, 2024; Seblova et al., 2022).

### **Limitations**

There are some notable limitations to the present findings. The sample size was relatively low and underpowered to detect small effect in both samples and medium effects in the blood glucose sample. Previous literature has found that the relationship between age and RAVLT performance traditionally is present as a medium to large effect (Bleeker et al., 1988; Gale et al. 2007) indicating that this relationship should have been detected in both samples. Notable within the current study, this effect only reached statistical significance in the blood glucose sample, indicating there may have been differences between the two samples that impacted this result.

This problem increased when it was determined that 30% of the sample was missing blood glucose data and when 14 additional participants (and their matched pair) were excluded during neuroimaging data processing quality control steps, resulting in the removal of 28 participants total. This loss of participants was exacerbated by the intentional matched sample design of the study, as when one person within the match was excluded their match counterpart was also excluded from analyses. Therefore, while the matched sample assisted in creating equivalence across to race, this reduced the overall sample size and power.

Another limitation is the lack of SDoH measures and use of race as a proxy. Participants were matched by education which increased experimental rigor but may have actually controlled important variance associated with SDoH, leading to null findings. Previous literature has supported educational inequalities between Black and White Americans and how this may impact cognition, which is often associated with other SDoH, including SES and access to a well-funded education (Owens et al., 2024; Rahmani et al., 2024; Stern et al., 1999). Being unable to tap into other factors such as income and physical environment, it is challenging to determine what factors could have been included that would have revealed significant effects (Stites et al., 2022).

Other limitations include an uneven distribution in the number of men and women in the sample, possible underlying interactive effects between SDoH such as education, limited data from the HCP project in regard to variables pertaining to SDoH, no current access to longitudinal data, and missing raw data on all learning trials of the RAVLT.

### **Future Directions**

Future research on cognitive aging should continue to strive for the integration of measures related to SDoH, health biomarkers, and multimethod assessments of neurocognitive functioning to better understand the factors that influence normal and abnormal aging. Regarding the use of the RAVLT to assess episodic verbal learning and memory, recent literature has demonstrated the utility of learning slopes or, more novelly, learning ratios to determine learning capacity across trials. Specifically, researchers have recently discovered that lower learning ratios are associated with poor performance on the RAVLT memory recall component and, in comparative analyses with learning slopes, were better predictors of cognitive performance on other measures of verbal memory, including WMS Logical Memory and ADAS-Cog Word

Recall (Hammers et al., 2022). As such, future researchers should consider the use of learning slopes or ratios as opposed to total words learned to better understand episodic learning.

Methodologically, it may also be beneficial for researchers to consider other ways of utilizing race as a variable beyond the scope of use in the current paper. In the current study, race is used as a proxy for SDoH, given the limited SDoH variables that were provided. While the current study was unable to examine the relationship between SDoH and race, future research should consider what statistical methods will help to capture this relationship. The use of additional methods, such as marginal structure models, may better capture the relationship between race and SDoH. Marginal structure modeling utilizes inverse probability weighting to create pseudo populations in which the exposure is not associated with covariates (Chen et al., 2022). This means that the sample characteristics such as lifetime stress due to racial discrimination could be statistically accounted for in a more meaningful way.

When considering health factors associated with cognition, inclusion of components of subjective memory complaints and biological risk factors for developing Alzheimer's disease (AD) is warranted, even among healthy older adult samples. Older adults who report subjective memory complaints, but present with a normal cognitive profile, actually appear to be at an elevated risk for subsequent neurocognitive impairment (Kawago et al., 2019; Wang et al., 2013). This group also exhibits decreased FC when compared to control participants without subjective complaints, but still exhibit higher FC than those with confirmed MCI or AD (Wang et al., 2013). Similarly inclusion of biological risk factors for AD (e.g., APOE4 genetic carriers, preclinical amyloid deposition), appears to be a promising approach, especially in longitudinal DMN FC research. Older adults with cognitively normal neuropsychological profiles, but at biological risk for developing AD, exhibit FC patterns similar to AD patients. Specifically, it has

been reported that cognitively normal older adults at biological risk for AD and older adults with a diagnosis of AD both exhibit weaker FC between DMN network nodes, including the precuneus, hippocampus, and anterior cingulate cortex compared to healthy controls (Hafkemeijer et al., 2012; Sheline et al., 2010). As such, when engaging in research with older adults who fall into the normal range on measure of cognition, additional measures such as genetic risk factors and subjective complaints may allow for differentiation in a normally aging sample on characteristics which may predict future cognitive decline.

Given that access to HbA1C data significantly decreased the overall sample in this study, it will be important to find novel ways of encouraging engagement in blood draws to obtain this data. Ways to assess for true fasting before a blood draw beyond self-report may be helpful in ensuring high HbA1C scores are reflective for true higher values rather than a blood draw collected after eating. Additionally, data on which participants did not complete the blood draw and why should be collected to determine if there are any factors that distinguish the participants who did and did not complete the blood draw.

Finally, researchers should continue to add relevant SDoH measures into their studies. In recent years there has been a call to better integrate various social and structural components of health into aging research (Stites et al., 2022; Zahodne et al., 2017). A framework that was proposed in an effort to improve structural and SDoH measurements in Alzheimer's disease and related dementia suggests that there are three systems that need to be measured. These are the microsystem (social stressors and perceived stress, social support, education and health literacy, and occupation), exosystem (social positioning and social environment/neighborhood), and macrosystem (social identity which includes things such as race, disability, religion and various other identity factors). This framework provides multiple variables and measurements used to

capture all of these domains and further integration of these systems when evaluating cognitive aging is imperative (Stites et al., 2022). The null findings in the current study provides support for further detailed measurement of SDoH factors to determine if there are specific components within micro-, exo-, and macro-systems that may be impacting cognitive performance. It is possible that grouping so many different components into a single proxy may have illuminated important variance these variables independently may provide.

In examining race and SDoH, both of these variables should be considered components of larger social factors that are associated with systemic problems that have occurred over long periods of time. Recently, there has been a call to better integrate a critical race theory framework into the medical model when assessing patients (Tsai et al., 2021). Researchers argue that critical race theory offers an interdisciplinary lens that negates the concept of biological racism and centers marginalized research within the context of institutional racism and historical context. These constructs, while challenging to measure within a research framework, should be considered when understanding which variables predict changes during cognitive aging (Tsai et al., 2021).

When evaluating race, it is important to consider variables of discrimination and how this may impact physiological health in these individuals. While the current study did not include any measures of discrimination, it remains important to consider how this unmeasured component in this study could have had reaching effects on the results. Based on past literature, discrimination has been associated with several age-related health outcomes including cardiovascular disease. Though the effect of discrimination may be modulated by socioeconomic status. Everyday discrimination has also been shown to predict greater incidence of metabolic syndrome in Black, Hispanic, and Japanese women. Major experiences of discrimination but not everyday

discrimination has also been shown to predict greater risks of incidence of type 2 diabetes (Hooten et al., 2022). Many of these variables are risk factors for poor cognitive aging as well, so better assessment of discrimination experienced across the lifespan may provide context when findings indicate race may be related to differences in cognitive aging. In the current study there were no significant racial differences, though this may be in part due to the matched nature of the sample which may have removed some effects that otherwise would have been attributable to race. Creating a matched sample helps to target other variables associated with racial health disparities beyond education. But future research should consider how race and variables associated with race, including discrimination, can share variance and be measured.

### **Conclusions**

This study was able to confirm age effects consistent with RAVLT norms but could not further account for variance in verbal episodic memory using DMN FC, glucose level or SDoH. Low statistical power due to small sample size likely contributed to these null findings. While the novel individual matching likely attenuated this problem, this approach may have introduced education/race SDoH confounds that should be considered in future research. Taken together, future research should continue to strive for a more intersectional approach to cognitive aging, emphasizing the social and biological factors and their interactions that may lead to poor health outcomes and a decrease in normal cognitive aging.

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