Using Partial Least Squares Analyses to Explore the Relationship between Alzheimer's Disease Biomarkers, Modifiable Health Variables, and Cognition in Older Adults with Mild Cognitive Impairment

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in the Graduate School of The Ohio State University

By

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2021

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Abstract

Objective: This thesis aims to identify novel relationships between modifiable physical and health variables, Alzheimer's disease (AD) biomarkers, and cognitive function in a cohort of older adults with mild cognitive impairment (MCI).

Methods: Metrics of cardiometabolic risk (e.g., body mass index), stress (e.g., cortisol), inflammation (e.g., c-reactive protein), neurotrophic/growth factors (e.g., brain-derived neurotrophic factor), and AD (e.g., plasma tau) were assessed in 154 MCI participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) at baseline (mean age = 74.1; sd =7.5; mean education = 16.0; sd = 2.9). Of these 154 participants, 126 had 2-year follow-up data available for analyses (mean age = 74.0; sd = 7.6; mean education = 16.0; sd = 2.9). Participants also completed a comprehensive neuropsychological battery. Individual test scores and composite scores of memory and executive function published by ADNI were assessed. Partial least squares correlation (PLSC), an unbiased and flexible multivariate technique, was employed to examine cross-sectional associations among these physiological variables and cognition. Partial least squares regression (PLSR), a multivariate technique that defines optimal combinations of variables that best predict an outcome, was used to identify which, if any, of these physiological variables are important in predicting memory or executive function at 2-year follow-up.

Results: The PLSC analysis revealed a latent variable describing a unique combination of AD biomarkers, neurotrophic/growth factors, education, and stress that were significantly associated with specific domains of cognitive function, including episodic memory, executive function, processing speed, and language, representing 45.2% of the covariance in the data. Age, BMI, and tests of basic attention and premorbid IQ were not significant. The PLSR analyses revealed that baseline metrics of cardiometabolic function, inflammation, and AD biomarkers were important in predicting memory and executive function performance at 2-year follow-up. Baseline education was important in predicting memory but not executive function performance at 2-year follow-up. Our two best models predicted 65.1% and 63.7% of the variance in memory and executive function respectively at 2-year follow-up.

Conclusion: Our data-driven analysis highlights the significant cross-sectional relationships between metrics associated with AD-pathology, neuroprotection, and neuroplasticity primarily with tasks requiring higher order cognitive abilities (episodic memory, executive function, verbal fluency), rather than cognitive tasks that do not require mental manipulation (premorbid IQ and basic attention). Baseline metrics of cardiometabolic function, inflammation, and AD pathology were statistically important in predicting future memory and executive function performance at 2-year follow-up, suggesting that variables associated with neuroprotection and neuroplasticity (such as brain-derived neurotrophic factor and platelet-derived growth factor) may hold relatively less importance in predicting future cognition.

Acknowledgments

The authors do not have any conflicts of interest. This research was supported by the National Institute on Aging (NIA) of the National Institutes of Health (NIH) R21AG056921 (awarded to SMH), NIA R01AG058822 (awarded to JPH); and The Ohio State University Discovery Themes Chronic Brain Injury Initiative (SMH and JPH). We would also like to thank Jena Moody for her contributions including sharing her knowledge of the ADNI database, as well as Randy McIntosh, for sharing his insight and expertise in PLS methods. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics,

LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

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Anderson-Hanley, C., **Stark, J.,** Wall, K. M., VanBrakle, M., Michel, M., Maloney, M., Barcelos, N., Striegnitz, K., Cohen, B. D., Kramer, A.F. (2018). The interactive Physical and Cognitive Exercise System (iPACES™): A three-month in-home pilot for Mild Cognitive Impairment (MCI) and caregivers. *Clinical Interventions in Aging, 18*, 1565 – 1577.

Fields of Study

Major Field: Psychology

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Chapter 1: Background

By the year 2050, the older adult population in the United States is estimated to reach 87.3 million, doubling the population of adults over 65 years of age in 2012 (Rios, 2014). The risk of Alzheimer's disease (AD) increases with age, and the number of AD cases is projected to double by 2050 ("2019 Alzheimer's disease facts and figures," 2019). The rapid increase in age and AD-related cognitive impairment will place a considerable burden on caregivers, healthcare systems, and the economy. Multiple aspects of cognition, such as episodic memory (memory for specific personal past events), executive function (ability to plan, inhibit responses, and sustain attention), and processing speed (ability to quickly and efficiently respond to stimuli) decline with age (Buckner, 2004; Salthouse, 2010; Tromp, Dufour, Lithfous, Pebayle, & Després, 2015). To date, there is no cure for age- or Alzheimer's-related cognitive decline, highlighting the need to identify variables that are most strongly associated with current and future cognition. Therefore, determining variables that could serve as targets for intervention to attenuate cognitive decline, particularly among those with Mild Cognitive Impairment (MCI), who are at the greatest risk for AD, will be important in maintaining independence and quality of life in our aging population.

Previous research indicates there is substantial variability in aging, and multiple factors have been shown to accelerate or mitigate cognitive decline or conversion to

dementia. For instance, prior literature has explored cardiometabolic and pro-inflammatory variables, which typically have negative associations with cognition (Femminella, Taylor-Davies, Scott, & Edison, 2018; Gao et al., 2018; Yaffe et al., 2004). Neurotrophic/growth factors, which are typically associated with neuroprotection and neuroplasticity, also have been explored in the context of cognitive decline and aging, with studies reporting largely positive associations between neurotrophic/growth factors and cognition (Lista & Sorrentino, 2010; Miranda, Morici, Zanoni, & Bekinschtein, 2019). Additionally, multiple plasma and cerebrospinal fluid (CSF) biomarkers have been associated with both AD pathology and cognition (Chiu et al., 2014; Diniz, Pinto, & Forlenza, 2008). However, these lines of literature typically explore single variables in these domains or a small group of variables in a single domain (such as multiple CSF biomarkers associated with AD pathology), rather than an array of physiological variables spanning multiple physiological domains. The following subsections briefly outline the current literature regarding cognition and its associations with cardiometabolic and inflammatory variables, neurotrophic factors and growth factors, and AD biomarkers, with a focus on studies that explore participants with MCI or without dementia.

Cardiometabolic, Stress, and Inflammation Variables

Recent studies have shown that modifiable cardiometabolic variables such as body mass index (BMI), cholesterol, and blood pressure are related to poorer cognitive performance at baseline and follow-up in MCI participants (Femminella et al., 2018). Several studies have related metabolic syndrome (definition of which differs by study, but typically involves high abdominal adiposity or obesity, high blood pressure, high

cholesterol, and dyslipidemia, or high amounts of triglycerides, cholesterol or fat phospholipids) to future cognitive decline (Yaffe et al., 2004) and MCI progression (Gao et al., 2018). More specifically, in older adults without dementia, triglycerides were negatively associated with executive function, even after controlling for other risk factors such as total cholesterol and *APOE* ε4 status (Parthasarathy et al., 2017). However, a recent systematic review of 25 research studies exploring metabolic syndrome demonstrated that only excess glucose was consistently associated with cognition in older adults, and that the relationship between metabolic syndrome and cognition revealed heterogenous results (Assuncao, Sudo, Drummond, De Felice, & Mattos, 2018).

Metabolic syndrome has also been related to inflammation and cognitive function (Yaffe et al., 2004). In a study by Yaffe and colleagues assessing older adults in their 70s without dementia, those with metabolic syndrome and high inflammation (operationalized as levels of CRP and IL-6) had an increased likelihood of cognitive impairment when compared to those without metabolic syndrome and with low inflammation. Participants with metabolic syndrome and high inflammation also had greater 4-year decline on the Mini Mental State Examination (MMSE) when compared to those without metabolic syndrome (Yaffe et al., 2004). In other work, CRP has been associated with MCI or very early dementia diagnoses (Bennett et al., 2013).

Recent literature has also explored how insulin (a biomarker associated with cardiometabolic function and inflammation) is related to cognition in aging (Hooshmand et al., 2019). In a study by Hooshmand and colleagues assessing a group of older adults without dementia, higher serum insulin at baseline was associated with poorer

performance on measures of global cognition at 7-year follow-up, even after controlling for demographics and other cardiovascular risk factors (Hooshmand et al., 2019). However, other work has shown that high insulin may actually be a protective factor later in life and potential risk factor during middle-age (Lee et al., 2019). A related analyte, glucose, was explored in a different study with older adult women without dementia, which found that higher fasting plasma glucose was associated with a higher probability of cognitive dysfunction (Neergaard et al., 2017). Hyperglycemia (high glucose levels) also showed consistent negative relationships with cognition in a recent systematic review (Assuncao et al., 2018). Research also suggests that cortisol, a marker of stress or hypothalamic-pituitary-adrenal-axis activity, is related to cognition in older adulthood (Udeh-Momoh et al., 2020). In a study assessing those with subjective or mild cognitive impairment, higher total cortisol levels were found to be associated with poorer overall cognitive performance, even after controlling for levels of AD biomarkers (Sindi et al., 2017).

Neurotrophic Factors and Growth Factors

Additionally, there is a largely separate line of literature regarding neurotrophic/growth factors and how they relate to brain health and cognition. For instance, brain-derived neurotrophic factor (BDNF) has been associated with brain plasticity and low BDNF levels are related to memory impairment in multiple neurological disorders, including AD (Miranda et al., 2019). Multiple studies have suggested that BDNF plays a mediating role in the benefits of exercise on memory (Lista & Sorrentino, 2010; Stillman, Cohen, Lehman, & Erickson, 2016). A related growth

factor, vascular endothelial growth factor (VEGF) has also been posited as a potential candidate for the mechanisms behind the benefits of exercise on memory (Lista & Sorrentino, 2010). VEGF is associated with angiogenesis, or the creation of new blood vessels (Lista & Sorrentino, 2010). Increasing vascularization of the brain increases blood flow, which we would expect to have a positive effect on the cognitive aging process (Lista & Sorrentino, 2010). Other work has shown that participants with frontotemporal dementia had significantly elevated levels of VEGF when compared to controls (Taipa et al., 2019).

Multiple other blood-based neurotrophic/growth factors have been related to AD and cognition. For instance, recent work explored levels of insulin-like growth factor binding protein 2 (IGFbp) in a large cohort of older adults who were cognitively normal, had MCI, or AD, and found that a one unit increase in IGFbp was associated with an increased likelihood in belonging to the MCI or AD group rather than the cognitively normal group (McLimans, Webb, Anantharam, Kanthasamy, & Willette, 2017). However, this study also found that higher IGFbp was associated with better cognitive outcomes in those who had two *APOE* ε4 alleles (McLimans et al., 2017). Other research has shown that epidermal growth factor (EGF) may be a novel biomarker in diagnosing AD, as previous research has found significantly elevated levels of EGF in platelets of AD patients when compared to MCI participants and healthy controls (Hochstrasser, Ehrlich, Marksteiner, Sperner-Unterweger, & Humpel, 2012). Additionally, a related growth factor, heparin-binding epidermal growth factor-like growth factor (HB-EGF-like-GF) has been shown to be neuroprotective against cell death in animal literature

(Shim & Madsen, 2018) and was determined to be an AD-related biomarker in human research exploring healthy control, MCI, and AD participants (P. F. Meyer, Savard, Poirier, Morgan, & Breitner, 2019). Recent research has also shown that platelet-derived growth factor bb (PDGF), an analyte associated with neuronal survival, is expressed at higher levels in those who were resilient to AD (Barroeta-Espar et al., 2019), and that higher PDGF was associated with slower cognitive decline at 1-year follow-up in those with AD (Taipa et al., 2019).

AD Biomarkers

Other blood and CSF based biomarkers have been shown to be associated with cognition and AD risk. For instance, one study showed that in those with MCI or early AD, plasma tau was significantly elevated when compared to healthy controls, and was negatively associated with performance in episodic memory visual reproduction, and verbal fluency (Chiu et al., 2014). Meta-analytic research has also shown that CSF levels of tau and $A\beta_{1\text{-}42}$ are consistently associated with impaired cognition (Diniz et al., 2008). Specifically, when a diagnosis of MCI was made at baseline, meta-analyses demonstrated that high CSF total tau (t-tau), high phosopho-tau-181 ($p\text{-}tau_{181}$) and low CSF $A\beta_{1\text{-}42}$ helped to predict conversion to AD when compared to control participants (Diniz et al., 2008). However, other research has shown that the relationship between CSF $A\beta_{1\text{-}42}$ and cognition may differ depend on an individual's *APOE* $\varepsilon 4$ allele status, as authors found that CSF $A\beta_{1\text{-}42}$ was associated with memory performance only in those who were *APOE* $\varepsilon 4$ positive (Thorvaldsson et al., 2010). CSF $A\beta_{1\text{-}42}$ was not associated with memory in those who were *APOE* $\varepsilon 4$ negative (Thorvaldsson et al., 2010). Additionally, other work

has shown that CSF levels of $A\beta_{1-42}$, t-tau, and p-tau_{181} were not significantly associated with cognition (assessed by total score on the mini mental state examination) in those with amnestic mild cognitive impairment (Vemuri et al., 2009).

Current Gap in the Literature

As described, these three groups of variables and their link to cognition are often examined in isolation or in small groups across different studies, rather than simultaneously and within the same study. One exception is a study conducted by Meyer and colleagues (2019), which assessed neurotrophic/growth factors, inflammatory indicators, and AD biomarkers in cognitively normal, MCI, and AD participants. Machine learning techniques were used to create predictor weights for both CSF proteins and AD biomarkers, which were subsequently used in three separate regression models predicting general cognitive function. They found that CSF protein and AD biomarkers accounted for 31% and 26% of the variance in cognitive scores respectively (P.-F. Meyer, Savard, Poirier, Morgan, & Breitner, 2019). However, this study did not examine metrics associated with cardiometabolic risk, which are linked to cognition and dementia risk, and did not assess specific domains of cognitive function, which are known to be differentially impacted by aging and AD.

Thesis Rationale and Hypotheses

To address this gap in the literature, the present study had two aims:

Aim 1: To address a gap in the literature by using a multivariate analysis to map associations between domain-specific cognitive function and multiple AD

biomarkers, neurotrophic/growth factors, inflammatory markers, and cardiometabolic metrics in older adults with MCI .

Aim 2: To use multivariate analysis to identify which of these physiological variables can best predict memory or executive function at a 2-year follow-up.

To address our first goal, we implemented a partial least squares correlational (PLSC) analysis, an unbiased and flexible multivariate technique for defining latent variables in a dataset, that does not require assigned predictor and outcome variables, but rather maps shared covariance between two sets of data (Abdi & Williams, 2013). Latent variables in PLSC refer to linear combinations of manifest variables that share significant amounts of covariance (Abdi & Williams, 2013). PLSC analysis was preferred to other multivariate or data-driven statistical approaches because it does not attempt to predict an outcome, making it an ideal fit for this cross-sectional data and the exploratory nature of our research question. Additionally, unlike multiple linear regression, PLSC analysis is well equipped to deal with a large number of variables, or with multiple collinear variables (Van Roon, Zakizadeh, & Chartier, 2014). Additionally, data do not need to be normally distributed (Van Roon et al., 2014). Thus, PLSC analysis was employed to identify and parse novel relationships across these identified physiological domains and current cognition in a cohort of older adults with MCI.

To address our second goal, partial least squares regression (PLSR) analysis, a statistical technique that predicts dependent variable(s) from a set of independent variables, was employed to identify which, if any, of these physical, health, and AD variables (matrix 1 in PLSC, with the addition of 2 AD biomarker variables: CSF t-

tau/Aβ_{1-42} and p-tau$_{181}$/Aβ_{1-42} and additional demographic variables) are important in predicting composite scores of memory and executive function after 2 years in a group of MCI participants. PLSR creates latent variables, or components, that maximize the covariance between the independent and dependent variables. This is followed by a regression step, where the latent variables (referred to as components) created from the predictor variables are used to predict the outcome(s) (Krishnan, Williams, McIntosh, & Abdi, 2011). There are several advantages of PLSR, including its ability to handle highly collinear data and work well with many predictor variables (Van Roon et al., 2014).

The goal of the present was to extend the literature by simultaneously examining multiple modifiable physical, health, and AD biomarkers in a single study while using multiple multivariate analysis approaches to identify novel relationships with current and future cognition in older adults with MCI. To accomplish this, data on modifiable health factors (such as those associated with cardiometabolic health: BMI, cholesterol), stress (e.g., cortisol), inflammation (e.g., CRP), neuroprotection (e.g., BDNF) and AD biomarkers (e.g., CSF Aβ_{1-42}, plasma tau) were obtained from the Alzheimer's Disease Neuroimaging Initiative Phase 1 (ADNI1). Cardiometabolic, stress, and inflammatory variables were examined in light of previous research suggesting that these variables are associated with cognition and are potentially modifiable by lifestyle or pharmacological interventions. Cardiometabolic, stress, and inflammatory variables were limited to what was available and passed quality control procedures in ADNI1. Previous research has also shown that certain neurotrophic/growth factors (such as BDNF, VEGF, and Insulin-like growth factor 1) are potentially

modifiable through physical exercise and are associated with neuroprotection (Lista & Sorrentino, 2010; Miranda et al., 2019). Thus, all other growth factors that passed quality control in ADNI1 were added into this multivariate analysis, to assess how other growth factors associated with neuroprotection may or may not relate to cognition in older adults with MCI. Lastly, prior research has also shown potential relationships among plasma and CSF AD biomarkers and cognition in older adults (Chiu et al., 2014; Diniz et al., 2008; Matura et al., 2019). Thus, all plasma and CSF AD biomarkers available in ADNI1 were added to this multivariate analysis as well, in order to assess the relative importance of AD biomarker variables when other modifiable cardiometabolic, stress, and inflammatory variables as well as modifiable and non-modifiable neurotrophic/growth factors are simultaneously considered. Results from these analyses will contribute to the multivariate cognitive aging literature by providing information on the associations between these physiological variables and domain-specific cognitive function (PLSC analysis, Aim 1) as well as the relative importance of these different types of physiological variables in predicting future memory and executive function performance (PLSR analyses, Aim 2). These findings have the potential to inform future recommendations for older adults to delay cognitive aging, particularly for cardiometabolic and inflammatory variables, which research has shown can be modified by exercise or other lifestyle changes.

Chapter 2: Methods

Participants

Participants with a diagnosis of MCI from the ADNI1 cohort were included in the current study. Full participant inclusion/exclusion criteria are available in the ADNI Procedures Manual, 2010, and are summarized here:

1. Hachinski scale score less than or equal to 4 (commonly used to diagnose degenerative or vascular dementia)
2. Age between 55-90 years
3. Stability of permitted medications for 4 weeks
4. Geriatric depression scale less than 6
5. Vision and hearing adequate for neuropsychological testing
6. Good general health with no diseases precluding enrollment
7. 6th grade education or work history
8. Fluency in English or Spanish

ADNI1 criteria for MCI diagnosis were:

1. Mini Mental State Examination (MMSE; a measure of global cognitive functioning) scores between 24 and 30 inclusive
2. Clinical Dementia Rating of 0.5 (a measure of dementia severity)
3. Subjective memory complaint by subject or study partner

4. Abnormal memory function shown by scoring below education adjusted scores on the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II (which assesses immediate and delayed episodic memory)

5. Sufficiently preserved general cognition and functional performance not meeting criteria for a diagnosis of AD at the time of the screening visit

Participants with missing data for any variables of interest were excluded, as complete data were necessary for PLSC analysis. One participant classified as MCI with an MMSE score of 23 and one participant with an extremely high and improbable triglycerides value were excluded. The final analysis for the PLSC included 154 MCI participants (age: 54.4 – 88.3 years; Mean = 74.1 years; SD = 7.5 years; education: 6 – 20 years; Mean = 16.0 years; SD = 2.9 years; 51 females; 150 White, 2 Asian, 2 Black; 152 Non-Hispanic; 2 Hispanic; 67 *APOE* ε4 negative). Of those 154, 126 had composite neuropsychological data available for follow-up analyses at 2 years (age: 55.1 – 88.3; Mean = 73.99; SD = 7.57; education: 6 – 20 years; Mean = 15.98; SD = 2.94; 43 females; 122 White, 2 Asian, 2 Black; 124 Non-Hispanic; 2 = Hispanic; 55 *APOE* ε4 negative). Other ADNI cohorts (ADNIGO, ADNI2, and ADNI3) were excluded from the analysis as these data sets did not include numerous biomarkers of interest (e.g., neurotrophic and growth factors were not available). Study procedures were approved by site-specific Institutional Review Boards and all participants and/or authorized representatives provided written informed consent consistent with the Declaration of Helsinki.

Neuropsychological Assessment

For the cross-sectional PLSC analysis, neuropsychological data were obtained from screening (MMSE and WMS-R Logical Memory II) and baseline visits (all other tests). Average time between appointments was 41.3 days. Nineteen raw scores from the tests described below were included in the PLS analysis (see **Table 1**). The following cognitive domains were assessed:

Episodic Memory –WMS-R Logical Memory I (immediate recall; number of story details correctly recalled), WMS-R Logical Memory II (delayed recall; number of story details correctly recalled), Rey Auditory Verbal Learning Test List 1 (RAVLT; number of words correctly recalled), RAVLT List B (number of words correctly recalled on the interference list); RAVLT List 6 (number of words correctly recalled on the original list after interference); and RAVLT 30-minute delay recall (number of words correctly recalled on the original list).

Working Memory –Digit Span Forward (length of the longest digit span correctly recalled).

Executive Function – Digit Span Backward (length of the longest digit span correctly recalled), Trail Making Test (Trail B; number of seconds to correctly complete the trail).

Processing Speed – Trail Making Test (Trail A; number of seconds to correctly complete the trail), Digit Symbol Substitution Test (number of correctly drawn symbols).

Visuospatial Ability – Clock Drawing Test (Clock Drawing; Clock Copy; number of clock details correctly drawn or copied).

Language – Category Fluency (number of words produced in the correct category for Animals and Vegetables), The Boston Naming Test (number of drawings correctly named).

Premorbid IQ – American National Adult Reading Test (number of words incorrectly pronounced).

Global Cognition –MMSE (total score), Alzheimer's disease Assessment Scale (ADAS-COG; total score).

Neuropsychological Composite Scores

For the PLSR analyses, composite scores published by ADNI were examined. Composite measures of memory and executive function were made available by ADNI for baseline, 6, 12, 18, 24, 36, 48 and 60 month follow-up assessments (Crane et al., 2012; Gibbons et al., 2012). For PLS regression analyses, these composite scores of memory and executive function were employed rather than individual cognitive tests used in the PLSC analysis. For the memory composite score, factor analytic methods and item response theory were used to create a composite score comprised of a weighted set of the following scores from the ADNI neuropsychological battery: RAVLT List 1, List 2, List 3, List 4, List 5, List 6, List B, delayed recall and recognition; ADAS Trial 1, Trial 2, Trial 3, Recall, Recognition Present, Recognition Absent; MMSE Ball, Flag, and Tree items; Logical Memory Immediate and Delay (for further details, please

see Crane et al., 2012). This memory composite accounted for version differences for the RAVLT and ADAS and was determined to have good validity (Crane et al., 2012). Additionally, the composite memory score was found to be better at detecting change than total RAVLT recall (number of items remembered, lists 1 through 5), and was found to be superior to or equivalent in predicting conversion from MCI to AD when compared to other individual cognitive test scores (Crane et al., 2012). For the executive function composite score, the same statistical techniques were employed, and the following scores from the ADNI neuropsychological battery were included in this weighted composite: Category Animals, Category Vegetables, Trails A, Trails B, Digit Span Backward, Digit Symbol Substitution Test, Clock Circle, Symbol, Number, Hands, and Time (for further details, please see Gibbons et al., 2012). This executive function composite score was found to be the equivalent or better than individual executive function measures in predicting future cognition, and was found to be the best predictor of conversion from MCI to AD when compared to all of the individual test scores (Gibbons et al., 2012).

Cardiometabolic, Stress, and Inflammation Variables

BMI (kg/m^2), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (per minute), cholesterol (mg/dL), triglycerides (mg/dL), and serum glucose (mg/dL) data were obtained. Insulin (uIU/mL), cortisol (ng/mL), CRP (ug/mL), and interleukin-6 receptor (ng/mL) data were assessed from fasting plasma blood samples;

these data were normalized and checked for the defined least detectable dose during the quality control process.

Growth Factors and Neurotrophic Factors

IGF-bp (ng/mL), EGF (pg/mL), HB-EGF-like-GF (pg/mL), hepatocyte growth factor (ng/mL), PDGF (pg/mL), BDNF (ng/mL), and VEGF (pg/mL) were analyzed. Data were normalized and checked for the defined least detectable dose during the quality control process. Certain growth factors and neurotrophic factors of interest (such as Insulin-like growth factor 1, Ciliary Neurotrophic Factor) were omitted from the present analysis if more than 10% of values in our set of participants (not all available data from ADNI1) were imputed due to not meeting threshold for a least detectable dose.

AD biomarkers

Plasma Apolipoprotein E (apoE; ug/mL), plasma tau (pg/mL), CSF total tau (t-tau; pg/mL), CSF Phospho-tau (181; p-tau$_{181}$; pg/mL), and CSF Aß$_{1-42}$ (pg/mL) were also examined. Only values within the given ranges were included for analyses: Aß$_{1-42}$ 200 – 1700 pg/mL, p-tau$_{181}$ 8 – 120 pg/mL, and t-tau 80 -1300 pg/mL, as these are the reported technical limits. Ratios of both CSF tau biomarkers compared with CSF Aß$_{1-42}$ levels were also calculated (p-tau$_{181}$/Aß$_{1-42}$ and t-tau/ Aß$_{1-42}$). These two ratios were only examined in PLSR analyses.

Data Processing and Analysis Aim 1 (PLSC to examine cross-sectional relationship between cognition and multiple physical, health, and AD biomarker variables)

ADNI1 data were scrubbed using RStudio. Raw data files for all blood- and CSF-based biomarkers were checked for imputed values. To ensure data integrity, all analytes with >10% imputed values were removed. Participants who had missing data or invalid data as indicated by the ADNI manual were excluded.

The PLS Command line package (Version 6, 2013) was downloaded from the open source PLS User Guide: http://pls.rotman-baycrest.on.ca/source/ and run in MATLAB (Version 2019b). A cross-covariance matrix between demographic (age, education), physical, health, and AD data (matrix 1) and cognitive data (matrix 2) was created and factorized using singular value decomposition into mutually orthogonal singular vectors (Abdi & Williams, 2013). The PLSC algorithm uses these singular vectors to create latent variables that express the largest amount of information common to both input matrices (Krishnan, Williams, McIntosh, Abdi, 2014). Thus, the latent variables described refer to the pattern of covariance between physical, health, and AD variables (matrix 1) and cognitive function (matrix 2). The PLSC algorithm outputs as many latent variables as there are behavioral variables (19).

We then determined the p-value for all 19 latent variables using permutation analyses. Permutation samples are created using our input dataset. Matrix 2 variables are randomly shuffled within participants, while matrix 1 variables remain intact. The PLSC model is re-run on each of these permutation samples, creating a distribution that can be used to determine a p-value for each latent variable (Krishnan, Williams, McIntosh, &

Abdi, 2011). Latent variables were determined as statistically significant if the latent variable had a p-value of < 0.05 after 1500 permutations of the data (Abdi & Williams, 2013). Reliability of a latent variable was assessed through split-half resampling, a procedure that determines the reliability of the associations described between the two matrices of data (physical, health, AD and cognitive) within a given latent variable (Kovacevic, Abdi, Beaton, & McIntosh, 2013). Latent variables are considered reliable if both sides of the data meet criteria for significance ($p < 0.05$; Kovacevic et al., 2013). Physical, health, and AD variables with a bootstrap ratio (BSR) with an absolute value greater than or equal to 1.96 (corresponding to $p \leq 0.05$), determined by 1000 resamplings with replacement of the data, were considered reliable contributors to the latent variables. Cognitive measures were considered to significantly contribute to the latent variable if their correlation with the latent variable was significantly different than zero ($p < 0.05$). Using these cutoffs, patterns of physical, health, AD variables, and cognitive scores that account for significant amounts of covariance in the data were determined (see **Table 1** for variables included in the analysis).

Data Processing and Analysis Aim 2 (PLSR to identify predictors of cognition at 2-year follow-up)

ADNI1 data scrubbed in the PLSC analysis were used for the PLSR analyses. A subset of the 154 participants run the PLSC were examined: those who had neuropsychological data at 2-year follow-up. This resulted in a dataset with 126 participants (see participants section for details). This 2-year (24-month) timepoint was

chosen over other timepoints (such as 36, 48, or 60 months) in order to maintain the maximum number of participants in the analysis.

PLSR scripts were adapted from Abdi, 2010, and downloaded from the author's source: www.utdallas.edu/~herve and run in MATLAB (Version 2019b). The built in PLSR MATLAB function, "plsregress" was also employed. PLSR combines techniques from principle components analysis and multiple regression. Its goal is to create a latent variable that models a set of input variables (matrix X), while best predicting an outcome variable (Y matrix). In this analysis, physical, health, and AD variables were the X matrix (the physiological variables assessed in the PLSC, plus CSF p-tau$_{181}$/Aß$_{1-42}$ and t-tau/Aß$_{1-42}$ biomarker ratios). PLSR can be run with multiple Y-outcomes. However, this complicates interpretation of the analysis: PLSR optimizes for all Y outcomes collectively, considering them part of a single covariance pattern, which did not align with Aim 2 of this study. Therefore, separate PLSR analyses were run per cognitive domain where either composite memory or executive function at 2-year follow-up were the Y matrix, or response variable. These analyses were done to examine how contributions of baseline physiological variables differed in predicting memory or executive function at 2-year follow-up.

In PLSR analyses, orthogonal factors are created by the PLSR model that maximize the covariance between each X variable and the best predictive power of Y. In our analysis, PLSR finds a model that best predicts either future composite memory or future executive function from a weighted subset of physical, health, and AD variables. To do this, the X and Y matrices are imported and z-scored to have a mean of 0 and

standard deviation of 1. Next, an optimal number of components was selected to improve performance and generalizability. [Unlike PLSC, the number of LVs for PLSR can be varied between 1 and the number of X variables inputted to make the regression model more generalizable to other datasets and less prone to overfitting.] A "leave one out" cross-validation procedure, also called a jackknife, was completed (Krishnan, McIntosh, Abdi, 2011). In this procedure, each observation is removed in turn from X and Y, and a PLSR model is re-created for each of the remaining observations. The model created by the remaining observations and outcome variable is used to predict the left-out observation. The predicted observations are stored in a new matrix and a predicted residual estimated sum of squares (PRESS) value is created to measure the quality of the prediction. This procedure is repeated and iteratively uses a different number of LVs (from one to the number of X predictors), and the PRESS value is calculated for each possible number of LVs. The optimal number of components for the PLSR model is chosen based on the PRESS value (See **Table 3** for model summaries). Next, the regression model is run using the chosen number of components and the "plsregress" function. To create a robust and reliable PLSR model, bootstrapping with replacement was employed. A built-in bootstrap function in MATLAB (bootstrp) was used and 1500 bootstrapped PLSR models were run. Bootstrapping allows us derive standard errors for each regression coefficient in the model nonparametrically (Efron and Tibshirani, 1986). Standard errors were used to derive 95% confidence intervals for the regression coefficients (also called beta values) per X matrix variable. Next, variable importance on projection (VIP) scores were calculated for every X matrix variable (Kuceyski et al.,

2018). A built-in MATLAB function, "bsxfun" was used to calculate the VIP score, using outputs from the "plsregress" function. Beta values indicate the strength and directionality of a given X matrix variable with the outcome; a higher value absolute value means that variable has a stronger relationship with the outcome (Kosse, De Groot, Vuillerme, Hortobágyi, & Lamoth, 2015). The VIP score summarizes the contribution an X matrix variable makes to the model, as it represents a combination of the loadings and weights for each X matrix variable in the PLSR model (Eriksson et al., 2009). Variables with a VIP score > 0.8 are considered important to the PLS model (Kuceyeski et al., 2018a). Thus, the VIP score informs us of the importance of that variable, and the beta value indicates the directionality of that important variable in regards to the outcome. Thus, variables that had VIP scores > 0.8 (meaning they were significantly important to the model) that also had beta values that did not have confidence intervals that crossed the x-axis (meaning that variable was significantly predictive of the outcome) were retained for each model (Kosse et al., 2015; Viala et al., 2007). Literature reporting PLSR analyses often use either VIP scores or beta values to decide which variables are retained in a given model (Kosse et al., 2015; Kuceyeski et al., 2018a; Viala et al., 2007). However, one study used both criteria (Vervoort, Vuillerme, Kosse, Hortobágyi, & Lamoth, 2016) . Given the lack of consensus in the literature, a more conservative approach to only include variables that met both the VIP and beta value criteria were retained in the final PLSR models. Lastly, the "plsregress" function then outputs the percent variance explained by the PLSR model for the X matrix, as well as the Y

response (composite memory or executive function at 2 years). Four PLSR models were run:

1. Predictor variables (X-matrix): Physical, health, and AD variables at baseline (for full list of variables entered into the analysis, please see **Table 2**)

   Outcome variable (Y response): composite memory at 2-year follow-up
2. Predictor variables (X-matrix): Physical, health, and AD variables at baseline (for full list of variables entered into the analysis, please see **Table 2**), composite memory at baseline

   Outcome variable (Y response): composite memory at 2-year follow-up
3. Predictor variables (X-matrix): Physical, health, and AD variables at baseline (for full list of variables entered into the analysis, please see **Table 2**)

   Outcome variable (Y response): composite executive function at 2-year follow-up
4. Predictor variables (X-matrix): Physical, health, and AD variables at baseline (for full list of variables entered into the analysis, please see **Table 2**), composite executive function at baseline

   Outcome variable (Y response): composite executive function at 2-year follow-up

To compare two models with the same outcome (either composite memory or executive function), Akaike Information Criterion (AIC) scores were calculated using the following equations:

Residual Sum of Squares = Sum ($Y_{residual}^2$)

AIC = N x log(Residual Sum of Squares/N) + 2(k -1)

Where, N = number of subjects, k = number of input variables.

AIC scores represent the quality or fit of a given model while considering the number of input variables and model complexity (Portet, 2020). The change in AIC can be used to compare two or more models, but the actual AIC value is meaningless (Portet, 2020). When looking at two or more models, the model with the lowest AIC is considered the best fit, and anything with a AIC change < 2 indicates substantial evidence for that model, a change in AIC between 2 and < 7 shows there is less support for that model, and a change in AIC > 10 indicates that the model is unlikely to be better (Kuceyeski et al., 2018b).

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Chapter 3: Results

Results Aim 1 (PLSC to examine cross-sectional relationship between cognition and multiple physical, health, and AD biomarker variables)

Three significant latent variables (all values $p < 0.01$) were identified. Latent Variable 1 (LV1; **Figure 1**) accounted for 45.2% of the crossblock covariance. LV1 was considered reliable, as it met criteria for split-half reliability (all values $p < 0.05$; Kovacevic et al., 2013). For LV1, neurotrophic/growth factors, AD biomarkers, a stress biomarker, and education were significantly associated with performance across multiple cognitive domains. Specifically, HB-EGF-like-GF, PDGF, BDNF, plasma tau, CSF t-tau, CSF p-tau$_{181}$, CSF Aß$_{1-42}$, cortisol, and education were significantly associated with performance on measures of episodic memory (WMS-R Logical Memory immediate and delayed recall, RAVLT List 1 and List B), processing speed (Trail A and Digit Symbol Substitution Test), executive function (Trail B), visuospatial ability (Clock Drawing), verbal fluency (Category Fluency Animals, Category Fluency Vegetables), language (Boston Naming Test), and global cognition (MMSE, ADAS-COG). All significant cognitive tests had equal contributions to LV1, as they all had error bars (representing 95% confidence intervals) overlapping with one another (Figure 1). Better performance on this subset of cognitive measures was associated with increased neurotrophic/growth factor levels, less AD pathology, lower levels of stress, and higher education (for

individual BSRs, see **Figure 1**). Of these variables, CSF AD biomarkers and education had the highest BSRs, revealing that these variables had the strongest associations with cognition, followed by growth factors such as HB-EGF-like-GF, PDGF, and BDNF, as well as a stress biomarker, cortisol.

LV2 and LV3 were also significant, accounting for 17.2% and 11.9% of the crossblock covariance respectively. For LV2, IL-6 receptor, neurotrophic/growth factors, and AD biomarkers were significantly associated with performance in measures of delayed episodic memory. Specifically, lower IL-6 receptor, BDNF, PDGF, CSF t-tau and CSF p-tau$_{181}$ and higher hepatocyte growth factor and CSF Aß$_{1-42}$ were associated with better performance on WMS-R Logical Memory delayed recall and RAVLT 30-minute delayed recall (see **Figure 3** for details). However, LV2 did not meet criteria for split-half reliability (matrix 2 had a value of $p > 0.05$), and many cognitive outcomes had correlations with 95% confidence intervals close to crossing the x-axis (0), and thus should be interpreted with caution. For LV3, lower levels of cardiometabolic variables and insulin-like growth factor binding protein, older age, and higher education were associated with better performance in executive function (longest digit span backward length), working memory (longest digit span forward length), and premorbid IQ (ANART), and worse performance in episodic memory (RAVLT List B; see **Figure 4** for details). LV3 met criteria for split-half reliability (all values $p < 0.05$). However, the significant cognitive outcomes in LV3 have correlations with 95% confidence intervals close to crossing the x-axis (0), and LV3 accounts for a relatively low percentage of the

overall crossblock covariance; thus, the relationships reported within LV3 should be interpreted with abundant caution.

Results Aim 2 (PLSR to identify predictors of cognition at 2-year follow-up)

PLSR analyses were used to determine the relationship between 30 different physiological and demographic variables and cognition (composite memory or executive function) at 2-year follow-up. Results from all four PLSR analyses are summarized in **Figures 5, 6, 7 and 8** and **Table 3**. Descriptive statistics for the 126 participants included in the analysis are in **Table 2**. Models 1 and 2 explored memory performance at 2-year follow-up. Models 3 and 4 explored executive function performance at 2-year follow up. Models 1 and 3 included physiological and demographic variables as input variables. Models 2 and 4 added baseline cognition (memory and executive function, respectively) into the X-matrix variables, to see how results would differ when performance at baseline could contribute to the model.

Model 1 explored memory performance at 2-year follow-up and included physiological and demographic variables as input variables. In Model 1, ten predictor variables were considered important to the model (VIP > 0.8) and had beta values that were significantly different from 0 (95% confidence interval for the beta value did not cross the x-axis). Variables meeting both of these criteria demonstrate that they are important to the model, and significantly contribute to predicting the outcome variable. Systolic blood pressure, triglycerides, EGF, CSF p-tau/Aß$_{1-42}$, and CSF t-tau/Aß$_{1-42}$ were negatively associated with memory performance at 2-year follow-up. Insulin, IL-6 receptor, HB-EGF-like-GF, education, and CSF Aß$_{1-42}$ were positively associated with

memory performance at 2-year follow-up. Model 1 predicted 37% of the variance in memory performance at 2-year follow-up, and overall identified a pattern in the data suggesting that baseline levels of multiple modifiable cardiometabolic variables, inflammatory markers, growth factors, AD biomarker variables, and education were important in predicting future memory performance.

Model 2 explored memory performance at 2-year follow-up and included physiological variables, demographic variables, as well as baseline memory performance as input variables. In Model 2, five predictor variables were considered important to the model (VIP > 0.8) and had beta values that were significantly different from 0 (95% confidence interval for the beta value did not cross the x-axis). CSF t-tau/Aß$_{1-42}$ was negatively associated with memory performance at 2-year follow-up. IL-6 receptor, education, CSF Aß$_{1-42}$ and baseline memory performance were positively associated with memory performance at 2-year follow-up. Of note, all variables except for memory performance at baseline overlapped with model 1 and maintained the same directionality. Model 2 predicted 65% of the variance in memory performance at 2-year follow-up, and overall identified a pattern suggesting that baseline levels of inflammation, AD biomarkers, education, and baseline memory were important in predicting future memory performance.

Model 3 explored executive function performance at 2-year follow-up and included physiological and demographic variables as input variables. In Model 3, ten predictor variables were considered important to the model (VIP > 0.8) and had beta values that were significantly different from 0 (95% confidence interval for the beta value

did not cross the x-axis). Systolic blood pressure, CSF t-tau, and CSF t-tau/Aß$_{1-42}$ were negatively associated with executive function performance at 2-year follow-up. Insulin, IL-6 receptor, HB-EGF-like-GF, CSF Aß$_{1-42}$, CSF p-tau$_{181}$, CSF ptau$_{181}$/Aß$_{1-42}$ and *APOE ε*4 allele status were positively associated with memory performance at 2-year follow-up. Model 3 predicted 43% of the variance in executive function at 2-year follow-up, and overall identified a pattern suggesting that baseline levels of cardiometabolic, inflammatory and AD biomarker variables were important in predicting future executive function performance.

Model 4 explored executive function performance at 2-year follow-up and included physiological and demographic variables, as well as baseline executive function performance as input variables. In Model 4, five predictor variables were considered important to the model (VIP > 0.8) and had beta values that were significantly different from 0 (95% confidence interval for the beta value did not cross the x-axis). Systolic blood pressure and CSF t-tau/Aß$_{1-42}$ were negatively associated with executive function performance at 2-year follow-up. IL-6 receptor, CSF Aß$_{1-42}$, and baseline executive function performance were positively associated with executive function performance at 2-year follow-up. Of note, all variables except for executive function performance at baseline overlapped with model 3 and maintained the same directionality. Model 4 predicted 64% of the variance in executive function at 2-year follow-up, and overall identified a pattern suggesting that baseline levels of cardiometabolic variables, inflammatory variables, AD biomarkers and executive function were important in predicting future executive function performance.

Chapter 4: Discussion

Discussion Aim 1 (PLSC to examine cross-sectional relationship between cognition and multiple physical, health, and AD biomarker variables)

To summarize, we identified a latent variable (LV1) that accounted for a large amount of crossblock covariance, revealing a pattern in the data suggesting that increased neurotrophic/growth factor levels, less AD pathology, lower stress, and higher education are associated with better performance largely on tasks associated with higher order cognitive abilities (episodic memory, executive function, processing speed, verbal fluency) as well as metrics of global cognition (**Figure 1**). Direct measures of basic attention (e.g., longest sequence recalled for digit span forward) and premorbid IQ were not significantly associated with this pattern. This pattern suggests that markers of neuroprotection, neuroplasticity, stress, and AD pathology may hold relatively less importance for cognitive metrics that do not require mental manipulation. Interestingly, modifiable cardiometabolic risk factors (such as BMI, cholesterol, etc.), which are often associated with cognition in older adults (Farooqui, Farooqui, Panza, & Frisardi, 2012; Yaffe et al., 2004), did not contribute to the pattern described. Chronological age also did not significantly contribute to the pattern described for LV1. This discussion mainly focuses on LV1, which accounted for the most cross-block variance and met criteria for split-half reliability.

Our results extend the literature by showing a novel association between HB-EGF-like-GF and cognition. Specifically, better cognitive performance was associated

with higher levels of plasma HB-EGF-like-GF in LV1. Previous research has shown that this growth factor may have neuroprotective properties, as infusions of HB-EGF-like-GF in rats one day post-stroke were associated with neuroprotection against cell death (Shim & Madsen, 2018). Moreover, in rats with cypermethrin exposure (a pesticide associated with AD neuropathology), exogenous administration of HB-EGF-like-GF inhibited cypermethrin-induced accumulation of $A\beta_{1\text{-}42}$ and p-tau in the frontal cortex and hippocampus, and led to decreases in learning and memory deficits caused by cypermethrin exposure (Maurya, Mishra, Abbas, & Bandyopadhyay, 2016). Our finding is consistent with animal models demonstrating HB-EGF-like-GF's potential neuroprotective role (Maurya et al., 2016; Shim & Madsen, 2018). To our knowledge, a link between HB-EGF-like-GF and human cognition has not been reported. However, in one study exploring older adults who were cognitively normal or had MCI, higher levels of CSF HB-EGF-like-GF were associated with decreased levels of CSF $A\beta_{1\text{-}42}$ and increased levels of CSF t-tau, which is contrary to our finding (P. F. Meyer et al., 2018), as our results suggest that HB-EGF-like-GF may be associated with potential cognitive benefits. This unique finding necessitates additional research in order to clarify the role of HB-EGF-like-GF in human cognition.

Our LV1 findings for two other neurotrophic/growth factors, BDNF and PDGF, support previous research showing positive assocations between these two neurotrophic/growth factors and cognition. Higher levels of BDNF were associated with better cognitive performance (on WMS-R Logical Memory immediate and delayed recall, RAVLT List1 and List B, Trail A and Digit Symbol Substitution Test, Trail B,

Clock Drawing, Category Fluency Animals and Vegetables, Boston Naming Test, MMSE, and ADAS-COG), consistent with the putative role of BDNF in neuroprotection (Lista & Sorrentino, 2010; Miranda et al., 2019). For LV1, higher PDGF was also related to better cognitive performance, which is consistent with studies showing higher levels of PDGF were associated with reduced cognitive decline (Taipa et al., 2019). However, it should be noted that the relationship between PDGF and cognition was not entirely consistent. For LV2, lower levels of PDGF were associated with better performance on WMS-R Logical Memory delayed recall and RAVLT delayed recall (although LV2 should be interpreted with caution).

AD biomarkers exhibited some of the strongest associations with cognition in LV1. Lower levels of plasma tau were associated with higher cognitive performance, supporting previous research demonstrating that plasma tau levels in those with MCI were negatively associated with episodic memory and verbal fluency performance (Chiu et al., 2014). Lower levels of CSF t-tau and CSF p-tau$_{181}$ were associated with better cognitive performance, consistent with recent work (Nathan et al., 2017). Lower levels of CSF Aß$_{1-42}$ were correlated with lower cognitive scores, a pattern similar to recent findings revealing that low CSF Aß$_{1-42}$ levels were associated with cognitive impairment in participants with MCI (Matura et al., 2019). Increased levels of CSF t-tau and CSF p-tau$_{181,}$ and lower CSF Aß$_{1-42}$ in those with MCI are all associated with increased risk of converting to dementia (Diniz et al., 2008). These associations between AD biomarkers and cognition contribute to our understanding of cognitive decline in MCI, demonstrating

that AD biomarkers are associated with a broad range of cognitive domains (see **Figure 1**).

Our results also demonstrate that cortisol, a marker of stress or hypothalamic-pituitary-adrenal-axis activity, had negative associations with cognition. Lower levels of cortisol were associated with higher cognitive performance, which is consistent with recent research demonstrating that cognitively normal older adults with elevated cortisol and CSF $A\beta_{1-42}$ were at a higher risk of clinical progression to MCI or AD (Udeh-Momoh et al., 2020). Interestingly, this relationship remained, even when controlling for cognitive reserve (Udeh-Momoh et al., 2020). Our results align with this finding, and contribute to the literature by demonstrating that lower cortisol was significantly associated with positive cognitive outcomes in an MCI group.

Regarding demographic variables, higher education was associated with superior cognitive performance in LV1, consistent with the well-documented role of education as a source of cognitive reserve (Stern, 2013). Surprisingly, chronological age did not significantly contribute to the pattern of covariance in LV1. This null finding was unexpected as multiple episodic memory and executive function tasks significantly contributed to LV1, and these cognitive domains typically decline with age (Buckner, 2004; Tromp et al., 2015). However, cognitive aging studies often do not include any array of physiological and health metrics. These data suggest neurotrophic/growth factors, AD biomarkers, stress, and education may better predict performance on tasks of episodic memory, executive function, processing speed, visuospatial ability, verbal fluency, language and global cognition than chronological age.

Variables associated with cardiometabolic function (such as BMI, blood pressure, triglycerides) also did not significantly contribute to LV1. Similar to age, this null finding was also unexpected as several previous research studies show that cardiometabolic variables are associated with memory, executive function, and global cognition in older adults (Levine et al., 2020; Parthasarathy et al., 2017; Rouch et al., 2019; Yaffe et al., 2004). However, none of these studies simultaneously explored markers of neuroprotection or AD biomarkers. Thus, our findings suggest that neurotrophic/growth factors, AD biomarkers, stress, and education might have relatively stronger associations with the above identified cognitive domains. This finding aligns with previous research suggesting that metrics of cardiometabolic function are associated with executive function and not memory performance (Parthasarathy et al., 2017; Philippou, Michaelides, & Constantinidou, 2018). Thus, it's possible that the multiple significant variables associated with memory in LV1 explain this null finding.

Overall, these findings emphasize that markers of neuroprotection, neuroplasticity, stress, and AD significantly contribute to episodic memory, executive function, and processing speed in older adults with MCI. Our results suggest that modifiable variables, such as BDNF and cortisol, which research has shown can be changed with physical exercise, may serve as potential targets for future interventions to slow cognitive impairment and progression to dementia (Lista & Sorrentino, 2010; Baker et al., 2011).

Discussion Aim 2 (PLSR to identify predictors of cognition at 2-year follow-up)

Predicting Memory Performance at 2-Year Follow-Up:

Two PLSR models were examined to predict memory performance at 2-year follow-up (models 1 and 2; **Figures 5 and 6** respectively). In model 1, baseline levels of multiple modifiable cardiometabolic variables, inflammatory markers, growth factors, AD biomarker variables, and education were identified as important in predicting 37% of the variance in memory performance at 2-year follow-up. In model 2, baseline memory was added as an input variable. An inflammatory marker, AD biomarkers, education, and baseline memory were identified as important in predicting 65% of the variance in memory performance at 2-year follow-up.

In model 1, baseline levels of a novel biomarker, EGF, were considered an important predictor that was negatively associated with memory at 2-year follow-up. This finding is inconsistent with prior research showing significantly elevated levels of EGF in platelets of AD patients compared to MCI and healthy control participants (Hochstrasser et al., 2012). Research has also shown that EGF is one of the proteins in a five-protein signature demonstrating 96% accuracy in predicting clinical AD, although levels of EGF associated with AD were not specified (Ravetti & Moscato, 2008). Additionally, animal literature has shown that exogenous administration of EGF mitigated memory and spatial deficits in *APOE* ε4 positive mice with advanced cognitive impairment, suggesting potential neuroprotective benefits (Zaldua et al., 2020). Baseline levels of HB-EGF-like-GF, a related analyte, were considered an important predictor, but was positively associated with memory at 2-year follow-up. This result is consistent with animal

literature discussed in Aim 1, which suggest that this growth factor may have neuroprotective properties (Maurya et al., 2016; Shim & Madsen, 2018). However, this finding does not align with research exploring older adults, where higher levels of CSF HB-EGF-like-GF were associated with decreased levels of CSF $A\beta_{1-42}$ and increased levels of CSF t-tau, as our results from both Aim 1 and model 1 suggest this growth factor may be neuroprotective. Thus, further research should explore the association between both EGF and HB-EGF-like-GF and human cognition.

Two modifiable cardiometabolic variables, systolic blood pressure and triglycerides, were important to model 1 and were negatively associated with memory at 2-year follow up. This aligns with findings from a recent study that assessed a cumulative mean measure of systolic blood pressure in a large cohort of participants without dementia or stroke, where authors found that mean cumulative systolic blood pressure was related to significantly faster declines in memory (average follow-up was 10 years; Levine et al., 2020). These associations also are consistent with literature indicating that older adults without dementia with metabolic syndrome (which includes high blood pressure and triglycerides) were at a higher risk of cognitive impairment compared to those without metabolic syndrome (Yaffe et al., 2004). However, this result contrasts research demonstrating that triglycerides were negatively associated with executive function, but not memory, as triglycerides were considered a variable important in predicting memory in model 1 but did not meet criteria for importance in models 3 and 4 predicting executive function (Parthasarathy et al., 2017). Additionally, in middle-aged adults 32 – 62 years old at baseline, hypertension was associated with poorer global

cognition at 10-year follow-up, of which assessments of immediate and delayed episodic memory were included, which is also in line with our finding (Rouch et al., 2019).

Model 1 also showed that higher levels of insulin were positively associated with memory performance at 2-year follow-up. This aligns with research showing that insulin-resistant older adult participants without dementia had decreased odds of incident dementia or AD at 3-year follow-up, suggesting that high insulin may actually be a protective factor later in life and a risk factor during middle-age (Lee et al., 2019). In contrast, this relationship is inconsistent with other research conducted in older adults without dementia indicating that high fasting insulin was associated with poorer memory and increased risk of AD (Luchsinger, Tang, Shea, & Mayeux, 2004). An additional marker related to inflammation, IL-6 receptor, was positively associated with memory performance at 2 years. IL-6 receptor is considered an anti-inflammatory marker that promotes neurogenesis when bound to IL-6 (Barroeta-Espar et al., 2019). Other findings support the notion that IL6-r may be protective against AD (Angelis, Scharf, Mander, Vajda, & Christophidis, 1998). In one study, levels of IL-6 receptor were compared in AD patients and controls, and AD patients had significantly lower IL-6 receptor when compared to control subjects, although sample sizes were small (Angelis et al., 1998). This finding aligns with our model showing a positive association between this receptor and future memory, suggesting it has potential neuroprotective benefits.

Several other variables that were considered important in predicting memory performance at 2-year follow-up in model 1 were AD biomarkers. CSF $A\beta_{1-42}$ was positively associated with follow-up memory performance, consistent with recent

literature reporting that higher CSF $A\beta_{1\text{-}42}$ levels were correlated with higher cognitive scores in participants with MCI and a decreased risk of converting to dementia (Diniz et al., 2008; Matura et al., 2019). CSF p-$tau_{181}/A\beta_{1\text{-}42}$ and CSF t-tau/$A\beta_{1\text{-}42}$ ratios were both negatively associated with memory at follow-up, which is also consistent with recent findings showing that lower CSF p-$tau_{181}/A\beta_{1\text{-}42}$ ratios were associated with longitudinal declines in episodic memory in those with MCI and AD (Prakash, Mckenna, Gbadeyan, Andridge, & Scharre, 2020). Recent research also demonstrated that a CSF t-tau/$A\beta_{1\text{-}42}$ ratio of below 0.33 was associated with more rapid clinical progression (both functional and cognitive) over a follow-up of two years in those with MCI (Hansson et al., 2018). This relationship between AD biomarkers and future memory performance bolsters previous PLSC cross-sectional analyses presented earlier in the thesis, such that several AD biomarkers were associated with multiple domains of cognition, including episodic memory, in LV1 (see **Figure 1**). Education was also considered important in the PLSC analysis, and had a significant positive association with memory at 2-year follow-up in model 1, aligning with literature showing that those with higher education can have slower trajectories of cognitive decline due to cognitive reserve (Stern, 2013).

For model 2, baseline memory performance was added to the predictors to see how this would affect predictions of memory at 2-year follow-up. EGF, the two variables associated with cardiometabolic function (systolic blood pressure and triglycerides), and CSF p-$tau_{181}/A\beta_{1\text{-}42}$ were not considered important in model 2. Baseline memory and four of the variables considered important in model 1 were considered also important in model 2 and maintained the same directionalities reported in model 1 (see **Figure 6).**

Additionally, baseline memory performance had an expected positive association with memory performance two years later. Thus, when baseline memory is also considered as a predictor among other physiological variables, AD biomarkers, inflammation, and education continue to be important and significantly predictive of memory at 2-year follow-up, while cardiometabolic variables carry relatively less importance.

When interpreting the AIC values for models 1 and 2 (see **Table 3**), the ΔAIC (change in AIC) indicates that model 2 has a superior fit when compared to model 1 (i.e., it is better at predicting memory performance at 2 years). Thus, findings from model 1 should be interpreted with more caution than those reported within model 2.

Predicting Executive Function Performance at 2-Year Follow-Up

Two PLSR models were examined to predict executive function performance at 2-year follow-up (models 3 and 4; **Figures 7 and 8** respectively). In model 3, multiple modifiable cardiometabolic variables, inflammatory markers, AD biomarker variables, and education were statistically important in predicting 43% of the variance in executive function at 2-year follow-up. In model 4, baseline executive function was added as an input variable, and several of the same modifiable cardiometabolic, inflammatory, and AD biomarker variables, as well as baseline executive function, were identified as important in predicting 64% of the variance in executive function performance at 2-year follow-up.

For model 3, a unique biomarker, HB-EGF-like-GF, was considered an important predictor that was positively associated with executive function at 2-year follow-up. This finding aligns with prior animal research showing HB-EGF-like-GF may have

neuroprotective effects and thus likely positive associations with cognition, as described in the discussion of Aim 2, model 1 and Aim 1 (Maurya et al., 2016; Shim, Joon W., Madsen, 2018). However, as detailed in the PLSC analysis discussion, the association between HB-EGF-like-GF and human cognition is sparsely reported, and the single study we found reported that CSF levels of HB-EGF-like-GF were associated with AD pathology (lower levels of CSF $A\beta_{1-42}$ and increased levels of CSF t-tau) in cognitively normal and MCI participants, contrasting our results suggesting that high HB-EGF-like-GF is predictive of better executive function (P. F. Meyer et al., 2018). The unique findings in both the PLSC and PLSR analyses necessitate additional research to clarify how plasma HB-EGF-like-GF relates to human cognition in those with MCI.

Systolic blood pressure was also considered important in predicting executive function performance at 2-year follow up. Consistent with model 1, this variable was negatively associated with executive function at 2-year follow-up. This aligns with research findings discussed in model 1, where high blood pressure was associated with faster declines in executive function and was associated with poorer cognition (Levine et al., 2020; Rouch et al., 2019). In a different study exploring community dwelling older adults, metabolic syndrome (assessed as a single latent variable where blood pressure was included) was found to be negatively associated with executive function, however this relationship was not maintained when age and education were controlled for (Philippou et al., 2018).

Two markers associated with inflammation, IL-6 receptor and insulin, were also important predictors of executive function at 2-year follow-up in model 3. To our

knowledge, no studies have specifically reported a relationship between IL-6 receptor and executive function in older adults. However, IL-6 receptor is considered an anti-inflammatory marker with neuroprotective properties as described in the discussion of model 1 (Angelis et al., 1998; Barroeta-Espar et al., 2019). Thus, the positive relationship between IL-6 receptor and executive function found herein is consistent with the notion that IL-6 receptor may confer neuroprotection. Insulin, which is also associated with inflammation, was important to model 3 and had positive associations with executive function at 2-years, consistent with the directionality reported in model 1. As discussed for model 1, recent research has hypothesized that high insulin later in life may actually be protective in developing dementia or AD (Lee et al., 2019). Additionally, in a small pilot study exploring post-menopausal middle aged women at risk for AD, those with higher levels of fasting plasma insulin had small but statistically significant differences in executive function, where those in the higher plasma insulin group had higher levels of executive function (Kenna et al., 2013).

Several AD biomarkers were important in predicting executive function in model 3 as well. CSF t-tau and CSF t-tau/Aβ_{1-42} ratios had negative associations with executive function, aligning with literature reporting worse performance on tasks of memory and sustained attention in those with higher CSF t-tau and t-tau/Aβ_{1-42} ratios in subjects with MCI (Nathan et al., 2017). CSF Aβ_{1-42} was positively associated with executive function, consistent with research showing that low CSF Aβ_{1-42} was associated with poorer cognition in those with MCI but not in healthy controls (Matura et al., 2019). However, this finding contrasts findings showing that low CSF Aβ_{1-42} was associated with multiple

tasks of memory, but not executive function (measured by a task of sustained attention), in participants with MCI (Nathan et al., 2017). These reported associations also supplement our cross-sectional PLSC findings, where lower CSF t-tau and higher CSF $Aß_{1-42}$ were associated with multiple domains of cognition, including executive function.

In contrast, CSF p-tau_{181} and CSF p-$tau_{181}/Aß_{1-42}$ ratios had positive associations with executive function at 2-year follow-up in model 3. These relationships contrast literature showing that higher CSF p-$tau_{181}/Aß_{1-42}$ ratios predicted declines in executive function longitudinally in healthy control, MCI, and AD participants (Prakash et al., 2020). The reported association between CSF p-tau_{181} and cognition also contrasts findings showing that higher levels of CSF p-tau_{181} were associated with poorer performance on a task of executive function (spatial working memory) in MCI participants (Nathan et al., 2017). This also contrasts findings showing that those who were MCI at baseline and converted to AD two years later had higher CSF p-tau_{181} at baseline when compared to those who remained MCI at 2-year follow-up (Brys et al., 2009). The PLSR analyses also had a larger percentage of men (66%, see participants section for details). Recent research has shown that CSF AD biomarker profiles may differ in women and that women may be at a higher risk for AD (Koran, Wagener, & Hohman, 2017). Thus, this relationship could be due the high percentage of men, as well as potentially different AD biomarker profiles that could be observed as a function of sex. Lastly, there were 390 participants diagnosed with MCI that also had the ADNI executive function composite score and CSF AD biomarker data available (Gibbons et al., 2012). Approximately one third of this sample was included in Aim 2 analyses (N =

126), as this was the number of participants that also had other biomarkers of interest available at baseline (such as cardiometabolic variables, neurotrophic/growth factors). Gibbons and colleagues assessed levels of p-tau$_{181}$ in the original 390 participant sample, and found that 70% of the sample had high levels of p-tau$_{181}$ (p-tau$_{181}$ > 23 pg/ml; (Gibbons et al., 2012). Thus, another potential explanation for this finding might be that the subset of 126 participants in this study disproportionately of the 30% of participants with lower p-tau, lending potential explanation to the unexpected relationship found with both p-tau$_{181}$ and p-tau$_{181}$/Aß$_{1\text{-}42}$ ratios and executive function in model 3.

*APOE ε*4 allele status also had positive associations with executive function at 2-year follow-up in model 3. It is well known that *APOE ε*4 allele status puts older adults at an elevated risk of AD (O'Donoghue, Murphy, Zamboni, Nobre, & Mackay, 2018). Thus, a positive association between number of alleles (which would indicate greater risk of AD) and executive function is inconsistent with what we would expect given the current state of the literature (O'Donoghue et al., 2018). There are several potential explanations for this unexpected finding. It is possible that certain characteristics of *APOE ε*4 positive and negative participants played a role in this result. For instance, it's possible that participants who were *APOE ε*4 allele positive had overall higher education on average. Alternatively, those with one or more *APOE ε*4 alleles might have been a group of participants that were threshold for meeting criteria for an MCI verses a cognitively normal diagnosis at baseline. On the other hand, *APOE ε*4 negative participants might have been a group that consisted of a greater number of people who were closer to the threshold for an AD diagnosis, yet still met criteria for MCI at baseline.

For model 4, systolic blood pressure, IL-6 receptor, CSF t-tau/Aß$_{1-42}$, and CSF Aß$_{1-42}$ were all important variables in predicting executive function 2-year follow-up. All four of these variables overlapped with and maintained the same directionality as those described in model 3. Baseline executive function also was an important predictor in model 4 and had an expected positive association with executive function at 2-year follow-up. Of note, when baseline executive function was included in model 4, a greater percent variance in future cognition was accounted for, and variables that were going in directions that were not always consistent with the literature were no longer significant in model 4. Additionally, similar to comparisons of models 1 and 2, the AIC value (see **Table 3**) indicates that model 4 is superior to model 3 in predicting executive function performance at 2-year follow-up. Thus, findings from model 3 should be interpreted with more caution than those reported within model 4.

Chapter 5: Summary

The goal of the present study was to address a gap in the literature regarding the relative importance of different types of physiological variables with known associations with cognition, and how they relate to current and future cognition when considered simultaneously in a multivariate analysis. Our findings from Aim 1 revealed that variables largely associated with neuroprotection, AD pathology and education were significantly associated with episodic memory, executive function, processing speed, verbal fluency, and global cognition. Age and metrics of cardiometabolic risk were not significant in LV1 in this cross-sectional analysis. Findings from Aim 2 revealed that when these same markers were entered into a PLSR analysis to predict memory at 2-year follow-up, metrics of cardiometabolic risk, inflammation, AD biomarkers, and education were considered important predictors of memory performance 2 years later (models 1 and 2; **see Figures 5 and 6**). Results were similar when executive function at 2-year follow-up was the Y-outcome: metrics of cardiometabolic risk, inflammation, and AD biomarkers were considered important in predicting executive function at 2-year follow-up. However, education was not an important predictor for the executive function PLSRs (models 3 and 4; **see Figures 5 and 6**). These findings suggest that education may have relatively more importance in predicting future memory rather than executive function performance, and that neurotrophic/growth factors associated with neuroprotection may have stronger associations with current rather than future cognition. On the other hand, AD biomarkers were significant in all analyses in Aims 1 and 2, suggesting that CSF AD biomarkers may be promising targets for assessments of risk or resilience to future

decline. Likewise, these analyses suggest that education may be a good indicator of current and future memory performance, but may not provide the cognitive reserve needed to maintain executive function abilities over time.

Limitations

This present study had limitations. This study sample was not representative of all older adults in the United States, as the 154 participants assessed in Aim 1 and the 126 participants assessed in Aim 2 were predominately white, non-Hispanic, and highly educated. Thus, these findings may not be generalizable to a more diverse and/or less educated sample. Some physiological variables such as Insulin-like Growth Factor 1 and Interleukin-6 did not pass ADNI's internal quality control processes, precluding inclusion in our analysis. Other neuropsychological variables, such as those assessing cognitive flexibility, were not included in the ADNI neuropsychological battery. Overall, the ADNI neuropsychological battery had more measures assessing memory rather than executive function. This was also shown by the ADNI executive function composite score, which heavily sampled from individual scores on clock drawing (Gibbons et al., 2012). Thus, it is possible the relationships identified herein might differ if the ADNI neuropsychological battery had a wider range of executive function measures in both its individual tests and composite executive function score. Other variables, such as sex or *APOE* ε4 status, were not included in the Aim 1 PLSC analysis because it is generally not recommended to include binarized variables (sex) or those with limited variability (*APOE* ε4 genotype: only 3 possible values: 0, 1, or 2 alleles) in a PLSC analysis (a variable with low variance is problematic for the calculation of correlation coefficients

and can lead to faulty bootstrap resampling, thus complicated interpretation of results). For Aim 2, follow-up data for MCI participants with the physical, health, AD, and cognitive data of interest were limited at more extended timepoints of 3, 4, and 5-year follow-up. Thus, a 2-year follow up was chosen in order to include as many participants as possible from the original PLSC analysis completed in Aim 1. The statistical analysis chosen for Aim 2 also comes with limitations, in that there is no way to directly compare models with different y-outcomes. AIC scores can be used to assess model fit when the y-outcome is the same, however, two models with different outcomes cannot be compared because actual AIC scores are meaningless, and only the change in AIC from one model to another can be interpreted. Thus, we were not able to assess whether or not the identified physiological variables were better at predicting memory or executive function performance.

Future Directions

To build off these findings, future work should explore both the cross-sectional and longitudinal associations between these physiological domains and brain health by exploring neuroimaging data. For instance, research exploring diffusion tensor imaging could answer questions regarding the associations between these physiological domains and structural connectivity, while research exploring resting-state functional neuroimaging could answer questions about functional connectivity and its associations to these physiological variables. Follow-up analyses should also explore how these relationships may differ in cognitively healthy older adults, or in cognitively healthy middle-aged adults. This research would allow us to move toward identifying those at

risk for cognitive decline at earlier stages, as well as target those who might be best fit for a lifestyle intervention. Lastly, the PLSR analyses completed as part of Aim 2 can be used to inform future PLS discriminant analyses, which would allow us to see if the variables considered important in predicting future memory or executive function are also able to effectively discriminate between MCI participants who remain MCI verses those who convert to AD at 2-year follow-up.

Figure 1. Correlation Profile and Bootstrap Ratios for Latent Variable 1.
The correlation between each cognitive test variable to the identified physical, health, and AD variables listed in panel B. Significant variables have 95% confidence intervals (error bars) that do not cross the x-axis (0). **B.** Each Physical, Health, and AD Variable's contribution to LV1 represented by their bootstrap ratios, indicating directionality with significant cognitive tests represented in A (for instance, performance on logical memory immediate was positively correlated with levels of brain-derived neurotrophic factor, and had a negative correlation with CSF tau). Error bars represent 95% confidence intervals. Variables with bootstrap ratios > |1.96| (equivalent to a p-value of < 0.05) are considered significant contributors to the LV and are indicated by *. (**KEY PANEL A:** ADAS-COG = Alzheimer's Disease Assessment Scale, Cognitive Subsection; ANART = American National Adult Reading Test; MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; **KEY PANEL B:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VEGF = vascular endothelial growth factor).

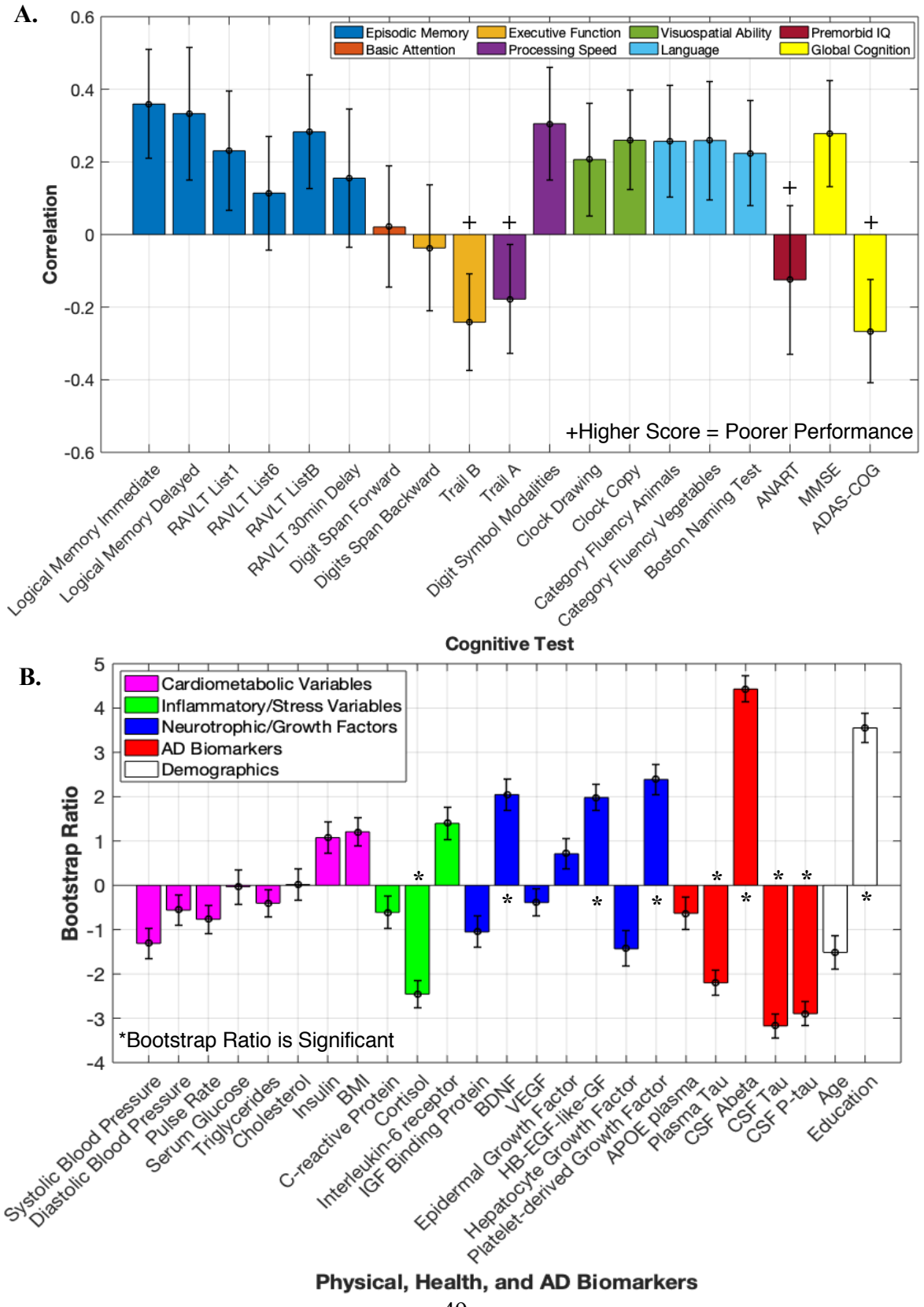
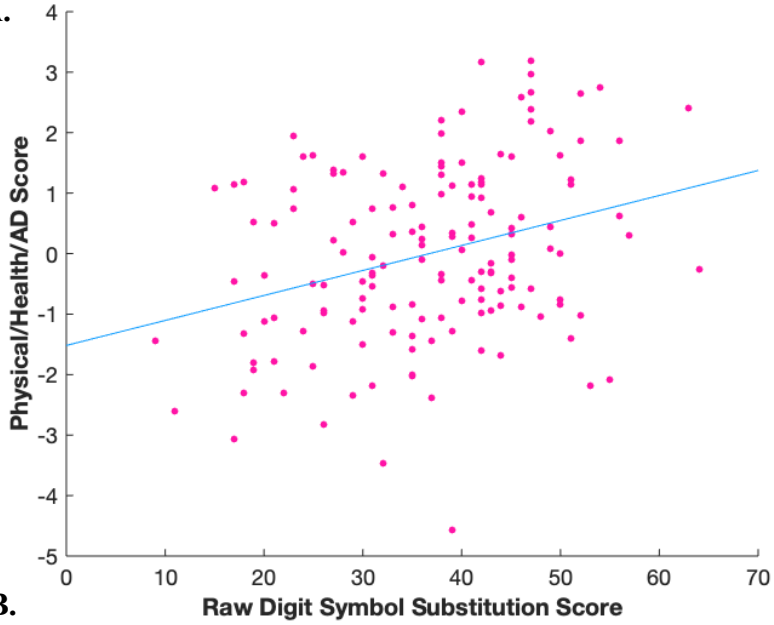

A.
Episodic Memory
Executive Function
Visuospatial Ability
Premorbid IQ
Basic Attention
Processing Speed
Language
Global Cognition
Correlation
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
+Higher Score = Poorer Performance
Logical Memory Immediate
Logical Memory Delayed
RAVLT List1
RAVLT List6
RAVLT ListB
RAVLT 30min Delay
Digit Span Forward
Digits Span Backward
Trail B
Trail A
Digit Symbol Modalities
Clock Drawing
Clock Copy
Category Fluency Animals
Category Fluency Vegetables
Boston Naming Test
ANART
MMSE
ADAS-COG
Cognitive Test
B.
Cardiometabolic Variables
Inflammatory/Stress Variables
Neurotrophic/Growth Factors
AD Biomarkers
Demographics
Bootstrap Ratio
5
4
3
2
1
0
-1
-2
-3
-4
*Bootstrap Ratio is Significant
Systolic Blood Pressure
Diastolic Blood Pressure
Pulse Rate
Serum Glucose
Triglycerides
Cholesterol
Insulin
BMI
C-reactive Protein
Cortisol
Interleukin-6 receptor
IGF Binding Protein
BDNF
VEGF
Epidermal Growth Factor
HB-EGF-like-GF
Hepatocyte Growth Factor
Platelet-derived Growth Factor
APOE plasma
Plasma Tau
CSF Abeta
CSF Tau
CSF P-tau
Age
Education
Physical, Health, and AD Biomarkers

Figure 2. Scatterplots of Participant Brain Scores Against Selected Cognitive Tests. Each participant's Digit Symbol Substitution raw score (**Panel A**) and WMS-R Logical Memory Delayed Recall raw score (**Panel B**) are plotted against their individual physical/health/AD score (representing how well an individual's physical/health/AD variables contribute to the overall pattern in LV1).

A.



B.

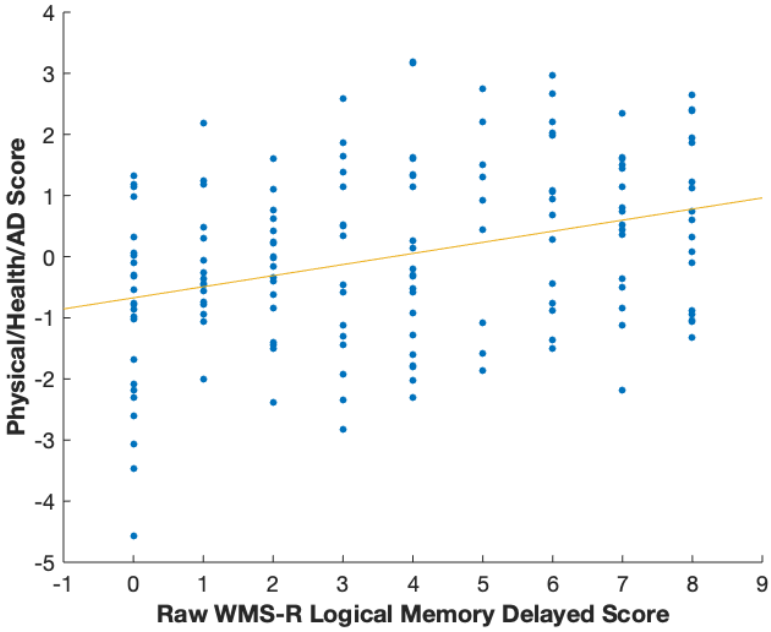
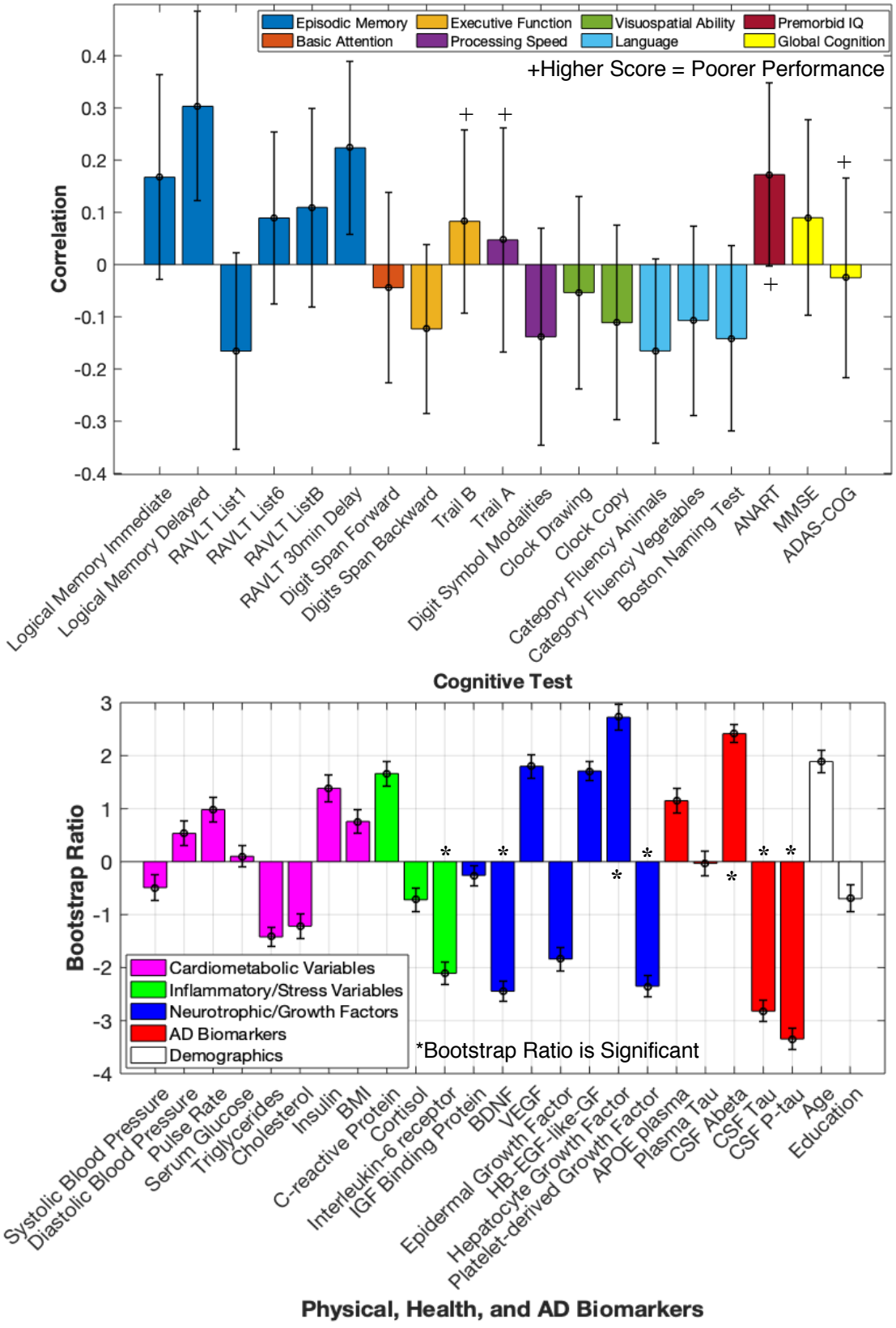


Figure 3. Correlation profile and bootstrap ratios for Latent Variable 2.
A. The correlation between each cognitive test variable to the identified physical, health, and AD variables listed in panel B. Significant variables have 95% confidence intervals (error bars) that do not cross the x-axis (0). **B.** Each Physical, Health, and AD Variable's contribution to LV2 represented by their bootstrap ratios, indicating directionality with significant cognitive tests represented in A (for instance, performance on logical memory delayed was positively correlated with CSF $A\beta_{1-42}$, and had a negative correlation with CSF tau). Error bars represent 95% confidence intervals. Variables with bootstrap ratios > |1.96| (equivalent to a p-value of < 0.05) are considered significant contributors to the LV and are indicated by *. (**KEY PANEL A:** ADAS-COG = Alzheimer's Disease Assessment Scale, Cognitive Subsection; ANART = American National Adult Reading Test; MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; **KEY PANEL B:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VEGF = vascular endothelial growth factor).


Episodic Memory
Executive Function
Visuospatial Ability
Premorbid IQ
Basic Attention
Processing Speed
Language
Global Cognition
+Higher Score = Poorer Performance
Correlation
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
Logical Memory Immediate
Logical Memory Delayed
RAVLT List1
RAVLT List6
RAVLT ListB
RAVLT 30min Delay
Digit Span Forward
Digits Span Backward
Trail B
Trail A
Digit Symbol Modalities
Clock Drawing
Clock Copy
Category Fluency Animals
Category Fluency Vegetables
Boston Naming Test
ANART
MMSE
ADAS-COG
Cognitive Test
Bootstrap Ratio
3
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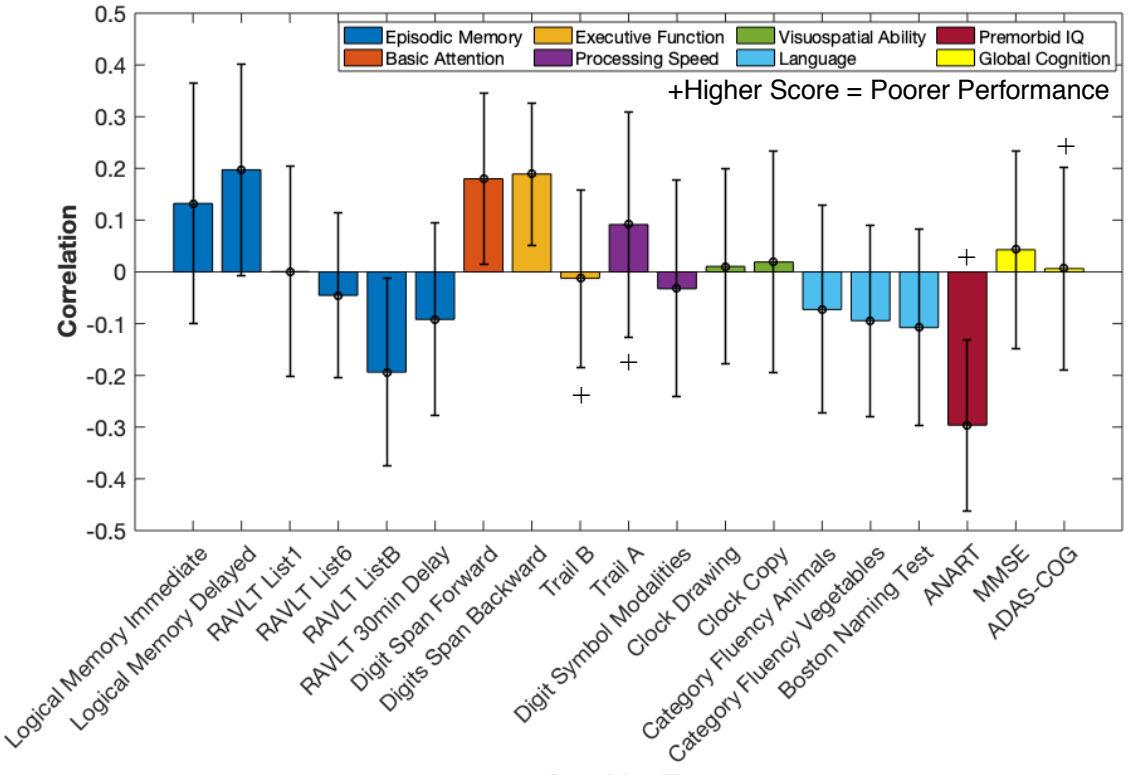
-1
-2
-3
-4
Cardiometabolic Variables
Inflammatory/Stress Variables
Neurotrophic/Growth Factors
AD Biomarkers
Demographics
*Bootstrap Ratio is Significant
Systolic Blood Pressure
Diastolic Blood Pressure
Pulse Rate
Serum Glucose
Triglycerides
Cholesterol
Insulin
BMI
C-reactive Protein
Cortisol
Interleukin-6 receptor
IGF Binding Protein
BDNF
VEGF
Epidermal Growth Factor
HB-EGF-like-GF
Hepatocyte Growth Factor
Platelet-derived Growth Factor
APOE plasma
Plasma Tau
CSF Abeta
CSF Tau
CSF P-tau
Age
Education
Physical, Health, and AD Biomarkers

Figure 4. Correlation profile and bootstrap ratios for Latent Variable 3.
A. The correlation between each cognitive test variable to the identified physical, health, and AD variables listed in panel B. Significant variables have 95% confidence intervals (error bars) that do not cross the x-axis (0). **B.** Each Physical, Health, and AD Variable's contribution to LV3 represented by their bootstrap ratios, indicating directionality with significant cognitive tests represented in A (for instance, performance on digit span backward was positively correlated with education, and had a negative correlation with BMI). Error bars represent 95% confidence intervals. Variables with bootstrap ratios > |1.96| (equivalent to a p-value of < 0.05) are considered significant contributors to the LV and are indicated by *. (**KEY PANEL A:** ADAS-COG = Alzheimer's disease Assessment Scale, Cognitive Subsection; ANART = American National Adult Reading Test; MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; **KEY PANEL B:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VEGF = vascular endothelial growth factor).


Episodic Memory
Executive Function
Visuospatial Ability
Premorbid IQ
Basic Attention
Processing Speed
Language
Global Cognition
+Higher Score = Poorer Performance
Correlation
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0.4
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-0.1
-0.2
-0.3
-0.4
-0.5
Logical Memory Immediate
Logical Memory Delayed
RAVLT List1
RAVLT List6
RAVLT ListB
RAVLT 30min Delay
Digit Span Forward
Digits Span Backward
Trail B
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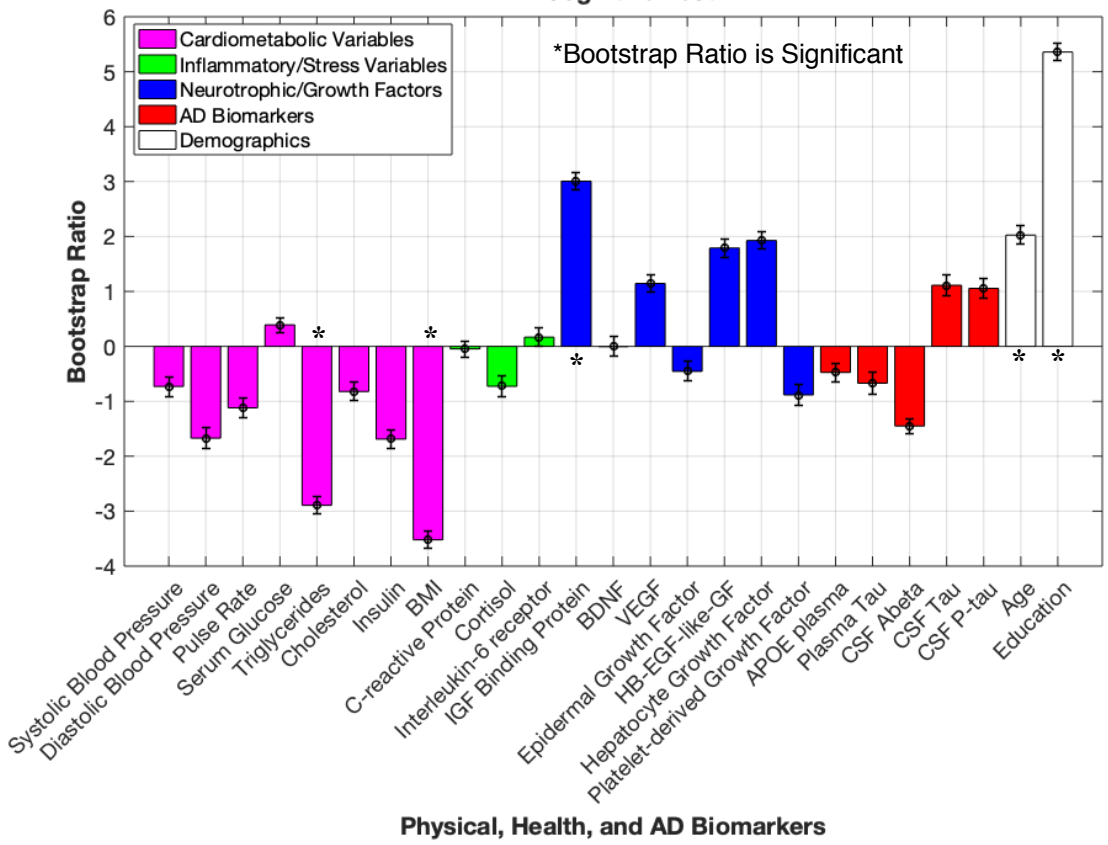
Clock Copy
Category Fluency Animals
Category Fluency Vegetables
Boston Naming Test
ANART
MMSE
ADAS-COG
Cognitive Test


Cardiometabolic Variables
Inflammatory/Stress Variables
Neurotrophic/Growth Factors
AD Biomarkers
Demographics
*Bootstrap Ratio is Significant
Bootstrap Ratio
6
5
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-2
-3
-4
Systolic Blood Pressure
Diastolic Blood Pressure
Pulse Rate
Serum Glucose
Triglycerides
Cholesterol
Insulin
BMI
C-reactive Protein
Cortisol
Interleukin-6 receptor
IGF Binding Protein
BDNF
VEGF
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HB-EGF-like-GF
Hepatocyte Growth Factor
Platelet-derived Growth Factor
APOE plasma
Plasma Tau
CSF Abeta
CSF Tau
CSF P-tau
Age
Education
Physical, Health, and AD Biomarkers

Figure 5. Beta Values (Absolute) and Variable Importance on Projection Scores, PLSR Model 1.
All physical, health, and AD variables (X-matrix variables) included in PLSR model 1 are on the x-axis. Bars represent absolute values of the beta values. Variables with positive beta values, to the right of the vertical dashed gray line, are associated with better composite memory at 2-year follow-up. Variables with negative beta values, to the left of the vertical dashed gray line, are associated with poorer composite memory at 2-year follow-up. VIP values are represented by the red dashed line. Variables considered statistically important to the model have VIP scores > 0.8. Variables with a VIP > 0.8 and an original beta value with a 95% confidence interval that did not include 0 were considered significant predictors the model, and are highlighted in dark blue. (**KEY:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VIP = Variable Importance on Projection; VEGF = vascular endothelial growth factor).

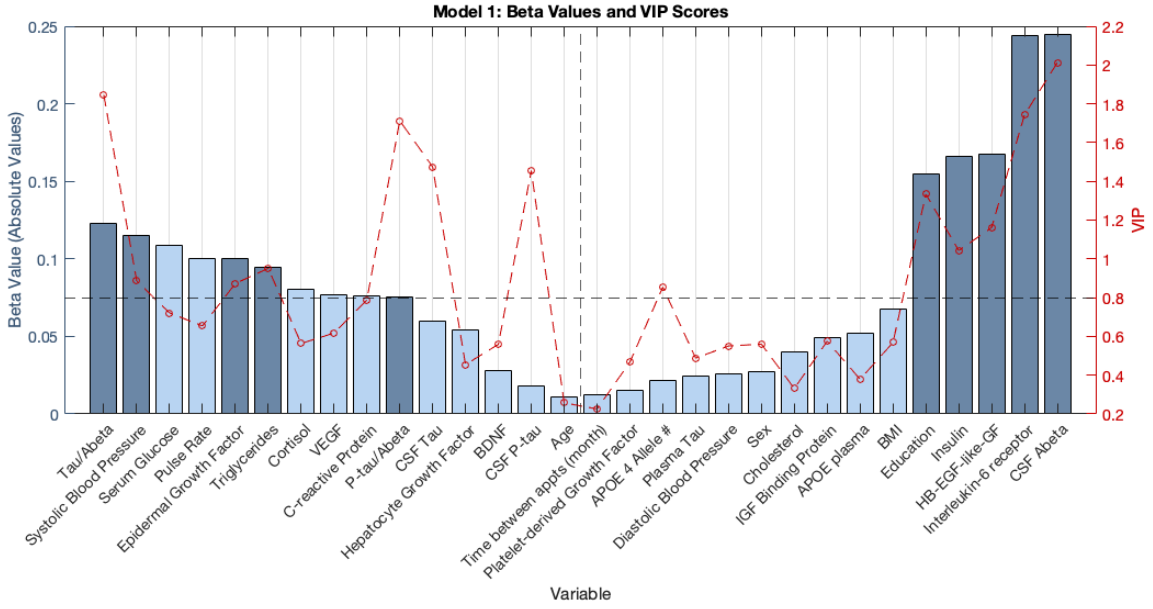

Figure 6. Beta Values (Absolute) and Variable Importance on Projection Scores, PLSR Model 2.
All physical, health, and AD variables (X-matrix variables) included in PLSR model 2 are on the x-axis. Bars represent absolute values of the beta values. Variables with positive beta values, to the right of the vertical dashed gray line, are associated with better composite memory at 2-year follow-up. Variables with negative beta values, to the left of the vertical dashed gray line, are associated with poorer composite memory at 2-year follow-up. VIP values are represented by the red dashed line. Variables considered statistically important to the model have VIP scores > 0.8. Variables with a VIP > 0.8 and an original beta value with a 95% confidence interval that did not include 0 were considered significant predictors in the model, and are highlighted in dark blue. (**KEY:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VIP = Variable Importance on Projection; VEGF = vascular endothelial growth factor).

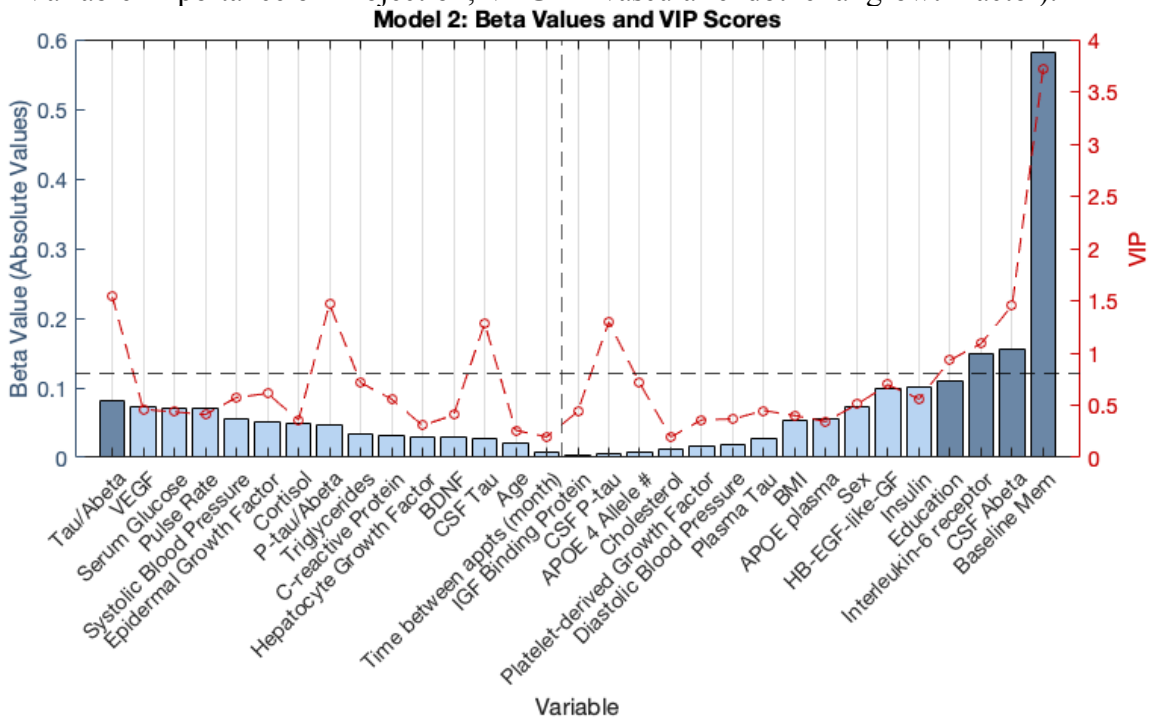

Figure 7. Beta Values (Absolute) and Variable Importance on Projection Scores, PLSR Model 3.
All physical, health, and AD variables (X-matrix variables) included in PLSR model 3 are on the x-axis. Bars represent absolute values of the beta values. Variables with positive beta values, to the right of the vertical dashed gray line, are associated with better composite executive function at 2-year follow-up. Variables with negative beta values, to the left of the vertical dashed gray line, are associated with poorer composite executive function at 2-year follow-up. VIP values are represented by the red dashed line. Variables considered statistically important to the model have VIP scores > 0.8. Variables with a VIP > 0.8 and an original beta value with a 95% confidence interval that did not include 0 were considered significant predictors in the model, and are highlighted in dark blue. (**KEY:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VIP = Variable Importance on Projection; VEGF = vascular endothelial growth factor).

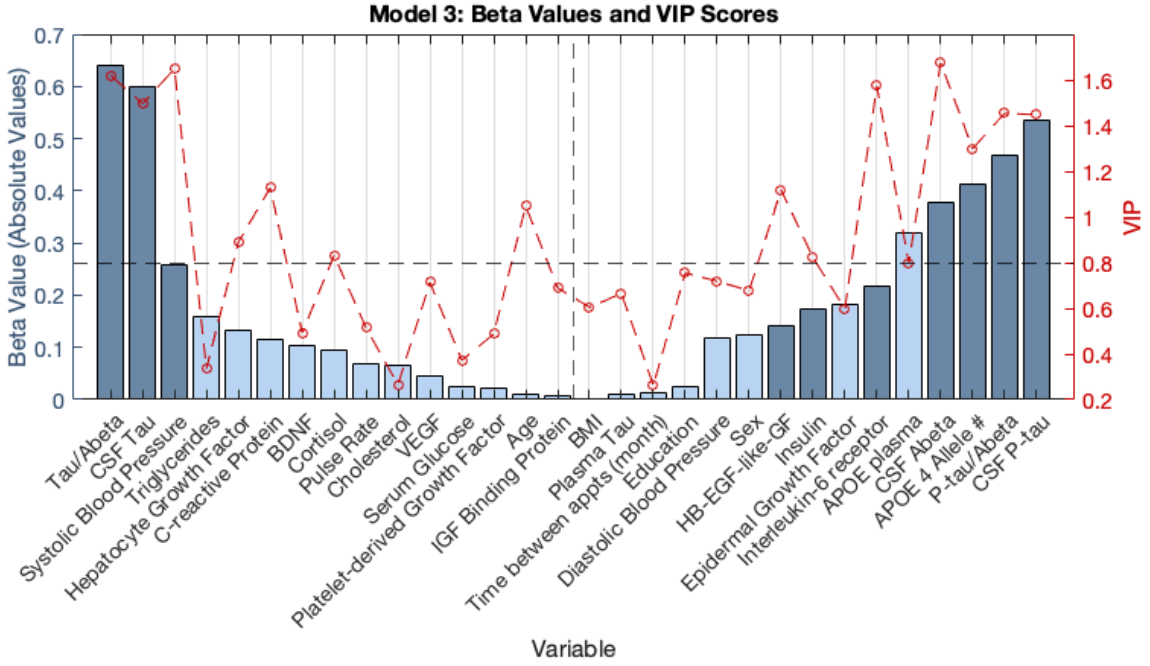

Figure 8. Beta Values (Absolute) and Variable Importance on Projection Scores, PLSR Model 4.
All physical, health, and AD variables (X-matrix variables) included in PLSR model 4 are on the x-axis. Bars represent absolute values of the beta values. Variables with positive beta values, to the right of the vertical dashed gray line, are associated with better composite executive function at 2-year follow-up. Variables with negative beta values, to the left of the vertical dashed gray line, are associated with poorer composite executive function at 2-year follow-up. VIP values are represented by the red dashed line. Variables considered statistically important to the model have VIP scores > 0.8. Variables with a VIP > 0.8 and an original beta value with a 95% confidence interval that did not include 0 were considered significant predictors in the model, and are highlighted in dark blue. (**KEY:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VIP = Variable Importance on Projection; VEGF = vascular endothelial growth factor).

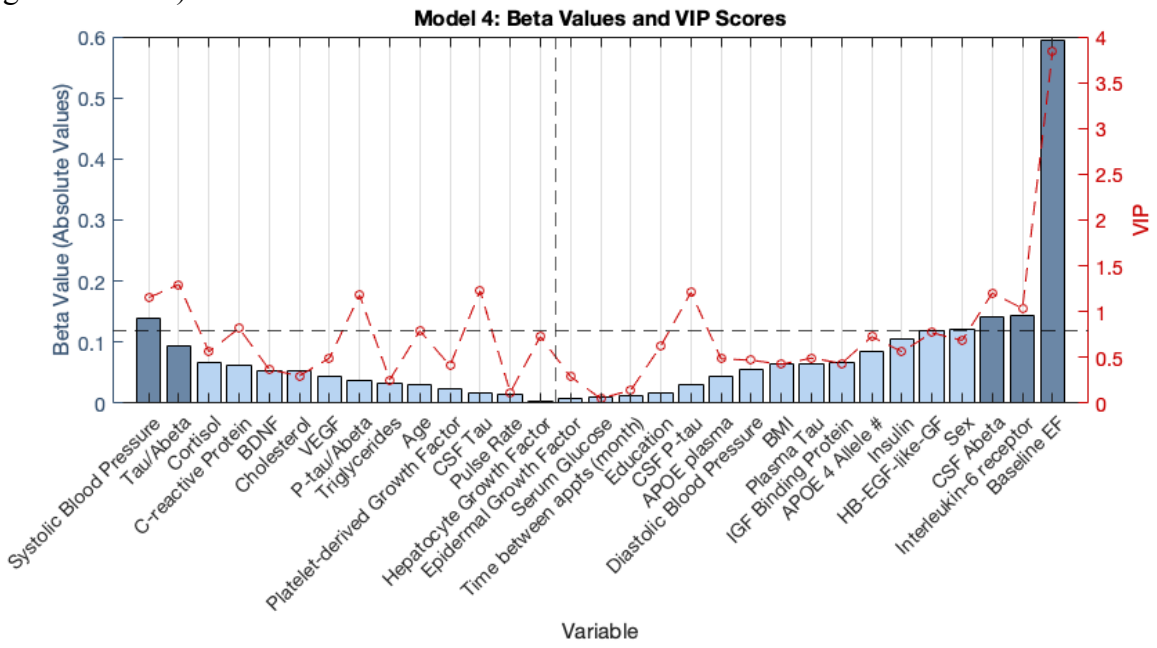

Table 1. Participant Demographic, Neuropsychological, Physical, Health, and AD Biomarker Data Entered into the PLSC Analysis (N=154).
KEY: ADAS-COG = Alzheimer's disease Assessment Scale, Cognitive Subsection; ANART = American National Adult Reading Test; MMSE = Mini Mental State Exam; CSF = Cerebrospinal Fluid; RAVLT = Rey Auditory Verbal Learning Test; WMS-R = Weschler Memory Scale – Revised.

Demographic Variables			**Physical, Health, and AD Variables**		
	Unit	**Mean (SD)**		**Unit**	**Mean (SD)**
Age	Years	74.1 (7.5)	**Body Mass Index**	kg/m^2	25.8 (3.7)
Education	Years	16.0 (2.9)	**Seated Systolic Blood Pressure**	mmHg	134.1 (17.8)
Race	N/A	N = 150 White; N =2 Asian; N = 2 Black	**Seated Diastolic Blood Pressure**	mmHg	74.2 (9.7)
Ethnicity	N/A	N = 152 Non-Hispanic; N = 2 Hispanic	**Seated Pulse Rate**	Per minute	64.2 (9.5)
Neuropsychological Variables			**Serum Glucose**	mg/dL	101.8 (31.7)
WMS-R Logical Memory Immediate Recall	Number of story details correctly recalled	6.9 (3.2)	**Triglycerides**	mg/dL	151.0 (102.5)
WMS-R Logical Memory Delay Recall	Number of story details correctly recalled	3.7 (2.7)	**Cholesterol**	mg/dL	198.7 (39.8)
RAVLT List 1	Number of words correctly recalled	4.0 (1.4)	**Insulin*** [+]	uIU/mL	0.3 (0.3)
RAVLT List 6	Number of words correctly recalled	3.4 (3.0)	**C-reactive Protein*** [+]	ug/mL	0.1 (0.5)
RAVLT List B	Number of words correctly recalled	3.6 (1.4)	**Cortisol*** [+]	ng/mL	2.2 (0.1)
RAVLT Delay Recall	Number of words correctly recalled	2.5 (3.0)	**Interleukin-6 Receptor*** [+]	ng/mL	1.5 (0.1)
Longest Digit Span Forward	Length of longest digit span correctly recalled	6.5 (1.1)	**Insulin-like Growth Factor Binding Protein*** [+]	ng/mL	2.0 (0.2)

Continued

Table 1 Continued

Longest Digit Span Backward	Length of longest digit span correctly recalled	4.6 (1.1)	**Vascular Endothelial Growth Factor*** +	pg/mL	2.8 (0.1)
Trail Making Test, Trail B Score**	Seconds to correctly complete the trail	135.8 (73.5)	**Epidermal Growth Factor*** +	pg/mL	1.6 (0.6)
Digit Symbol Substitution Score	Number of correctly drawn symbols	36.7 (10.8)	**Heparin-binding Epidermal-Growth-Factor-like Growth Factor *+**	pg/mL	1.9 (0.4)
Clock Drawing Score	Number of clock details correctly drawn based on verbal command	4.1 (1.1)	**Hepatocyte Growth Factor*+**	ng/mL	0.6 (0.1)
Clock Copy Score	Number of clock details correctly drawn when visual clock stimulus is present	4.6 (0.8)	**Platelet-derived Growth Factor BB*** +	pg/mL	3.2 (0.5)
Category Fluency: Animals	Number of words produced in the correct category	15.7 (4.7)	**Apolipoprotein E*** +	ug/mL	1.7 (0.2)
Category Fluency: Vegetables	Number of words produced in the correct category	10.7 (3.4)	**Tau**+	pg/mL	2.8 (1.7)
Boston Naming Test Total Correct	Number of drawings correctly named	25.8 (3.9)	**Aß$_{1-42}$ (CSF)**	pg/mL	742.0 (337.3)
ANART Errors**	Number of words incorrectly pronounced	14.5 (9.9)	**Total tau (CSF)**	pg/mL	311.6 (129.7)
MMSE	Total score	26.9 (1.8)	**P-tau$_{181}$ (CSF)**	pg/mL	31.1 (15.1)
ADAS-COG**	Total Score	11.7 (4.6)			

***these values are normalized **higher scores = poorer performance +plasma levels**

Table 2. Participant Demographic, Neuropsychological, Physical, Health, and AD Biomarker Data Entered into the PLSR Analyses (N=126).
KEY: CSF = Cerebrospinal Fluid

Physical, Health, and AD Variables					
	Unit	**Mean (SD)**		**Unit**	**Mean (SD)**
Body Mass Index	kg/m^2	26.0 (3.8)	**Vascular Endothelial Growth Factor*** +	pg/mL	2.8 (0.1)
Seated Systolic Blood Pressure	mmHg	134.4 (18.1)	**Epidermal Growth Factor*** +	pg/mL	1.5 (0.6)
Seated Diastolic Blood Pressure	mmHg	73.4 (9.3)	**Heparin-binding Epidermal-Growth-Factor-like Growth Factor *+**	pg/mL	1.9 (0.4)
Seated Pulse Rate	Per minute	64.5 (9.2)	**Hepatocyte Growth Factor*+**	ng/mL	0.6 (0.1)
Serum Glucose	mg/dL	102.6 (34.0)	**Platelet-derived Growth Factor BB*** +	pg/mL	3.2 (0.4)
Triglycerides	mg/dL	157 (106.1)	**Apolipoprotein E*** +	ug/mL	1.7 (0.2)
Cholesterol	mg/dL	198.8 (38.7)	**Tau**+	pg/mL	2.8 (1.8)
Insulin* +	uIU/mL	0.3 (0.3)	**$A\beta_{1-42}$ (CSF)**	pg/mL	733.1 (337.6)
C-reactive Protein*+	ug/mL	0.04 (0.5)	**Total tau (CSF)**	pg/mL	308.4 (120.4)
Cortisol*+	ng/mL	2.2 (0.1)	**P-tau_{181} (CSF)**	pg/mL	30.7 (13.7)
Interleukin-6 Receptor* +	ng/mL	1.5 (0.1)	**P-tau181/Aß1-42 (CSF)**	Ratio	0.1 (0.03)
Insulin-like Growth Factor Binding Protein*+	ng/mL	2.0 (0.2)	**Total tau/Aß1-42 (CSF)**	Ratio	0.5 (0.3)
Brain-derived Neurotrophic Factor*+	ng/mL	0.3 (0.4)	**APOE e4 status**	Number of alleles	0.7 (0.7)

Continued

Table 2 Continued

Demographic Variables					
	Unit	**Mean (SD)**		**Unit**	**Mean (SD)**
Age	Years	74.0 (7.6)	**Education**	Years	16.0 (2.9)
Time between appointments	Months	24.8 (1.2)	**Sex**	N/A	N/A
Race	N/A	N = 122 White; N =2 Asian; N = 2 Black	**Ethnicity**	N/A	N = 124 Non-Hispanic; N = 2 Hispanic
Neuropsychological Variables					
	Unit	**Mean (SD)**		**Unit**	**Mean (SD)**
ADNI Composite Memory Baseline	Z-scores	-0.1 (0.6)	**ADNI Composite Executive Function Baseline**	Z-scores	-0.1 (0.1)
ADNI Composite Memory 24 Months	Z-scores	-0.3 (0.8)	**ADNI Composite Executive Function 24 Months**	Z-scores	-0.3 (1.0)

***these values are normalized **higher scores = poorer performance $^{+}$plasma levels**

Table 3. Summary statistics for all four PLSR models run.
KEY: AIC = Akaike Information Criterion

Model	Number of Components	AIC (ΔAIC)	Percent Variance Explained in X	Percent Variance Explained in Y
1	3	-0.04 (72.73)	25.55	36.91
2	3	-72.77 (0)	25.45	65.14
3	9	-11.71 (55.84)	50.76	42.49
4	3	-67.55 (0)	25.99	63.66

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