LONGITUDINAL EFFECTS OF AMYLOID ON COGNITIVE DECLINE

IN MIDDLE-AGED AND OLDER ADULTS

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DISSERTATION

Presented to the Faculty of

The University of Texas at Dallas

in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY IN

COGNITION AND NEUROSCIENCE

THE UNIVERSITY OF TEXAS AT DALLAS

December 2017

ACKNOWLEDGMENTS

First and foremost, I would like to thank my advisor, Denise Park, for her years of guidance and mentorship. Thank you for always believing in me and providing me with countless opportunities I never dreamed of having.

I would like to thank the members of my committee, Mick Rugg, Karen Rodrigue and Kristen Kennedy, for their time, expertise and guidance on this project. Thank you for challenging me to think in new ways and helping me to grow as a scientist.

Thank you to Gérard Bischof, Jenny Rieck and Micaela Chan for your help in my early years as a grad student. You were all always so willing to drop whatever you were working on to help me, and I will be forever indebted to you.

Thank you to Sara Festini and Xi Chen. You two have been my rocks in the lab. You are both brilliant scientists and wonderful people and I feel privileged just to know you.

Thank you to all the members of the Park Lab and CVL, past and present, who have worked to collect, process and analyze the amazing wealth of data that is the Dallas Lifespan Brain Study. I am honored to have worked amongst you.

Thank you to Mike Devous, for giving me the foundation I needed to study amyloid, and for your continuing support in my career.

An emotional thank you to my fellow Apples, Marci Horn, Melissa Boone, David Martinez and Ariel Ketcherside. Without the 4 of you I doubt that I would be where I am today. You are my Yesterland Farms.

Thank you to my family for all your love and support. Thank you for always making sure I know how proud you are of me, even when it ends up encouraging me to do crazy things like move 2,000 miles away. I hope to continue making you proud.

An extra thank you to my Dad, for putting up with countless hours on the phone listening to me ramble on about amyloid. At least it's not politics.

November 2017

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The University of Texas at Dallas, 2017

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Understanding the role of amyloid pathology in cognitively normal adults is of utmost importance to the potential treatment and prevention of Alzheimer's disease. The present dissertation utilizes PET imaging with the tracer florbetapir at baseline and after a four year follow-up in cognitively normal adults from the Dallas Lifespan Brain Study to assess the impact of baseline mean cortical amyloid burden and change in regional amyloid burden on cognitive decline. Study 1 demonstrated a dose-response relationship between the magnitude of amyloid burden at baseline and the rate of cognitive decline over a four-year follow-up, particularly for episodic memory. These results suggest that the magnitude of amyloid deposition at baseline predicts those likely to be on a more pathological cognitive trajectory, potentially heading towards dementia. Additionally, Study 2 demonstrated a regionally specific relationship between the rate of amyloid accumulation over four years across multiple posterior regions and episodic memory decline. These findings demonstrate the importance of assessing regional changes in amyloid to monitor disease progression. Additionally, secondary analyses were conducted in middle-aged adults (age 30-59) and initially amyloid negative adults to assess whether a

relationship between amyloid and cognitive decline is apparent both early in the lifespan as well as early in disease progression. In Study 1, relatively high baseline mean cortical amyloid burden compared with one's peers was not predictive of cognitive decline in either group. In contrast, Study 2 was able to leverage longitudinal changes in amyloid in middle-aged and initially amyloid negative individuals to detect early amyloid-related changes in episodic memory across multiple posterior regions including the posterior cingulate, parietal and occipital lobes. Consequently, it may be useful to focus on these regions in both research and clinical trials aimed at early intervention of Alzheimer's disease.

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CHAPTER 1

INTRODUCTION

Beta-amyloid (henceforth, amyloid) is an abnormal protein fragment that aggregates extracellularly into plaques in the brains of patients with Alzheimer's disease (Hardy & Selkoe, 2002). Along with tau tangles, amyloid plaques are the markers upon which a diagnosis of Alzheimer's disease is based at autopsy (Hardy & Selkoe, 2002; McKhann et al, 2011). However, there is little correlation between the amount of amyloid plaques in the brain and the degree of cognitive impairment in AD patients (Bennett, Schneider, Wilson, Bienias, & Arnold, 2004; Gomez-Isla et al, 1997). Furthermore, autopsy studies have long established that amyloid is detectable in the absence of clinical symptoms of Alzheimer's disease (Crystal et al, 1988), as early as middle age (Braak & Braak, 1991, 1996). These findings led to the amyloid cascade hypothesis (Hardy & Selkoe, 2002), which posits that the deposition of amyloid occurs over decades, peaking prior to dementia onset and initiating a cascade of downstream events, including the spread of tau, neurodegeneration and cognitive decline and eventually leading to dementia. Thus, the most dynamic period of amyloid accumulation occurs in cognitively normal adults, for whom amyloid deposition may have subtle, subclinical consequences for brain and behavior. The overarching goal of the present dissertation is to evaluate amyloid deposition as a predictor of cognitive decline in cognitively normal adults.

Autopsy studies allow only for retrospective analysis and are not suited to assess the future consequences of amyloid, which requires prospective longitudinal design in living humans. Importantly, the recent advent of PET radiotracers that bind amyloid plaques in the living brain (Klunk et al, 2004; Wong et al, 2010) has allowed for the visualization and

quantification of amyloid plaques in living persons. The present dissertation utilizes PET imaging with the tracer florbetapir at baseline and after a four year follow-up in cognitively normal adults to measure amyloid deposition in two ways: 1) the magnitude of amyloid deposition at baseline and 2) the rate of change in amyloid over the four year interval. Broadly, Study 1 examines whether baseline amyloid burden predicts cognitive decline over a four-year interval in cognitively normal adults, whereas Study 2 examines whether changes in amyloid over the four-year interval relate to cognitive decline over the same interval.

More specifically, Study 1 of the present dissertation examines whether the amount of amyloid burden at baseline, rather than the presence of amyloid alone, is a useful predictor of how rapidly an individual's cognition may decline over four years. To date, longitudinal studies of an amyloid-cognition relationship in cognitively normal adults are limited, and most studies have evaluated amyloid deposition as a categorical variable, classifying individuals as "amyloid positive" or "amyloid negative" on the basis of study-specific thresholds for tracer uptake. Importantly, the techniques used to determine the threshold for positivity is highly variable across studies, resulting in differences across studies as to what is above threshold and thus considered amyloid positive. Despite this variability, longitudinal studies have demonstrated that higher amyloid tracer uptake in those considered amyloid positive is associated with greater cognitive decline than is observed in the lower tracer uptake or amyloid negative group (Lim et al, 2013; Mormino et al, 2014a; Petersen et al, 2016; Villemagne et al, 2013; Wirth et al, 2013). However, it is unclear from these studies whether there is a continuous relationship between amyloid burden and cognitive decline, such that an increase in the magnitude (or "dose") of amyloid burden at baseline is predictive of a corresponding increase in the rate of cognitive

decline (or "response"). Such a "dose-response" relationship would have important implications for both research and clinical use, as it would suggest that the magnitude of amyloid burden might provide additional prognostic information about the predicted rate of future cognitive decline that is unavailable from a simple positive/negative classification. Utilizing four-year longitudinal data from the Dallas Lifespan Brain Study, Study 1 of the present dissertation examines the dose-response relationship between the magnitude of amyloid burden at baseline and the rate of cognitive decline over four years. Specifically, I hypothesize that increasing amyloid burden at baseline will predict increasing cognitive decline over four years, such that the highest baseline amyloid deposition will be associated with the steepest cognitive decline.

Study 2 builds off this work to additionally examine whether the rate at which amyloid accumulates over an interval may also relate to cognitive decline. Does a greater increase in amyloid burden over time result in faster cognitive decline over the same interval? To date, there are limited published data on the relationship between change in amyloid deposition and cognitive decline. Villemagne et al. (2013) found that the rate of amyloid accumulation was related to the rate of episodic memory decline, but that this relationship was not significant after controlling for baseline amyloid burden, leading them to conclude that the extent of amyloid at baseline was more predictive of decline than the rate at which amyloid accumulated over the interval. However, Villemagne et al. used a measure of the mean rate of accumulation across most of the neocortex, and such a gross measure may not be the optimal metric for describing change in amyloid over time and its impact on cognitive decline. Using a voxel-wise analyses, Villain et al. (2012) demonstrated some regional variability in the rate of amyloid accumulation. Therefore, it may instead be optimal to measure where in the brain amyloid accumulated over the

follow-up interval and whether focal accumulation has effects on the cognitive domain subserved by that region. Therefore, Study 2 of my dissertation will explore whether there is regional specificity in the impact of amyloid accumulation on cognitive decline.

In addition, a secondary aim of my dissertation is to better understand the beginnings of amyloid deposition and its early relationship to cognitive decline in cognitively normal adults. To do so, my dissertation will focus on groups of individuals in which the earliest signs of amyloid deposition are likely to appear: individuals at an early stage in terms of age (middle-aged adults) and individuals at an early stage in terms of disease progression (initially amyloid negative adults).

To date, most amyloid PET studies have focused on older adults (ages 60 and above). However, amyloid may start to accumulate as early as middle age (Braak and Braak 1996), taking 10-20 years to spread throughout the neocortex (Bateman et al, 2012; Buchhave et al, 2010; Jack et al, 2013; Rowe et al, 2010). Thus, middle age affords an opportunity to examine the earliest evidence of amyloid deposition and its possible impact on cognitive decline. Furthermore, middle age may prove a critical period for intervention to prevent AD. Notably, clinical trials conducted in MCI and AD patients have successfully removed amyloid plaques from the brain using anti-amyloid therapies, but the removal of amyloid failed to halt the progression of cognitive decline in these patients (Sperling, Mormino, & Johnson, 2014). Researchers have posited that targeting MCI and AD patients is too late in the amyloid cascade, resulting in a shift towards earlier intervention in middle-aged, cognitively normal adults (Sperling et al, 2014) and adding impetus to the need for studies of amyloid in middle age.

Unique at its inception, the Dallas Lifespan Brain Study includes participants across the lifespan (aged 30-89), enabling examination of amyloid and its effects in middle-aged adults. Therefore, each study of the present dissertation also includes secondary analyses focused on middle-aged individuals, both providing novel information about this little-studied group as well as potentially providing a window into the earliest consequences of amyloid deposition. Likewise, each study will also focus on initially amyloid negative adults, as a second, complimentary avenue to examine the beginnings of amyloid deposition and its early relationship with cognition. Trends from recent studies (Insel et al, 2016; Mormino et al, 2014b) have provided some impetus for the possibility that relatively high amyloid burden within the amyloid negative range may be predictive of future cognitive decline. Therefore, in Study 1, the dose-response approach will be utilized to examine whether relatively high amyloid burden compared to one's peers within middle age, as well as within amyloid negative adults, is already predictive of cognitive decline.

Importantly, regional changes in amyloid may provide a particularly salient marker of the earliest stage of AD. Longitudinal increases in regional amyloid burden within both initially amyloid negative adults and middle-aged adults may represent one of the earliest detectable sign of amyloid pathology. Consequently, by examining whether greater rates of amyloid accumulation over four years are associated with greater cognitive decline, it may be possible to identify some of the earliest cognitive effects of amyloid deposition. Autopsy studies (Braak & Braak, 1991) and recent longitudinal PET imaging studies (Sepulcre, Sabuncu, Becker, Sperling, & Johnson, 2013; Villain et al, 2012) have indicated that orbitofrontal and penumbral inferior frontal cortices may be among the first sites to exhibit amyloid deposition in the AD pathological

cascade. Deposition in these regions appears to precede spread to the more posteromedial regions (i.e. posterior cingulate, precuneus) (Sepulcre et al, 2013; Villain et al, 2012) that typically exhibit the highest amyloid burden in amyloid positive adults (Mintun et al, 2006; Rodrigue et al, 2012). Accordingly, Study 2 of my dissertation will examine whether focal amyloid accumulation is already present in some regions in middle-aged and initially amyloid negative adults, such as the orbitofrontal cortex, while accumulation in others, like the precuneus and posterior cingulate, is more restricted to older and initially amyloid positive adults. Additionally, Study 2 will investigate whether regional amyloid accumulation is already associated with subtle, detrimental cognitive consequences in middle age and in initially amyloid negative adults, far in advance of the expected onset of clinical symptoms.

In summary, the studies of the present dissertation are organized as follows:

Study 1. Baseline amyloid as a predictor of cognitive decline

Hypothesis 1. A dose-response relationship exists between the magnitude of amyloid at baseline and the rate of cognitive decline, such that increasing amyloid burden at baseline predicts a corresponding increase in the rate of cognitive decline over four years.

Hypothesis 2. Relatively high amyloid burden compared to one's peers within both middle-aged as well as amyloid negative adults is already predictive of cognitive decline.

Study 2. Regional change in amyloid as a predictor of cognitive decline

Hypothesis 1. Regional differences in accumulation are apparent, with some regions, including orbitofrontal and penumbral inferior frontal cortices, accumulating earlier while others, including posteromedial regions, accumulate later.

Hypothesis 2. Overall, amyloid accumulation in specific regions will relate to cognitive decline in the domain subserved by that region.

Hypothesis 3. Additionally, earlier regional amyloid accumulation in middle-aged adults and initially amyloid negative adults will already be associated with cognitive decline even at this early stage.

CHAPTER 2

BACKGROUND

2.1. INSIGHTS INTO AMYLOID FROM EARLY AUTOPSY STUDIES

The diagnosis of Alzheimer's disease is based upon the presence of amyloid plaques and tau tangles at autopsy (Hardy & Selkoe, 2002; McKhann et al, 2011). Neuropathologists use a variety of staining techniques to visualize and quantify the amyloid and tau pathology present in the brain at the microscopic level. Autopsy studies have provided information regarding the temporal and spatial progression of amyloid and tau and their correlation with neurodegeneration and retrospective cognition. The present dissertation focuses on amyloid deposition, which can be detected as early as the 30s and 40s, and with prevalence increasing with age (Braak, Thal, Ghebremedhin, & Del Tredici, 2011). Approximately 30% of adults over age 60 exhibit some amyloid deposition (Braak & Braak, 1991; Crystal et al, 1988), and the prevalence continues to increase with age such that approximately 70% of 90-99 year olds have at least moderate neocortical amyloid deposition at autopsy (Braak et al, 2011). Furthermore, autopsy studies suggest that amyloid deposition spreads throughout the neocortex over the course of 10-20 years, during which time individuals typically remain cognitively normal (Hardy & Selkoe, 2002; Price & Morris, 1999). However, autopsy studies are limited in their ability to assess amyloid and its impact on cognitive decline in living persons, as they are limited to cross-sectional and retrospective analyses. Instead, *in vivo* measures of amyloid pathology are needed that can relate pathology to measures of cognition over time.

2.2. *IN VIVO* MEASURES OF AMYLOID DEPOSITION

The first *in vivo* technique introduced to measure amyloid in living persons involved the extraction of cerebrospinal fluid (CSF) via lumbar puncture. This method allowed for the measurement of the concentration of soluble amyloid proteins in spinal fluid to provide a rough approximation of the magnitude of amyloid pathology in the brain. However, the data provided by CSF studies are limited and the invasiveness of the procedure makes study recruitment difficult, particularly within cognitively normal adults. Thus, the advent of PET radiotracers for amyloid in the last decade (Klunk et al, 2004; Wong et al, 2010) provided an important breakthrough for the study of amyloid pathology in living persons and its consequences for brain and behavior in cognitively normal adults.

Amyloid PET imaging involves the use of radiotracers that bind with high affinity to amyloid (Klunk et al, 2004; Wong et al, 2010) and emit a signal that can be read by a PET scanner to estimate the location and quantity of amyloid pathology. However, the tracer is also known to bind non-specifically, particularly in white matter. To estimate amyloid deposition, tracer uptake is typically expressed as a signal-to-noise ratio referred to as the standardized uptake value ratio (SUVR). This SUVR is computed by measuring the signal intensity from a voxel or a group of voxels (assumed to include both cortical amyloid signal and non-specific noise) and then dividing by signal intensity from a reference region (assumed to include only noise due to non-specific binding). Typically, studies either use this continuous SUVR metric, or classify individuals as amyloid positive or negative based on a threshold. The method for establishing this threshold varies considerably across studies, with some studies using AD patients to define a threshold (Gomperts et al, 2008; Hedden et al, 2009; Johnson et al, 2007),

others basing the cutoff on young adults presumed to be amyloid negative (Mormino et al, 2012; Oh et al, 2011; Villeneuve et al, 2015; Wirth et al, 2013), and still others using a variety of statistical techniques including linear regression across age (Rodrigue et al, 2012, Kennedy et al, 2012), iterative outlier removal (Aizenstein et al, 2008) and Gaussian mixture modeling (Mormino et al, 2014a).

Using these measures, amyloid imaging studies have demonstrated high concordance with autopsy studies, confirming that approximately 30% of cognitively normal older adults exhibit elevated amyloid deposition (Aizenstein et al, 2008; Jack et al, 2008; Mintun et al, 2006). Cross-sectional amyloid PET studies also confirmed that amyloid deposition in healthy older adults is typically widespread throughout the neocortex, with limited uptake in the medial temporal lobe and largely sparing primary sensory and motor, striatal, diencephalon, brainstem and cerebellar regions until late in disease progression (Aizenstein et al, 2008; Jack et al, 2008; Mintun et al, 2006). Furthermore, amyloid PET studies in individuals close to death have demonstrated high correspondence between amyloid PET imaging and subsequent autopsy results in the same patients (Clark et al, 2011; Sojkova et al, 2011).

2.3. AMYLOID CASCADE HYPOTHESIS

Amyloid PET imaging now allows for evaluation of amyloid and its role in the development of AD. The prevailing hypothesis describing the development of AD is the amyloid cascade hypothesis (Hardy & Selkoe, 2002). This hypothesis posits that Alzheimer's disease starts with amyloid deposition, which then initiates a cascade of pathological events: amyloid leads to the proliferation of tau tangles, which in turn leads to neurodegeneration, which then leads to cognitive decline. These biomarkers continue to progressively worsen, and individuals

eventually become impaired enough to be diagnosed with dementia. Animal and *in vitro* evidence support the hypothesis that amyloid induces tau pathology through hyperphosphorylation of the normal tau protein (Busciglio, Lorenzo, Yeh, & Yankner, 1995; Greenberg & Kosik, 1995). Once hyperphosphorylated, abnormal tau aggregates into the characteristic tangles, which disrupt neurons and lead to neurodegeneration (Grundke-Iqbal et al, 1986), particularly in the medial temporal lobe (Braak et al, 2011; Price & Morris, 1999). In autopsy studies, the magnitude of tau in brain and neurodegeneration correlate more closely than amyloid with the magnitude of cognitive and clinical symptoms prior to death (Gomez-Isla et al, 1997, Bennett et al, 2004).

2.4. PRECLINICAL MODEL OF AD

Utilizing these new neuroimaging tools, a committee chartered by the National Institute on Aging, in collaboration with the Alzheimer's Association, proposed the Preclinical Model of AD (Sperling et al, 2011) based on the amyloid cascade hypothesis. This model terms the developmental and asymptomatic phase of AD "preclinical AD" and breaks the continuum of AD pathological progression into stages:

> **Stage 1**. Amyloid starts to deposit.
> **Stage 2**. Amyloid continues to accrue and evidence of neurodegeneration, including tau, begins to be detectable.
> **Stage 3.** Amyloid continues to deposit and neurodegeneration spreads, but now cognitive decline is also evident.

Consistent with the amyloid cascade hypothesis, individuals with amyloid deposition but no other AD biomarkers are considered to be in Stage 1 of preclinical AD. In Stage 2, the continuing accumulation of amyloid is thought to induce the spread of tau, which in turn results

in neurodegeneration. In the Stage 3, the combined effects of amyloid, tau and neurodegeneration are thought to lead to cognitive decline, particularly in episodic memory.

Longitudinal studies support the Preclinical Model of AD. In a recent longitudinal study, Vos et al. (2013) reported that over 5 years the conversion rate to symptomatic Alzheimer's disease was 2% for individuals with no initial pathology (stage 0), 11% for those with amyloid only at baseline (Stage 1), 26% for those both amyloid and neurodegeneration positive at baseline (Stage 2), and 56% for those exhibiting amyloid, neurodegeneration and impaired cognition at baseline (Stage 3). Other studies have found a similar increase in conversion rates with increasing stage (Knopman et al, 2012; Villemagne et al, 2011). The increasing probability of conversion to dementia in later stages of the Preclinical Model of AD model provides confidence that it is an appropriate and useful model of preclinical progression towards dementia.

It is notable that the Preclinical Model of AD considers any cognitively normal individual with amyloid deposition to be in at least Stage 1 preclinical AD. However, it is important to note that there is no definitive evidence indicating that amyloid inexorably leads to AD dementia. Indeed, while the presence of amyloid (as well as downstream AD biomarkers) increases the risk of progression to dementia, many studies find that amyloid positive adults do not progress to dementia over the study interval, ranging from 1.5 years (Villemagne et al, 2011) to 5 years (Vos et al, 2013). While it is possible that with a long enough study interval all amyloid positive individuals would progress to dementia (provided they do not die first), it is also possible that amyloid is necessary but not sufficient for the development of Alzheimer's disease. Furthermore, it is possible that amyloid deposition is an aspect of normal aging that predisposes individuals

towards developing Alzheimer's disease rather than being itself a component of the disease. Thus, to further elucidate the role of amyloid in normal aging and preclinical AD, it is important to study amyloid and its impact on brain and behavior in cognitively normal adults. The present dissertation evaluates whether amyloid deposition, evaluated both as the baseline magnitude of amyloid (Study 1) and change in amyloid over time (Study 2), predicts cognitive decline over a four-year interval.

2.5. MECHANISM UNDERLYING AMYLOID-COGNITION RELATIONSHIP

Based on the amyloid cascade hypothesis and the Preclinical Model of AD, the link between amyloid and cognitive decline is indirect, with amyloid leading to cognitive decline via its effects of tau. The very recent advent of tracers for tau (Xia et al, 2013) promises to help clarify the interaction of amyloid and tau and their role in the development of AD in living persons. Emerging tau PET results from cognitively normal adults indicate that proliferation and spread of abnormal tau is present only in amyloid positive individuals and is related to poorer episodic memory (Johnson et al, 2016; Ossenkoppele et al, 2016; Scholl et al, 2016). While it is beyond the scope of the present dissertation, future research will hopefully help to elucidate the role of tau. In the present dissertation, high amyloid tracer uptake is presumed to provide a marker of not only amyloid pathology but also a proxy for expected tau pathology and neurodegeneration in cognitively normal adults. Therefore it is hypothesized that the higher amyloid burden is at baseline, the more rapidly cognition will decline over the four year follow-up, particularly in episodic memory.

While the evidence outlined above indicates that tau, rather than amyloid, is more directly linked to the clinical symptoms of Alzheimer's disease, it is unclear if amyloid itself

may have direct effects on cognitive performance. *In vitro* and rat studies have demonstrated that amyloid is neurotoxic to synapses and results in synaptic dysfunction (Cleary et al, 2005; Shankar et al, 2007; D. T. Walsh et al, 2002). Therefore it seems likely that amyloid may have direct and measurable effects on brain and behavior via synaptic disruption, though they may be subtle compared with the deleterious effects of tau. However, since amyloid is believed to be the first step in the AD pathological cascade, subtle effects of amyloid on cognition may already be apparent at this early stage. In order to fully understand the development of AD and potentially find interventions to halt the progression of AD, it is important to not only study AD pathology just prior to dementia, but to find the earliest possible signs of incipient AD.

It is important to note, however, that evidence from *in vitro* and animal studies suggest it is the soluble form of amyloid, rather than the insoluble form of amyloid deposits measured with florbetapir and other PET tracers, that is toxic to synapses (Benilova, Karran, & De Strooper, 2012; Ferreira & Klein, 2011; Hayden & Teplow, 2013; Sakono & Zako, 2010; Selkoe, 2008) and impairs cognitive function through impairments of synaptic plasticity (Cleary et al, 2005, Shankar et al, 2008). However, *in vitro* evidence also indicates that soluble (Aβ oligomers) and insoluble fibrillar (plaque) forms of amyloid are largely in equilibrium, such that PET signal from plaques provide a good spatial correlate of soluble amyloid (Cirrito et al, 2003; Hong et al, 2011; Takeda et al, 2013). Interestingly, plaques are now thought to be part of the brain's protective response, sequestering the neurotoxic soluble oligomers from disrupting synapses (Baglioni et al, 2006; Cheng et al, 2007; Treusch, Cyr, & Lindquist, 2009). Thus, while the amyloid plaques measured with florbetapir may not have direct effects on cognition, they nonetheless provide a useful marker of soluble amyloid, as well as other AD biomarkers like tau,

that evidence suggests may have direct effects on cognition. In the present dissertation, I will examine the relationship between amyloid deposition and cognitive decline, acknowledging that other unmeasured variables, especially tau, may mediate the relationship. Regardless of whether the impact of amyloid on cognition is direct, it is important to evaluate whether amyloid deposits are associated with subtle, preclinical declines in cognition in adults still performing within the cognitively normal range.

2.6. AMYLOID IN COGNITIVELY NORMAL ADULTS: THE DALLAS LIFESPAN BRAIN STUDY

Amyloid PET imaging ushered in a new (and highly productive) era of research evaluating the Preclinical Model of AD and its hypothesized role of amyloid in the development of AD in cognitively normal adults. The present dissertation utilizes data from one such study, the Dallas Lifespan Brain Study (DLBS). The DLBS is a large-scale, longitudinal study of aging in cognitively normal adults across the adult lifespan (aged 20-89). At both baseline and four-year follow-up, participants underwent cognitive assessment and multiple structural and functional neuroimaging measures. A subset of these individuals (aged 30-89) underwent amyloid PET imaging with f-18-florbetapir (n=296 at baseline). The baseline DLBS amyloid PET results demonstrated elevated amyloid deposition is primarily observed in older adults over age 60 (Rodrigue et al, 2012). However, it is important to note that there is also considerable variance in SUVR in middle-aged adults (Rodrigue et al, 2012). This is in accordance with autopsy studies, which find a subset of middle-aged adults who exhibit low to moderate amyloid pathology (Braak & Braak, 1996; Braak et al, 2011).

It is possible that those with higher SUVR relative to their peers in middle age may be exhibiting the earliest signs of amyloid pathology and over time will accumulate more amyloid and eventually progress to dementia. Indeed, longitudinal studies suggest that amyloid accumulates over 10-15 years, starting in middle/old age, and plateaus 5-11 years before dementia onset (Buchhave et al, 2010; Fleisher et al, 2012; Jack et al, 2013). Thus middle age may provide an important window into the earliest stage of amyloid pathology and its possible consequences for brain and behavior. However, most amyloid imaging studies do not enroll adults under age 60. The inclusion of adults across the lifespan in the DLBS thus affords a unique opportunity to examine the earliest signs of amyloid pathology and whether subtle effects may already be apparent in middle age.

2.7. EARLY DETECTION OF ALZHEIMER'S DISEASE

AD clinical trials are increasingly moving towards early intervention, testing whether the use of anti-amyloid therapies early in AD pathological progression may prevent the further accumulation of amyloid as well as downstream pathological events. Thus, the earlier AD can be detected, the earlier it can potentially be stopped. If the amyloid cascade hypothesis and the Preclinical Model of AD are correct, then amyloid PET scans enable the detection of AD pathology much earlier than would be possible by waiting for the appearance of clinical symptoms. To evaluate this possibility, it is important to examine whether amyloid deposition in cognitively normal adults is associated with cognitive decline, as is assessed in the present dissertation.

However, by pinpointing the earliest signs of amyloid pathology, detection of AD may be shifted even earlier. Deposition of amyloid is continuous and increasing in cognitively normal

adults, so the earliest signs of amyloid pathology must be at low SUVR. However, at low SUVR, it becomes difficult to differentiate between tracer uptake that reflects binding to real amyloid pathology and non-specific binding. However, there are some features of early amyloid deposition that may aid detection. First, if amyloid continues to accrue over time, there is an increased likelihood that the SUVR reflects real amyloid accumulation. The present dissertation utilizes this feature in Study 2, measuring amyloid with florbetapir PET at baseline and after a four-year interval. Second, autopsy (Braak and Braak, 1991) and PET evidence (Sepulcre et al, 2013; Villain et al, 2012) suggest that amyloid deposits initially more focally, particularly in the orbitofrontal cortex, before spreading throughout the neocortex. Study 2 therefore focuses on regional amyloid accumulation, enabling the identification of earlier focal deposits in regions like the orbitofrontal cortex. Third, by focusing on specific groups likely to include individuals at beginnings of amyloid deposition, it may be possible to improve the ability to detect early amyloid pathology and its relationship to cognition. The present dissertation focuses of two groups that may provide a window into early amyloid pathology: 1) individuals at an earlier stage in the lifespan (middle-aged adults) and 2) individuals at an earlier stage in disease progression (amyloid negative adults). Both studies of the present dissertation take advantage of these early groups by conducting additional analyses within middle-aged adults and amyloid negative adults.

Using these features, the present dissertation seeks not only to detect early signs of amyloid pathology, but also to determine whether cognitive consequences of amyloid pathology may already be apparent at an early stage. Identification of early consequences of amyloid pathology is important not only to understand the development of AD and the effects of amyloid,

but also to inform clinical trials aimed at early intervention about appropriate treatment outcome measures. However, these additional analyses on early detection of amyloid pathology and its cognitive consequences are secondary to the primary question of whether amyloid deposition in cognitively normal predicts cognitive decline, providing more general evidence of the role of amyloid in cognitive decline towards possible AD.

2.8. CROSS-SECTIONAL STUDIES OF AMYLOID DEPOSITION AND COGNITION

Over the decade since amyloid PET imaging was first developed, many studies have examined the link between amyloid deposition and cognition in cognitively normal older adults. The first studies examined whether there was a correlation between amyloid and poorer cognition at a single time point. The results from these studies have been inconsistent. While some studies found a relationship between amyloid burden and lower episodic memory performance (Aizenstein et al, 2008; see Hedden, Oh, Younger, & Patel, 2013 for review; Pike et al, 2011; Resnick et al, 2010; Sperling et al, 2013), others have failed to find a significant effect (Ewers et al, 2012; Rodrigue et al, 2012; Storandt, Mintun, Head, & Morris, 2009; Tolboom et al, 2009).

Since episodic memory impairment is an early symptom of AD, many studies have prioritized testing for a link between amyloid burden and episodic memory. While fewer studies have evaluated the effects of amyloid on other cognitive domains, the findings are even more inconsistent than those for episodic memory. Some studies found null results (Lim et al, 2012; Oh, Madison, Haight, Markley, & Jagust, 2012), while others found associations between amyloid and executive function/reasoning (Resnick et al, 2010; Rodrigue et al, 2012; Schott, Bartlett, Fox, & Barnes, 2010) working memory (Rentz et al, 2010; Rodrigue et al, 2012; Rolstad

et al, 2011), processing speed (Rodrigue et al, 2012; Stomrud et al, 2010), and visuospatial function (Pike et al, 2011; Rentz et al, 2010). A recent meta-analysis of over 60 studies (Hedden et al, 2013), including both amyloid PET and CSF biomarkers, found that across studies amyloid was associated with subtle impairment in episodic memory, executive function/reasoning and global function, measured using the Mini-Mental State Exam (MMSE).

However, it is important to note that these studies are correlational, as it is not possible to experimentally manipulate amyloid burden and randomly assign participants with or without amyloid. Thus, these studies cannot conclusively establish that amyloid burden leads to lower cognition and not the reverse. In fact, there is evidence in support of the possibility that poor neural efficiency (which may result in lower cognitive performance) may lead to amyloid deposition (Jagust & Mormino, 2011; Lazarov et al, 2005). Longitudinal studies may help to clarify the temporal precedence in the relationship between amyloid and cognition, by demonstrating that amyloid deposition at baseline predicts subsequent cognitive decline.

2.9. BASELINE AMYLOID AND COGNITIVE DECLINE

As longitudinal data become available, directional evidence is starting to support amyloid burden as a predictor of subsequent cognitive decline. To date, longitudinal studies have demonstrated that the presence of amyloid at baseline is predictive of greater decline in episodic memory (Lim et al, 2014; Mormino et al, 2014a; Petersen et al, 2016; Resnick et al, 2010; Villemagne et al, 2013; Wirth et al, 2013), semantic memory (Petersen et al, 2016), and executive function (Petersen et al, 2016). However, due to their use of amyloid as a dichotomized positive/negative variable, it is unclear from these studies whether there is a continuous relationship between amyloid burden and cognitive decline, such that an increase in

the magnitude (or "dose") of amyloid burden at baseline is predictive of a corresponding increase in the rate of cognitive decline (or "response"). Utilizing four-year longitudinal data from the Dallas Lifespan Brain Study, Study 1 of the present dissertation examines the dose-response relationship between the magnitude of amyloid burden at baseline and the rate of cognitive decline over four years. Furthermore, Study 1 utilizes the middle-aged and amyloid negative subsamples in the DLBS, to examine whether amyloid-related cognitive decline may already be apparent at an early stage. Chapter 3 presents Study 1 and provides additional background relevant to the effect of baseline amyloid burden on cognitive decline.

2.10. CHANGE IN AMYLOID AND COGNITIVE DECLINE

It is important to consider not just whether amyloid burden at baseline is predictive of cognitive decline, but whether the rate at which amyloid changes correlates with cognitive decline. Demonstrating that changing amyloid is associated with changes in cognition would provide additional support for the hypothesis that amyloid has a detrimental impact on cognition and may eventually lead to dementia. However, to date there are limited published data on the relationship between change in amyloid deposition and cognitive decline. Villemagne et al. (2013) did find that the rate of amyloid accumulation was related to the rate of episodic memory decline, but this relationship was not significant after controlling for baseline amyloid burden, leading to the conclusion that the extent of amyloid at baseline was more predictive of decline than the rate at which amyloid accumulated over the interval. However, Villemagne et al. used a measure of the mean rate of accumulation across most of the neocortex, and such a gross measure may not be the best metric for describing change in amyloid over time and its impact on cognitive decline. For rate of accumulation to be a sensitive predictor of cognitive decline, it may

instead be important to address where in the brain amyloid accumulated over the follow-up interval. Furthermore, focusing on specific regions may be particularly useful for detecting the earliest signs of amyloid pathology and related subtle cognitive deficits. Converging evidence from autopsy (Braak and Braak, 1991) and amyloid PET (Sepulcre et al, 2013; Villain et al, 2012) studies suggest that amyloid deposits focally in regions that include the orbitofrontal cortex before spreading throughout the neocortex. Therefore, Study 2 will utilize the lifespan sample of the DLBS to whether there are regionally specific effects of amyloid on cognitive decline, and whether early-accumulating regions may be leveraged to detect early amyloid-related cognitive decline in middle-aged and initially amyloid negative adults. Chapter 4 presents Study 2 and provides a more detailed background on regional changes in amyloid and how this may relate to cognition.

CHAPTER 3

STUDY 1. BASELINE AMYLOID AND COGNITIVE DECLINE

3.1. OVERVIEW

This study was published in JAMA Neurology (Farrell et al, 2017) and is reprinted below in full (article and supplemental material) with an extended introduction and discussion.

3.2. INTRODUCTION

3.2.1. Cross-Sectional Evidence of a Dose-Response Effect of Amyloid on Cognition

Cross-sectional studies in cognitively normal adults seeking to determine whether amyloid deposition is related to subtle cognitive deficits have proved inconsistent, with some finding a relationship between amyloid and cognition (Aizenstein et al, 2008; see Hedden et al, 2013 for review; Pike et al, 2011; Resnick et al, 2010; Sperling et al, 2013) while others have failed to find a significant effect (Ewers et al, 2012; Rodrigue et al, 2012; Storandt et al, 2009; Tolboom et al, 2009). However, some of these inconsistencies may be explained by differences in how amyloid was measured. Most studies convert SUVR to a categorical variable, dichotomizing continuous SUVR into 'amyloid positive' and 'amyloid negative' groups. The method for setting the threshold between positive and negative is highly variable across studies, with no standardized approach. Some studies use more conservative thresholds, calling only those with high SUVR amyloid positive, while the amyloid negative group is assumed to include some individuals with lower amyloid burden. Other studies use liberal thresholds, setting the threshold lower in an attempt to ensure that most individuals with actual amyloid burden are identified as positive, but also increasing the probability of false positives. It is very likely that

these different thresholds for amyloid positivity contribute to the inconsistency across studies in the amyloid-cognition relationship.

Our lab has taken an alternative approach, avoiding the selection of a threshold and keeping SUVR continuous to examine the linear relationship between the amount of amyloid burden and cognitive performance. Cross-sectionally, Rodrigue et al. (2012) demonstrated using the baseline DLBS data that a dose-response relationship between amyloid burden and cognitive performance, such that increasing amyloid burden was associated with slower processing speed and lower reasoning ability, with those with the highest amyloid also showing the greatest cognitive deficit. These findings led Rodrigue et al. to posit that there may be a dose-response relationship between amyloid and cognition, such that the 'dose' of amyloid results in a corresponding negative 'response' in cognition. However, as noted above, these cross-sectional data do not allow for any evaluation of the temporal precedence, thus leaving the possibility that lower cognition may actually lead to amyloid rather than the assumed amyloid leading to poorer cognition. We now have four year follow-up data on these subjects, as well a 2nd cohort, and Study 1 of the present dissertation evaluates longitudinally the dose-response effect of amyloid burden at baseline as a predictor of change in cognition over the following four years.

3.2.2. Dose-Response Effect of Baseline Amyloid on Change in Cognition

As longitudinal data become available, directional evidence is starting to support amyloid burden as a predictor of subsequent cognitive decline. To date, longitudinal studies have largely used the categorical approach described above, demonstrating that amyloid positive individuals exhibit greater decline than amyloid negative individuals in episodic memory (Lim et al, 2014;

Mormino et al, 2014a; Petersen et al, 2016; Resnick et al, 2010; Villemagne et al, 2013; Wirth et al, 2013), semantic memory (Petersen et al, 2016), and executive function (Petersen et al, 2016).

A recent longitudinal study by Lim et al. (2014) supports the possibility of a dose-response relationship between amyloid and cognitive decline. Lim et al. divided amyloid positive participants (including both cognitively normal adults and MCI) into higher and lower amyloid burden groups. They reported greater cognitive decline in the higher compared to the lower amyloid group, supporting the possibility of a dose-response relationship. Study 1 of the present dissertation differs from Lim et al. (2014) and other studies by treating amyloid as a continuous variable, thus avoiding potentially missing effects due to the selection of a positivity threshold. In turn, this dose-response approach allows us to evaluate whether an increase in the magnitude of amyloid deposition at baseline is predictive of a corresponding increase in the rate of cognitive decline over the four-year follow-up. It is hypothesized that a dose-response relationship exists between the magnitude of amyloid at baseline and the rate of cognitive decline across multiple domains. Moreover, Study 1 of the present dissertation also controls for dichotomized amyloid positive/negative status, and compares the results yielded by both continuous and dichotomous approaches. These additional analyses allow us to test the hypothesis that magnitude of amyloid burden at baseline provides additional prognostic information about the rate of cognitive decline that is not available from a simple positive/negative classification.

3.2.3. Dose-Response Analysis in Middle Age

A second important feature of the present study is the inclusion of both middle-aged and older adults (ages 40-89). As mentioned previously, most amyloid imaging research to date has

focused only on older adults (age 60 and above). However, autopsy studies have consistently demonstrated that amyloid deposition may start as early as the 40s (Braak and Braak, 1996, 2011) and is already quite prevalent by the 50s, particularly for APOE ε4 carriers (Kok et al, 2009). Furthermore, clinical trials are increasingly targeting middle-aged adults for early intervention (Sperling et al, 2014), but almost nothing is known about the impact of amyloid burden in middle age. In the report of cross-sectional findings for the Dallas Lifespan Brain Study, Rodrigue et al. (2012) demonstrated that middle-aged adults have lower amyloid burden than older adults, but there is considerable variance in baseline amyloid levels. Very few of these middle-aged adults would be considered amyloid positive, even using a liberal threshold for amyloid positivity. It is possible that those middle-aged adults with relatively high amyloid burden compared to their peers may be showing early signs of amyloid deposition. Thus a dose-response approach that measures amyloid burden as a continuous variable provides an important opportunity to evaluate the hypothesis that early amyloid burden may already be predictive of cognitive decline as early as middle age. Likewise, a dose-response approach also allows us to test whether relatively high amyloid burden that nonetheless falls below the threshold for positivity (in amyloid negative adults) may be associated with cognitive declines even at this early disease stage, regardless of age.

3.2.4. Hypotheses

In summary, Study 1 will examine whether baseline amyloid predicts change in cognition over four years in cognitively normal adults. It is hypothesized that by utilizing continuous SUVR instead of a categorical amyloid positive/negative classification, a dose-response relationship will be detected between the magnitude of amyloid at baseline and the rate of

cognitive decline. Furthermore, the use of continuous SUVR in middle-aged and initially amyloid negative individuals will allow for the early detection of detrimental effects of amyloid on cognition, such that relatively high amyloid burden compared to one's peers is already predictive of cognitive decline.

3.3. METHODS

3.3.1. Participants

The study includes the first 184 DLBS participants who completed amyloid PET scans, structural MRI scans, a cognitive battery at baseline, and returned for a four-year follow-up. A total of 255 participants were eligible to return, and 189 returned (retention rate= 74%). Reasons for non-returns included: 7 deceased, 18 poor health, 14 not interested, and 28 lost to follow-up. In addition, 3 participants were excluded for poor MRI image quality and 2 participants were excluded due to computer malfunctions, for a final sample of 184 adults. Those retained did not differ significantly from those lost to follow up as a function of age, baseline SUVR, years of education, gender or APOE carrier status (*p* values ranged from 0.46 to 0.83).

The median follow-up time was 3.82 ± 0.32 years. At baseline, all participants had MMSE performance ≥ 26. At follow-up, MMSE scores were ≥ 25. All participants were recruited locally from advertisements and public talks and were screened for neurological and psychiatric disorders, loss of consciousness >10 minutes, drug or alcohol abuse, major heart surgery or chemotherapy within 5 years. All were native English speakers and right-handed. This study was approved by The University of Texas Southwestern and The University of Texas at Dallas Institutional Review Boards. All participants provided written informed consent and were debriefed according to human investigations committee guidelines.

3.3.2. Cognition

Five cognitive outcome measures were derived from the cognitive battery. Three were averaged composites: *Episodic Memory* (Hopkins Verbal Learning (Brandt, 1991); CANTAB Verbal Recognition Memory (Robbins et al, 1994)), *Processing Speed* (WAIS Digit Symbol (Wechsler, 1997); Digit Comparison (Hedden et al, 2002; Salthouse & Babcock, 1991)), and *Reasoning* (Raven's Progressive Matrices (Raven, 1996); ETS Letter Sets (Ekstrom & Harman, 1976)). Additionally, we had a single measure of vocabulary (ETS Vocabulary (Ekstrom & Harman, 1976)). Baseline scores for each task were converted to z-scores in the 40-89 year olds, and the follow-up scores were z-transformed using the baseline mean and standard deviation. Finally, raw MMSE scores were used as an estimate of global cognitive function.

3.3.3. MRI Protocol

Participants were scanned on a 3T Philips Achieva scanner with an 8-channel head coil. High-resolution anatomical images were collected with a T1-weighted MP-RAGE sequence with 160 sagittal slices; FOV=204x256x160mm; voxel size=1×1×1mm3; TR=8.1ms, TE=3.7ms, flip-angle=12°. Anatomical images were processed using FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu/; (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999)) with thorough manual editing, as detailed previously (Savalia et al, 2017). FreeSurfer volumetric segmentation was used to obtain cortical parcellations according to the Desikan-Killiany atlas (Desikan et al, 2006).

3.3.4. PET Acquisition

Participants were injected with a 370 MBq (10 mCi) bolus of 18F-Florbetapir. A 2-frame by 5-minute each dynamic emission acquisition was started 50 minutes post-injection on the

same Siemens ECAT HR PET scanner for all participants. At 30 minutes post-injection, subjects were positioned on the imaging table of a Siemens ECAT HR PET scanner. Soft Velcro straps and foam wedges were used to secure the participant's head and the participant was positioned using laser guides. A 2min scout was acquired to ensure the participant's brain was completely in the field-of-view and there was no rotation in either plane. A 2-frame by 5-minute each dynamic emission acquisition was started 50 minutes post-injection and immediately after an internal rod source transmission scan was acquired for 7 minutes. The transmission image was reconstructed using back-projection and a 6mm FWHM Gaussian filter. The emission images were processed by iterative reconstruction, with 4 iterations and 16 subsets and a 3mm FWHM ramp filter.

3.3.5. PET Preprocessing and Analysis

Each baseline PET scan was coregistered to the corresponding baseline MRI using FLIRT (Jenkinson & Smith, 2001) with a mutual-information cost function. No partial volume correction was performed. Mean cortical SUVR was computed as a continuous measure of amyloid burden by averaging across 7 FreeSurfer-derived regions of interest (dorsolateral prefrontal, orbitofrontal, lateral parietal, lateral temporal, precuneus, isthmus cingulate, and rostral anterior cingulate cortices) and normalizing to whole cerebellum.

Two different dichotomous measures of amyloid status were generated. The first amyloid status variable defined positivity as in past studies (Mormino et al, 2012; Oh et al, 2011; Villeneuve et al, 2015; Wirth et al, 2013), by setting the threshold at 2SDs above the mean SUVR for a young reference group (30-39 year olds in our sample; SUVR threshold=1.09). We also generated a second amyloid status variable using a more stringent threshold of 3SD above the young mean (SUVR threshold=1.12). Figure 3.1 shows the resulting distributions across age.

Amyloid burden at baseline (Baseline Mean Cortical SUVR) is plotted as a function of age at baseline. Additionally, the dichotomization of SUVR into Amyloid Positive (red) and Amyloid Negative (yellow) groups is shown, with a threshold at 1.09 (left) and 1.12 (right) based on 2SD or 3SD thresholds. Only participants aged 40-89 were included in subsequent analyses.

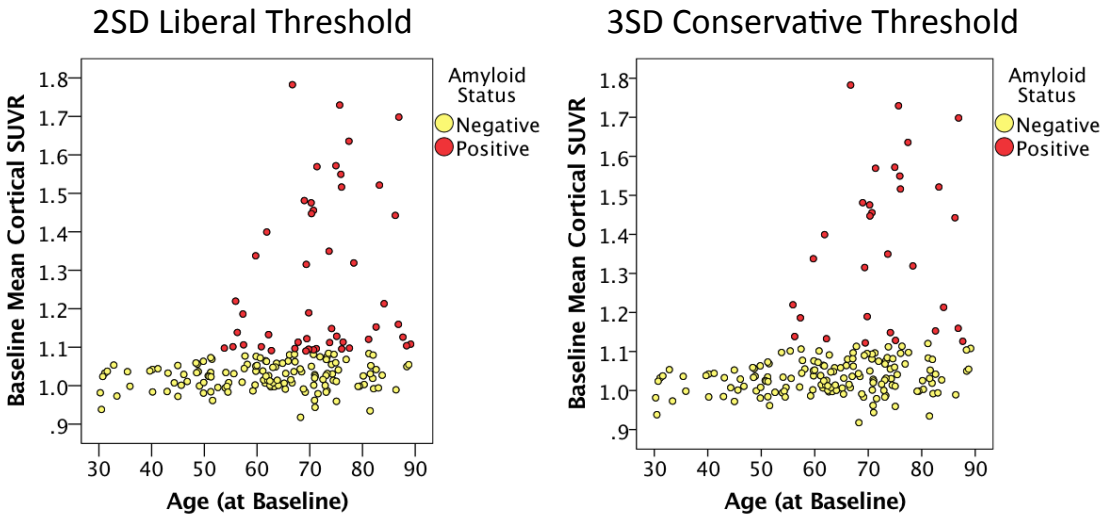

Figure 3.1. Amyloid Burden throughout the Lifespan with Different Positivity Thresholds.

3.3.6. Data Analysis.

All analyses were performed in SPSSv23. For the primary analysis, linear mixed models were conducted with SUVR (treated as a continuous variable), time of test (baseline vs. 4-year follow-up) and the SUVR x Time interaction to predict change in each cognitive measure. Baseline age, APOE, sex, and education were included as covariates to account for main effects. The Covariate x Time interactions were tested and removed if they did not approach significance ($p > .10$) to conserve statistical power. The Age x SUVR x Time interaction was tested to ensure that the impact of amyloid on cognitive decline did not differ as a function of age, but did not approach significance in any model and was removed. Finally, cognitive score intercept was included as a random effect to account for individual differences in baseline performance.

A secondary analysis was performed identical to that described above, but with dichotomized amyloid status added as a covariate, allowing us to assess whether continuous SUVR explained additional variance beyond dichotomized amyloid status. Next, we conducted the same linear mixed models analyses, removing continuous SUVR as a predictor and examining the effect of dichotomized amyloid status on cognitive decline. Finally, subsample analyses were conducted separately on amyloid negative and positive subgroups and on middle-aged adults (age 40-59) and older adults (age 60-89).

In order to evaluate the cause of the significant SUVR x time interactions, estimated means were computed for four values of SUVR that ranged from low to high (1.0, 1.2, 1.4, 1.6) across four years for each cognitive measure that was significant. Estimated means were computed using simple slope analysis. First, the full linear model was built for each cognitive variable with all fixed effects and their associated parameter estimates as generated by the linear mixed model. Next, the x value of each term was entered into the linear model. Covariate terms in the model were set to defaults for categorical variables (Sex = male; APOE: non-carrier) and means for continuous variables (Age = 66.4, Education years = 15.6). Time was set to 0 to generate baseline predicted values and 1 to generate follow-up values. Finally, each of the four values of SUVR was entered separately to generate model projections of cognitive performance at baseline and at the follow-up interval four years later. The baseline and follow-up model projections for each of the four SUVR values were then used to estimate trajectories of change in cognition over time at increasing values of SUVR.

3.4. RESULTS

3.4.1. Demographics

Table 3.1 presents descriptive information about the sample. Means and standard deviations (or percentages for categorical variables) are presented for all predictors and covariates and cognitive for the full sample. Independent *t*-tests indicated that amyloid positive participants were older and more educated than amyloid negative participants and chi-square tests showed a trend for a higher proportion of APOE ε4 carriers in amyloid positives. No demographic differences occurred when paired samples *t*-tests compared amyloid positive and negative groups for the two thresholds.

Table 3.1. Sample Demographics. p<.05 in bold.

	Whole Sample (age 40-89) (n=174)	Amyloid Status (2SD)		Amyloid Status (3SD)	
		Amyloid Positive (n=49)	Amyloid Negative (n=125)	Amyloid Positive (n=31)	Amyloid Negative (n=143)
Age, mean years (SD)	66.44 (11.74)	**71.98 (9.52)**	**64.13 (11.77)**	**72.86 (9.17)**	**64.92 (11.74)**
SUVR, mean (SD)	1.09 (0.16)	**1.27 (0.21)**	**1.02 (0.03)**	**1.37 (0.20)**	**1.02 (0.03)**
Education, mean years (SD)	15.55 (2.29)	**16.17 (2.49)**	**15.29 (2.17)**	**16.65 (2.15)**	**15.30 (2.26)**
Time between visits, *mean years (SD)*	3.82 (0.32)	3.80 (0.31)	3.82 (0.33)	3.84 (0.23)	3.81 (0.34)
Gender, n males (% male)	65 (37%)	48 (38%)	16 (33%)	55 (38%)	9 (29%)
APOE, n ε4 carriers (% ε4 carriers)	38 (23%)	14 (29%)	24 (20%)	11 (31%)	27 (20%)

3.4.2. Dose-Response Relationship between Amyloid and Cognitive Decline in Whole Sample

The primary analysis examined the dose-response relationship between continuous baseline SUVR and cognitive change over four years. The analysis yielded significant SUVR x Time interactions for four cognitive measures: episodic memory, processing speed, vocabulary

and MMSE, but not reasoning (Table 3.2). Practice effects were pervasive, as was evidenced by a positive significant main effect of Time across all domains except the MMSE. Importantly, the SUVR x Time effects demonstrate significant negative effects on amyloid on cognition over time over and above the observed practice effects.

Table 3.2. Summary of Parameter Estimates from Linear Mixed Models for Whole Sample (40-89 year olds). Parameter estimates, standard errors and *p*-values are reported above for each cognitive outcome. $p < .05$ in bold

		Episodic Memory (z)		Processing Speed (z)		Vocabulary (z)		Reasoning (z)		MMSE	
		Est (SE)	**p**	**Est (SE)**	**p**	**Est (SE)**	**p**	**Est (SE)**	**p**	**Est (SE)**	**p**
Effects of Time	**Time**	**1.27 (-0.40)**	**0.002**	**0.83 (0.27)**	**0.003**	**0.60 (0.21)**	**0.004**	**0.86 (0.37)**	**0.023**	0.87 (1.04)	0.403
	SUVR x Time	**-1.18 (0.37)**	**0.001**	**-0.46 (0.22)**	**0.04**	**-0.54 (0.19)**	**0.004**	-0.26 (0.30)	0.392	**-1.67 (0.75)**	**0.028**
	Age x Time	-	-	**-0.01 (0.00)**	**0.001**	-	-	**-0.01 (0.00)**	**0.019**	-	-
	Ed. x Time	-	-	-	-	-	-	-	-	0.10 (0.05)	0.066
Other Main Effects	**SUVR**	-0.18 (0.36)	0.62	-0.50 (0.40)	0.21	-0.75 (0.46)	0.103	-0.74 (0.40)	0.067	-0.01 (0.62)	0.987
	Age	**-0.02 (0.00)**	**<0.001**	**-0.04 (0.01)**	**<0.001**	**0.02 (0.01)**	**0.004**	**-0.03 (0.01)**	**<0.001**	**-0.02 (0.01)**	**0.001**
	Ed.	**0.07 (0.02)**	**0.001**	0.04 (0.03)	0.096	**0.21 (0.03)**	**<0.001**	**0.10 (0.03)**	**<0.001**	0.04 (0.04)	0.404
	Sex	**0.76 (0.10)**	**<0.001**	**0.38 (0.12)**	**0.002**	0.23 (0.14)	0.097	0.06 (0.12)	0.596	**0.50 (.15)**	**<0.001**
	APOE	0.003 (0.11)	0.98	-0.21 (0.14)	0.122	-0.03 (0.16)	0.851	0.16 (0.13)	0.224	-0.30 (0.18)	0.095

We also detected a significant Age x Time interaction for processing speed and reasoning, such that old age was also associated greater cognitive decline, independent of amyloid burden. The Age x Time interaction failed to reach marginal significance ($p > .10$) for the remaining cognitive variables are was removed. There was a marginally significant

Education x Time interaction, such that increasing education was associated with more positive change in MMSE. The Education x Time interaction failed to reach marginal significance for the other cognitive variables and was removed. APOE x Time and Sex x Time estimates for all cognitive variables failed to reach marginal significance and were removed from the models.

To interpret the significant SUVR x Time interactions of interest, simple slope analysis was used to project trajectories of cognitive change for four values of SUVR (1.0, 1.2, 1.4, and 1.6), holding all other fixed effects constant, see Figure 3.2.

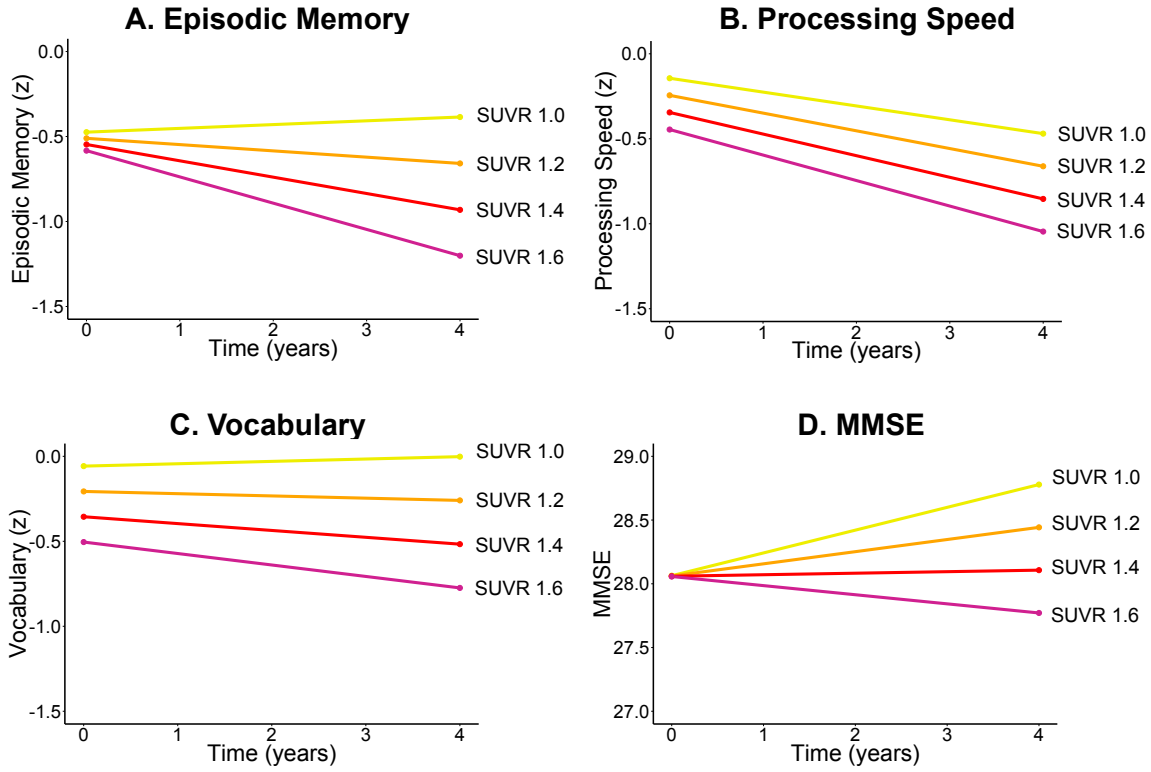

Figure 3.2. Projections of the Impact of Increasing Magnitude of Baseline SUVR over a 4-Year Time Interval on 4 Measures of Cognition.

These values were chosen as meaningful markers of the magnitude of amyloid burden, with 1.0 corresponding to amyloid negativity, 1.2 to low amyloid burden, 1.4 to moderate amyloid

burden, and 1.6 to high burden. As shown in Figure 3.2, the four interactions occurred because increasing baseline SUVR was associated with increasing cognitive decline. For episodic memory and vocabulary, estimated change at an SUVR of 1.0 reflected no change (EM = +0.09; Vocab = +0.06), while an SUVR of 1.6 was associated with declines (EM =-0.62; Vocab = -0.27). Decline in processing speed was predicted even at an SUVR of 1.0 (-0.33) but the rate of decline increased with SUVR such that an SUVR of 1.6 was associated with greater decline (-0.60). At an SUVR of 1.0, MMSE was associated with an increase (+0.72) that is presumed to be a practice effect, but this effect diminished with increasing SUVR and at an SUVR of 1.6 MMSE declined (-0.29).

Figure 3.3 depicts participant's individual trajectories of change as a function of age and amyloid burden.

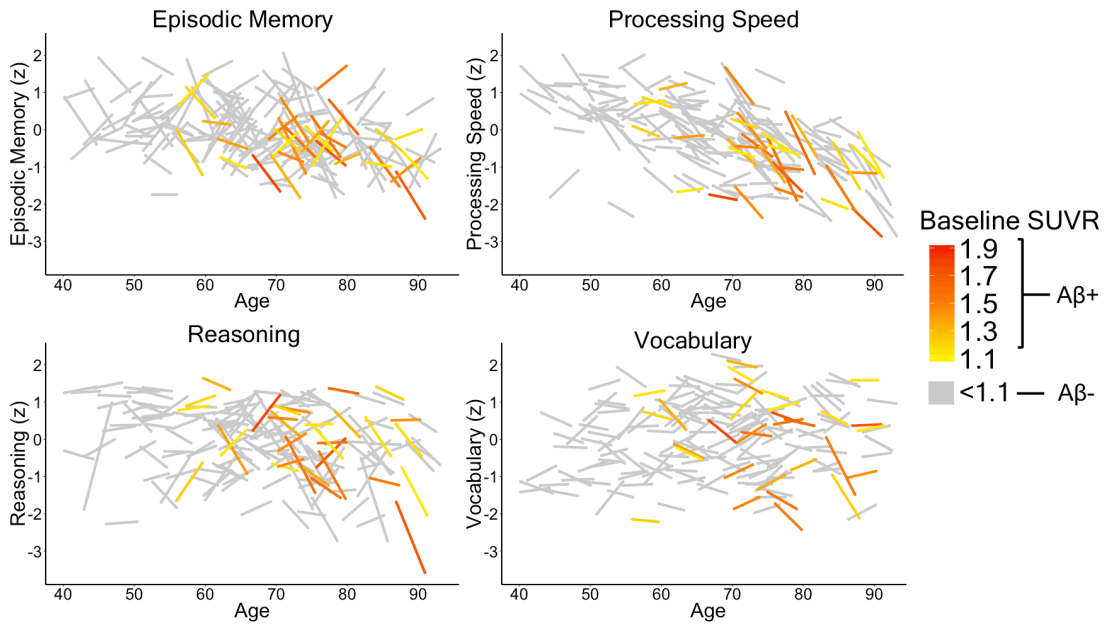

Figure 3.3. Individual Trajectories of Cognitive Change over 4 years as a Function of Age. Gray lines represent amyloid negative individuals. Amyloid positive individuals are shown in color, with the color scale ranging from yellow (lowest SUVR) to red (highest SUVR).

Although there was considerable variability in individual trajectories of cognitive change, declines are more consistently observed in older adults with high amyloid.

Next we examined the SUVR x Time interaction, while controlling for dichotomized amyloid status. Using the 2SD amyloid status variable as a covariate, the interaction remained significant for episodic memory (*Est(SE)* = -1.20 (0.52), $p = 0.021$), vocabulary (*Est(SE)* = -0.54 (0.26), $p = 0.040$) and MMSE (*Est(SE)* = -2.17 (1.05), $p = 0.039$). Using the more stringent 3SD threshold, the SUVR x Time interaction remained significant for MMSE (*Est(SE)*= -2.54 (1.27), $p = 0.048$) and marginally significant for episodic memory (*Est(SE)*= -1.18(0.63), $p = 0.064$) (see Table A1 for full model results). Notably, there is a high correlation between SUVR and the 2SD amyloid status variable ($r = .71$, $p < .001$) and the 3SD amyloid status variable ($r = .82$). While this indicates a high degree of collinearity between these two measures of amyloid, there is still some remaining variance in SUVR unexplained by amyloid status (50% for 2SD and 33% for 3SD), consistent with the results reported above for SUVR while controlling for amyloid status.

3.4.3. Dichotomized Amyloid Status

We also modeled the effect of dichotomized amyloid status alone on cognitive decline. Using the 2SD amyloid status variable, we found significant Amyloid Status x Time interactions for episodic memory (*Est(SE)= -0.29 (0.13*), *p = 0.028)* and vocabulary (*Est(SE)*= -0.14 (0.07), $p = 0.044$), while processing speed (*Est(SE)* = -0.11 (0.08), $p = .161$) and MMSE (*Est(SE)* = -0.19 (0.27), $p = 0.472$) were not significant. Using the 3SD amyloid variable, we again found significant Amyloid Status x Time interactions for only episodic memory (*Est(SE)= -0.40(0.15),*

p = .009) and vocabulary (*Est(SE)= -0.20(0.08), p* = .011; see Table A2). Figure 3.4 shows that at both thresholds amyloid positives exhibited cognitive decline while negatives do not.

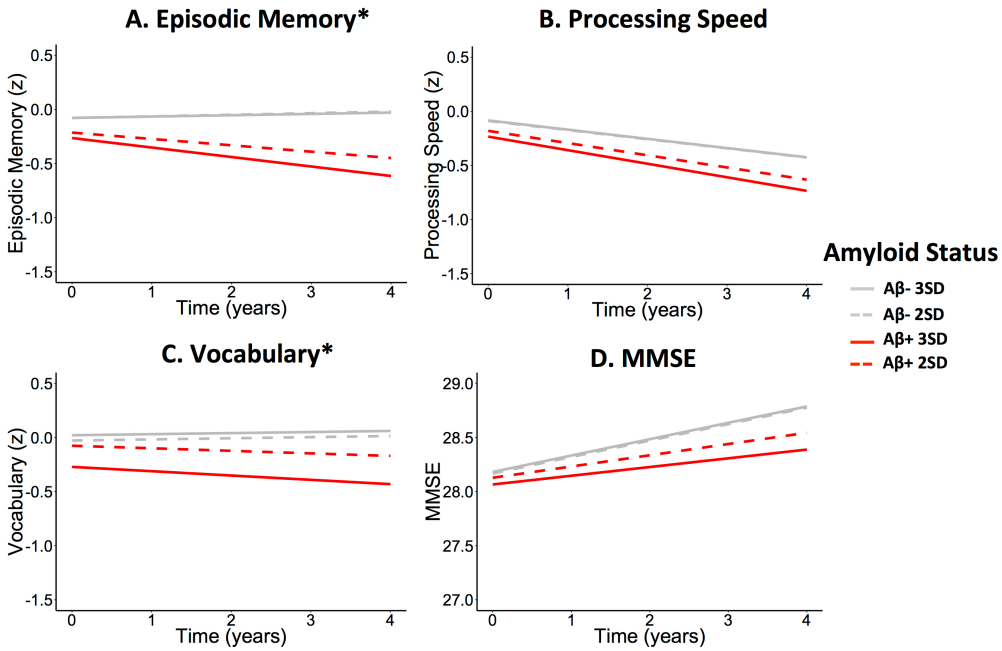

Figure 3.4. Projections of the Impact of Amyloid Positivity over a 4-Year Time Interval on 4 Measures of Cognition. Lines represent trajectory of change between estimated marginal means of cognitive performance at Year 0 and Year 4 for the amyloid positive and negative groups, at both 2SD and 3SD thresholds.

Qualitatively, these results contrast with the model projections shown in Figure 3.4, which display more pronounced declines across four cognitive measures resulting from increasingly high amyloid burden.

3.4.4. Amyloid Positive and Negative Subsample Analyses

To further verify the continuous relationship of amyloid burden to cognitive decline, we conducted the same dose-response analyses separately for amyloid positive and negative participants. For the amyloid positive group using the 2SD threshold (n = 49), the SUVR x Time interaction was again significant for episodic memory (*Est(SE)* = -1.33(0.54), p = .018), and

approached significance for MMSE (*Est(SE)* = -1.91(1.05), p = .075) (see Table A3 for full model results). Using the more stringent 3SD threshold (n = 31), the SUVR x Time interaction was significant only for episodic memory (*Est(SE)* = -1.36(0.66), p = .048). Figure 3.5 shows scatterplots of the individual episodic memory change scores (adjusted for age, sex, education and APOE) as a function of baseline SUVR, based on the 2SD (left) and 3SD (right) thresholds.

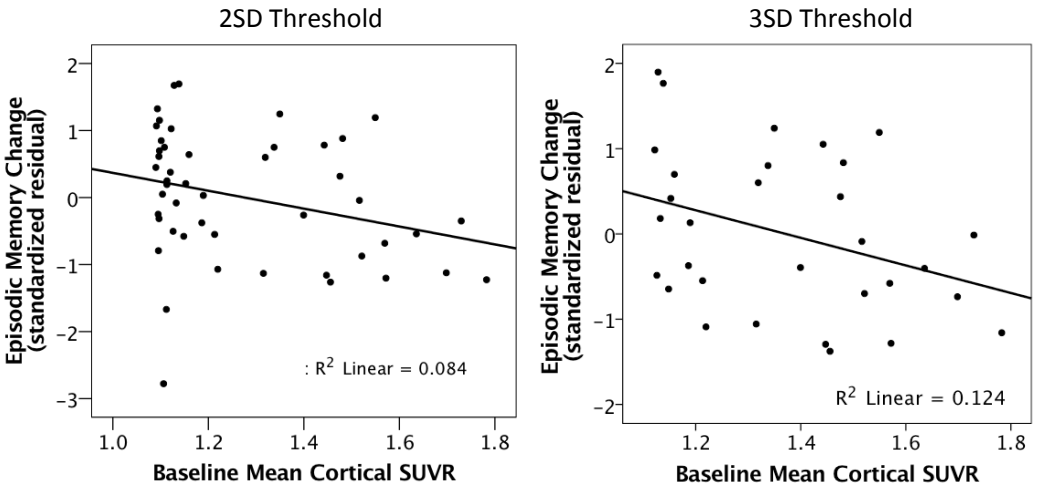

Figure 3.5. Dose-Response Relationship between Baseline Amyloid Burden and Episodic Memory Decline in Amyloid positive Individuals

For the amyloid negative group, significant SUVR x Time interactions were not detected for any cognitive measure at either threshold (Table A4). However, there was a significant Age x Time interaction for processing speed (*Est(SE)* = -0.009(0.003), p = .01) and a trend for reasoning (*Est(SE)* = -0.008(0.004), p = .059), as shown previously in the full sample. Using simple slope analysis, the projected trajectory of processing speed and reasoning change over time was plotted for different ages in the amyloid negative subsample, as depicted in Figure 3.6. Increasing age was predictive of greater decline in processing speed, and marginally predictive of greater decline in reasoning.

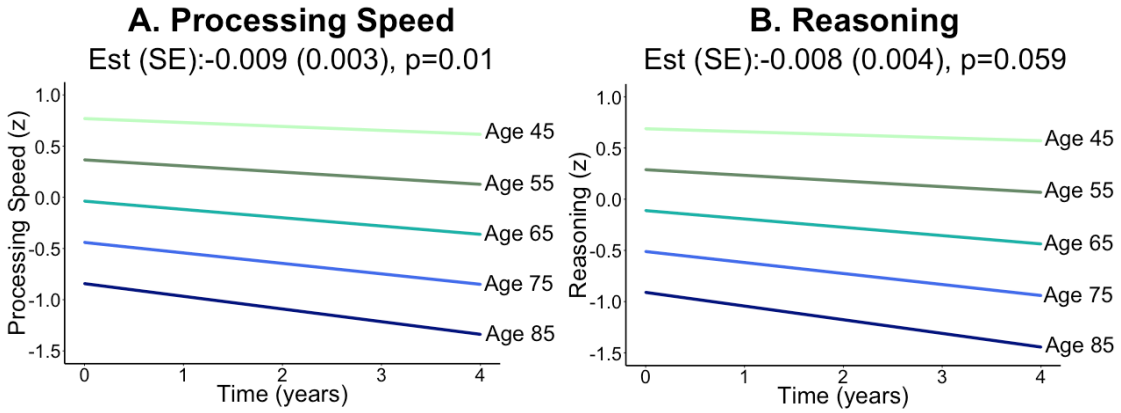

Figure 3.6. Older Age Associated with Increasing Decline in Processing Speed and Reasoning

3.4.5. Middle-aged and Older Adult Subsample Analyses

Although amyloid burden was lower in middle-aged compared to older adults (Figure 3.1), we considered that a dose-relationship could still exist in only middle-aged adults (n = 51). The analyses yielded one significant SUVR x Time interaction for vocabulary (*Est(SE)* = -2.05(0.86), p = .021, see Table A5). However, the interaction was driven by one individual with the highest SUVR and greatest vocabulary decline (Figure 3.7).

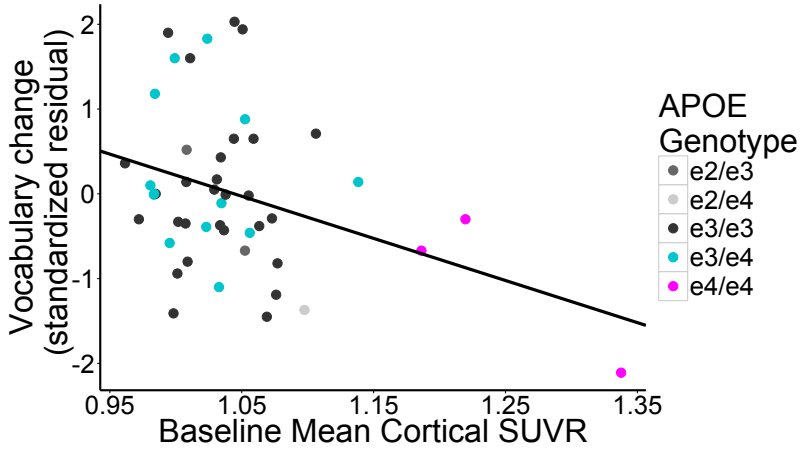

Figure 3.7. Dose-Response Relationship Between Baseline Amyloid Burden and Vocabulary in Middle-Aged Adults Driven by Three APOE-ε4 Homozygotes.

When the individual was removed, the interaction became non-significant (p = .207). Interestingly, post-hoc examinations revealed that this outlier and the two other individuals with the highest SUVR in middle age were APOE ε4/ε4 and exhibited vocabulary decline.

Finally, for comparability to other studies that included only older adults, we repeated the analyses in the 60-89 year olds only. Like the whole sample, we found significant SUVR x Time interactions for episodic memory (*Est(SE)* = -1.03(0.38), p = .008), processing speed (*Est(SE)= -0.53(0.22),* p = .019), vocabulary (*Est(SE)= -0.46(0.19),* p = .02) and MMSE (*Est(SE)* = -1.63(0.79), p = .041) (see Table A6).

3.5. DISCUSSION

The present study provides evidence of a dose-response effect whereby the magnitude of baseline amyloid burden predicts the rate of cognitive decline over four years in cognitively normal adults. These results suggest that the degree of amyloid burden provides potentially important additional information about the rate of expected cognitive decline that is not available from a dichotomous positive/negative categorization. These findings may have important implications for projecting clinical outcomes on the basis of an amyloid PET scan, as well as for understanding the impact of amyloid in preclinical AD. Additionally, we report on the effects of amyloid on cognitive decline in middle-aged adults, who have rarely been studied, and found limited evidence for a dose-response relationship between greater amyloid burden at baseline and vocabulary decline, but it was driven by APOE ε4 homozygotes.

3.5.1. Dose-Response Effect of Baseline Amyloid on Cognitive Decline.

Episodic memory decline is the signature behavioral characteristic of AD and longitudinal studies that model amyloid as a dichotomous variable have confirmed that the

presence of amyloid in cognitively normal adults predicts greater episodic memory decline (Lim et al, 2013; Mormino et al, 2014a; Petersen et al, 2016; Villemagne et al, 2013; Wirth et al, 2013). Here, we observed a dose-response effect of baseline amyloid burden on four-year episodic memory decline. At low SUVR, there was no change in episodic memory, but increasing SUVR predicted steeper rates of episodic memory decline. These findings remained after controlling for amyloid positivity using a liberal 2SD threshold as well as when the analysis sample was limited to only amyloid positive adults. In addition to episodic memory, we also found significant dose-response effects across a range of cognitive variables (processing speed, vocabulary, and MMSE), attesting to the breadth of the effect of amyloid.

In a related study, Lim et al. (2014) focused on only amyloid positive adults, combining cognitively normal adults with MCI patients, and then dichotomizing them into low and high amyloid groups. They reported greater memory decline for higher compared to lower amyloid. The present study expands on these findings by demonstrating a continuous dose-response relationship between amyloid burden and cognitive decline across a broad range of domains in healthy adults. These findings suggest that the magnitude of amyloid burden may be useful in predicting the rate of future cognitive decline, with those with the greatest amyloid burden at baseline expected to decline most rapidly.

3.5.2. Dichotomous vs. Continuous Amyloid.

When we treated amyloid as a dichotomous variable, analyses yielded fewer significant effects of amyloid on cognitive decline, and the decline trajectories appeared more modest for amyloid status (Figure 3.4) compared to the results for continuous SUVR (Figure 3.2). Furthermore, when dichotomized amyloid status was included as a covariate, the continuous

SUVR effect remained significant for a number of cognitive variables. This provides additional evidence supporting the use of a dose-response approach.

We also found that varying the positivity threshold used to define dichotomized amyloid status resulted in somewhat different outcomes in predicting cognitive decline. When two different thresholds were used to define positivity, significant effects of amyloid status were observed for episodic memory and vocabulary, though the effects using a more conservative 3SD threshold were of slightly greater magnitude than when using the more liberal 2SD threshold. The distribution using the more conservative 3SD was more normally distributed, while the more liberal 2SD threshold resulted in a more skewed distribution with a high number of individuals with low SUVR. This is consistent with expectations when using more liberal vs. more conservative thresholds: liberal thresholds are intended to include more individuals with low but real amyloid (true positives), but result in a higher proportion of false positives, while conservative thresholds may result in false negatives. Indeed, a recent study by Villeneuve et al. (2015) that included both PET and autopsy data in the same subjects found that more liberal thresholds had much higher sensitivity to detect amyloid pathology than more conservative thresholds, but in turn they had lower specificity. Furthermore, when amyloid status was a covariate in the continuous SUVR analysis, the dose-response effect remained significant for episodic memory, vocabulary and MMSE at the 2SD threshold, but was significant only for the MMSE at the 3SD threshold. These findings highlight that dichotomous measures of amyloid may result in discarding useful information and that the selection of a positivity threshold may influence results. Without autopsy data to confirm amyloid positivity status, the use of

thresholds introduces uncertainty that may be avoided by utilizing SUVR as a continuous measure.

Additionally, the use of continuous vs. dichotomized variables becomes even more relevant due to the recently proposed A/T/N framework (Jack et al, 2016), which relies on dichotomous classification for multiple AD biomarkers (amyloid/tau/neurodegeneration) to group individuals along the continuum of the Preclinical Model of AD. Compared with amyloid, it is even less clear what might constitute an appropriate threshold for tau and neurodegeneration. As has been demonstrated in the present findings, important information may be lost by focusing on classifying individuals as positive or negative for different AD biomarkers.

3.5.3. Tau and Neurodegeneration

As mentioned in Section 2.5, it is posited by the amyloid cascade hypothesis and the Preclinical Model of AD that tau and neurodegeneration mediate the effects of amyloid on cognitive decline. In the present study, we demonstrated that the amount of amyloid at baseline is predictive of how rapidly an individual may decline over four years. However, it is important to note that this does not mean that amyloid itself disrupts cognitive functioning. Rather, amyloid may lead to greater proliferation of tau, which then leads to neurodegeneration and finally cognitive decline. Emerging tau PET results from cognitively normal adults indicate that the magnitude of tau in amyloid positive individuals and is related to poorer episodic memory (Johnson et al, 2016; Ossenkoppele et al, 2016; Scholl et al, 2016). Likewise, Mormino et al. (2014b) demonstrated in a recent two-year longitudinal study that only those cognitively normal adults who were both amyloid positive and neurodegeneration positive at baseline exhibited episodic memory decline. Thus, in order to fully understand the pathological cognitive trajectory

in cognitively normal adults with amyloid, future studies are needed to examine the continuous relationships amongst amyloid, tau, neurodegeneration and cognitive decline.

3.5.4. Early Amyloid Deposition and Cognitive Decline

In order to assess whether a relationship between amyloid deposition at baseline and cognitive decline may emerge early, the present dissertation also assessed whether relatively high amyloid burden within middle-aged and amyloid negative adults might already be associated with cognitive decline. Although SUVR uptake observed in middle-age is typically relatively low (Rodrigue et al, 2012), we hypothesized that middle-aged individuals with high SUVR relative to their peers would exhibit steeper cognitive decline. In this group there was a dose-response relationship of amyloid burden to vocabulary decline. We noted, post hoc, that this result was driven by three outliers with the highest SUVRs, who upon closer examination were found to be the only three APOE ε4/ε4 homozygotes in the 40-59 age group. This finding, while anecdotal, provides qualitative evidence suggesting APOE ε4 is an important factor in preclinical AD in middle-age. This is consistent with autopsy findings (Kok et al, 2009) demonstrating that amyloid plaques are already prevalent in middle age (particularly 50-59 year olds) in APOE ε4 carriers.

Recent findings (Insel et al, 2016; Mormino et al, 2014b) provided some impetus for the possibility that relatively high amyloid burden within the amyloid negative range might be predictive of future cognitive decline. However, we failed to find evidence for this in our results when treating SUVR as a continuous variable within the amyloid negative participants, or in middle age after removing the APOE ε4/ε4s. Thus the present results do not provide evidence of early effects of amyloid on cognitive decline. However, it may be that relatively high amyloid

burden within the amyloid negative range is not a good indicator of low but meaningful amyloid burden, due to the obscuring effect of non-specific binding. Instead, longitudinal measurement of increasing amyloid burden within both initially amyloid negative adults and middle-aged adults in Study 2 may allow for detection of early effects of amyloid on cognitive decline.

3.5.5. Practice Effects

Importantly, we did find a significant and positive main effect of time across all domains (except MMSE), indicating that across all participants, regardless of age of amyloid, a practice effect was observed. Thus the most accurate prediction of an individual's change in performance takes into account both the expected practice effect as well as the decrease associated with their amyloid load. In contrast, the presence of practice effects on the MMSE differed: there was not a main effect of time, but the SUVR x Time interaction included a practice effect. Our model indicates that individuals with low SUVRs exhibited a practice effect at follow-up on the MMSE, but as SUVR increased this practice effect diminished and at high SUVRs a decline in MMSE was observed. These findings suggest that while on the other cognitive measures familiarity with the test from prior years is beneficial to even those with the highest amyloid burden, on the MMSE this benefit is dependent of amyloid pathology. This may reflect differences in the design of these different measures. Each cognitive composite is composed of measures intended to assess that cognitive ability in a cognitively normal population and thus practice effects are present across the population. In contrast, the MMSE was designed to assess the degree of cognitive impairment in a pathological population, and thus practice effects are dependent on the degree of pathology.

3.5.6. Cognitive Decline in Normal Aging

An important facet of studying the effects of amyloid pathology on cognitive decline is the need to establish that the observed declines are related to amyloid pathology rather than normal aging. Since amyloid deposition increases with age, it is important to ensure that our amyloid-related declines are not confounded by age. By including age as a covariate, we demonstrate that these amyloid effects are significant over and above the effects of normal aging. It is important to note, however, that age and amyloid are highly collinear. Thus it may be that by controlling for age we may be underestimating the effects of amyloid on cognitive decline.

Differentiating between effects of amyloid and effects of normal aging becomes particularly important with variables like processing speed and reasoning, which in the present study we found to exhibit declines over a period as short as four years simply as a function of increasing age. Nevertheless, we were still able to detect a small effect of baseline amyloid burden on declining processing speed, indicating that amyloid contributes to additional decline, over and above the effects of normal aging. In contrast, episodic memory exhibited a main effect of age, such that older adults had lower episodic memory, but only amyloid was predictive of the rate of decline over four years. Given that older adults exhibit lower episodic memory than younger adults, it is likely that with a longer follow-up interval we would find that both age and amyloid contribute to the rate of the episodic memory decline.

Interesting relationships between amyloid and cognition emerge for variables that do not exhibit similarly marked age-related decline. Most notably, since vocabulary typically increases or does not change with age, as was observed in the present study, it was possible to detect a small but significant dose-response effect of amyloid on vocabulary. While the magnitude of the

effect of amyloid pathology on vocabulary decline was weaker than that observed for episodic memory, it was more easily dissociable from the effects of normal aging. Likewise, while MMSE did show age-related decline, the magnitude of the effect of age on MMSE was weak compared with the other cognitive variables, again allowing for the detection of an effect of amyloid on MMSE decline. It thus becomes easier to detect effects of amyloid pathology when they are more readily dissociable from the effects of normal aging.

3.5.7. Limitations

We note that the present sample may be underpowered to detect subtle effects, particularly in subsamples. Secondly, an issue that pervades research on amyloid is its non-normal distribution. However, the amyloid positive sample has a more normal distribution, and the dose-response effect remains significant for episodic memory within amyloid positives. Finally, because our sample was recruited to be healthy, we do not have assessments of clinical function on these participants, which would be desirable as the participants age and a subset progresses to MCI and AD. However, these findings establish that increasing amyloid burden is predictive of cognitive decline in our sample, regardless of clinical status.

3.6. CONCLUSION

Study 1 of the present dissertation demonstrates a dose-response relationship between the magnitude of amyloid burden at baseline and the rate of cognitive decline over a four-year follow-up in cognitively normal adults, particularly for episodic memory. These results suggest that the magnitude of amyloid deposition predicts those likely to be on a more negative cognitive trajectory, potentially heading towards dementia. However, the magnitude of baseline amyloid burden across the neocortex was not predictive of cognitive decline within middle-aged and

initially amyloid negative adults, therefore failing to provide evidence of early effects of amyloid on cognitive decline in those with relatively high amyloid burden compared to one's peers. The use of longitudinal changes in regional amyloid burden in Study 2 may provide a more sensitive measure of early amyloid deposition, potentially enabling detection of early cognitive consequences of amyloid.

CHAPTER 4

STUDY 2. REGIONAL AMYLOID ACCUMULATION AND COGNITVE DECLINE

4.1. INTRODUCTION

4.1.1. Longitudinal Studies of Change in Amyloid and Change in Cognition

The longitudinal measurement of change in amyloid over time provides an additional method to evaluate the relationship of amyloid deposition to cognitive decline. However, as mentioned in Section 2.9, to our knowledge the only published study to date to examine the relationship of change in amyloid to change in cognition (Villemagne et al, 2013), found that change in amyloid did not provide any additional information about cognitive decline that cannot be measured more easily with a single baseline measure. However, Villemagne et al. used a measure of the mean rate of accumulation across most of the neocortex, and such a gross measure may not be the best metric for describing change in amyloid over time and its impact on cognitive decline. For rate of accumulation to be a sensitive predictor of cognitive decline, it may instead be important to address where in the brain amyloid accumulated over the follow-up interval. Indeed, a recent autopsy study (Sojkova et al, 2011), that included participants who underwent amyloid PET imaging just prior to death, revealed that the use of an averaged global SUVR instead of regional measures resulted in incorrectly categorizing individuals with focal amyloid deposits as amyloid negative. Thus, the use of an averaged global measure of SUVR may result in a loss of information about amyloid accumulation and its consequences in cognitively normal adults, particularly at lower levels of amyloid when deposits are likely to be more focal. Therefore, Study 2 of my dissertation will explore regional amyloid accumulation across the lifespan and whether leveraging regional amyloid accumulation will allow for the

detection of a relationship between the rate of amyloid accumulation and cognitive decline over four years.

4.1.2. Regional Effects of Amyloid Accumulation on Cognition

An association between regional amyloid accumulation and cognitive decline rather than global amyloid accumulation relies on the presence of regionally specific relationships between amyloid accumulation and cognitive decline. Regional specificity may reflect a local effect of amyloid on nearby neural circuitry necessary to perform specific cognitive tasks. It has been established from *in vitro* and rat studies that amyloid is neurotoxic to synapses and results in synaptic dysfunction (Cleary et al, 2005; Shankar et al, 2007; D. M. Walsh et al, 2002), thus providing evidence of a potential direct link between amyloid and disruption of neural activity. As discussed in Section 2.3, it is notable that it is the soluble form of amyloid that is thought to be neurotoxic (Selkoe, 2008), rather than the insoluble fibrillar (plaque) form to which florbetapir binds. However, the soluble and insoluble forms of amyloid are thought to be in equilibrium (Takeda et al, 2013). Thus by detecting plaques using amyloid PET imaging, we may be able to indirectly assess soluble amyloid and its possible effects on neural activity.

To date, more direct *in vivo* evidence of a link between amyloid deposits and synaptic disruption has been limited. To our knowledge no cross-sectional studies have found correlations between regional amyloid deposition and poorer cognitive performance on tasks that rely on that same region. However, it is possible that by utilizing longitudinal imaging, regional increases in amyloid over time may provide a more sensitive measure of the local effects of amyloid on cognition.

There is some evidence from amyloid PET imaging of a possible relationship between amyloid deposits and local disruption of brain function using fMRI. The pattern of amyloid deposition in cognitively normal older adults overlaps greatly with the default mode network (Buckner et al, 2009), and resting state fMRI studies have consistently demonstrated that amyloid deposition is correlated with disruption of functional connectivity of the default mode network (Drzezga et al, 2011; Elman et al, 2014; Mormino et al, 2011; Sheline et al, 2010). In addition to disrupting the integrity of this network, amyloid deposition also has been related to decreases in the ability to suppress the default mode network in response to task demands (Hedden et al, 2009; Huijbers et al, 2014; Kennedy et al, 2012; Sperling et al, 2009; Vannini et al, 2012). These findings provide some preliminary support for a local effect of amyloid on the surrounding neural circuitry, which may result in regionally specific cognitive decline.

4.1.3. Staging of Amyloid Accumulation by Region

In examining regional changes in amyloid and their relationship to cognitive decline, it is first important to consider the temporal regional dynamics of amyloid accumulation in the neocortex. Autopsy staging studies (Braak & Braak, 1997; Braakhuis, van Dongen, Vermorken, & Snow, 1991) have described the spread of amyloid in 3 general stages:

Stage A: Low density of amyloid deposits in basal portions of frontal, temporal and occipital lobe. None in hippocampus.

Stage B: Moderate level of deposition widespread throughout the neocortex, excluding primary sensory and motor regions.

Stage C: High density across entire cortex, including primary sensory and motor regions

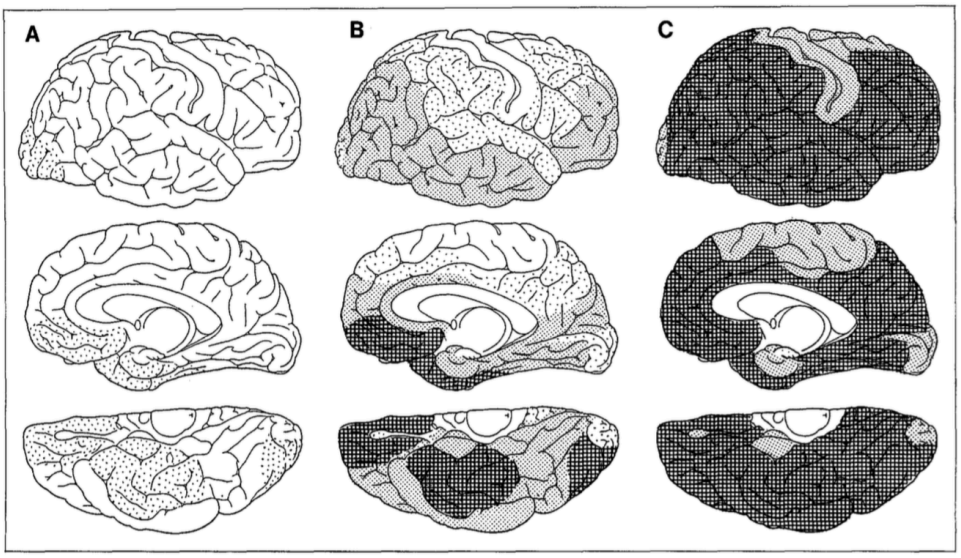

Figure 4.1. Stages of Amyloid Pathology (Braak & Braak, 1991). Amyloid deposition progresses from low deposits in basal frontal, ventral temporal and occipital lobes (Stage A) to all neocortex, sparing sensory and motor cortices (Stage B) to entire cortex (Stage C).

As shown in Figure 4.1, the spatial pattern of amyloid deposition outlined by Braak and Braak (1991) involves deposition in basal frontal, ventral and anterior temporal and lateral occipital cortices before spreading throughout the neocortex, though initially sparing primary motor and sensory regions. When amyloid is detected at autopsy in individuals who were non-demented in life, they are typically either in the first or second stage (Thal, Rub, Orantes, & Braak, 2002). Thus, autopsy evidence suggests that the most distinctive regional differences in amyloid deposition may emerge via the existence of two stages of amyloid deposition in cognitively normal adults: an earlier stage associated with more focal deposits, particularly in orbitofrontal, anterior temporal and lateral occipital cortices, and a later stage with more diffuse deposition throughout the neocortex. These regional differences in the spatial and temporal dynamics of amyloid accumulation suggest that some regions may be particularly useful markers

of the early stages of amyloid pathology and its subtle effects on cognition in cognitively normal adults.

4.1.4. Early and Later Stages of Amyloid Accumulation

In order to focus on early stages of amyloid accumulation, the present dissertation utilizes two groups of individuals in which the beginnings of amyloid accumulation are likely to appear: middle-aged adults and initially amyloid negative adults. Recent amyloid PET studies have used initially amyloid negative adults to demonstrate regional patterns of amyloid accumulation that converges with autopsy findings. Villain et al. (2012) demonstrated that participants who were considered amyloid negative at baseline exhibited small but significant increases in amyloid over 18 months in the orbitofrontal cortex (OFC), as well as the insula and temporal pole (Figure 4.2, left), while individuals who were amyloid positive at baseline exhibited significant accumulation throughout most of the neocortex, sparing primary sensory and motor regions (Figure 4.2, right).

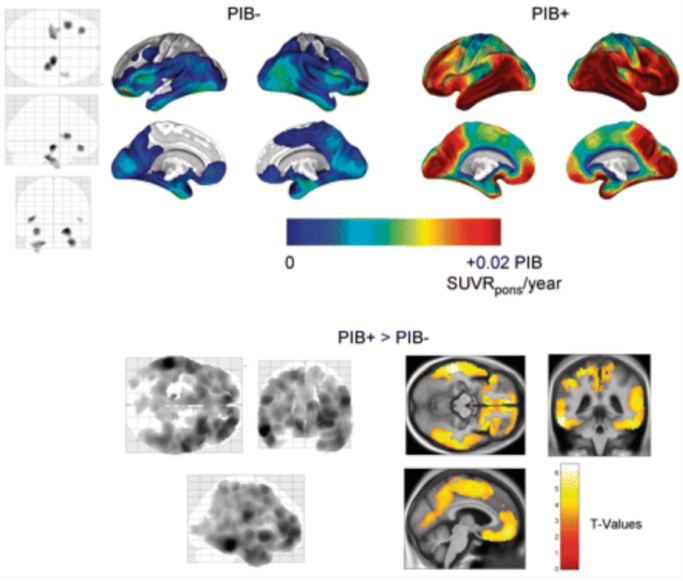

Figure 4.2. Longitudinal Amyloid Accumulation over 18 months (Villain et al, 2012). Left panel shows initially amyloid negative adults (PIB-) and right panel shows amyloid positive adults (PIB+).

These results are consistent with the autopsy staging, showing more focal accumulation, particularly in the OFC, in individuals likely to be at an early stage in disease progression (initially amyloid negative adults) and more diffuse accumulation at a later stage (initially amyloid positive adults).

Recently, Sepulcre et al. (2013) used stepwise connectivity analyses to build a more detailed picture of the spread of amyloid throughout the brain. They demonstrated that amyloid appears to spread through functional networks, starting in the OFC before spreading to distant regions of the brain that are functionally connected, including the posterior cingulate/precuneus and the lateral temporal lobe, and from there spreading throughout the neocortex. Likewise, Villeneuve et al. (Villeneuve et al, 2015) found a similar pattern of amyloid deposition starting in the medial OFC, spreading to posteromedial regions and then throughout the neocortex. Thus converging evidence from autopsy and amyloid PET imaging highlight the OFC in particular as one of the earliest sites of amyloid accumulation. Furthermore, consistent evidence also indicates that accumulation in posteromedial regions appears later, after spreading out from the OFC. Notably, the highest accumulation is typically found in the precuneus and posterior cingulate in amyloid positive adults (Mintun et al, 2006; Rodrigue et al, 2012). Thus, the precuneus and posterior cingulate in particular may be useful as representative regions for a later-stage of amyloid accumulation.

As described above, both Villain et al., (2012) and Sepulcre et al. (2013) utilized individuals that were categorized as amyloid negative at baseline to detect early signs of amyloid deposition, and the use of middle-aged adults may also allow for the detection of early amyloid deposition. Autopsy studies indicate that amyloid may start depositing in middle age (Braak &

Braak, 1997; Braak et al, 2011) and accumulate over 10-20 years (Buchhave et al, 2010; Fleisher et al, 2012; Jack et al, 2013). The first step in Study 2 of my dissertation will therefore be to utilize our lifespan sample to address whether specific regions may be useful as markers of early vs. later stages of amyloid accumulation. As described above, it is expected that the OFC will be sensitive to early amyloid accumulation, exhibiting significant accumulation even when restricting the sample to middle-aged adults and those who were amyloid negative at baseline. In comparison, it is hypothesized that posteromedial regions will exhibit amyloid accumulation later, predominately in older adults and those who were already amyloid positive at baseline. Additional exploratory analyses will also examine amyloid accumulation in the remainder of the neocortex to provide a comprehensive picture of amyloid accumulation across the lifespan.

4.1.5. Earliest Cognitive Consequences of Amyloid

Due to the more focal nature of early amyloid deposition, regional measures of amyloid accumulation may be a particularly useful tool for examining the earliest consequences of amyloid deposition in cognitively normal adults. In amyloid PET imaging, individuals categorized as amyloid positive most often exhibit a dispersed pattern of deposition across most of the neocortex (Aizenstein et al, 2008; Jack et al, 2008; Mintun et al, 2006). This results in a high degree of inter-correlation between regions, making it difficult to identify regionally specific effects of amyloid on cognition. In contrast, the regional differences at early stages may improve the ability to detect a regionally specific effect of amyloid on cognition. The present study therefore examines whether regional relationships between amyloid accumulation and cognition may be detected early, both in terms of age (as measured in middle-aged adults) and in terms of AD pathological progression (as measured in initially amyloid negative adults). Such

findings would also provide important and novel evidence that amyloid pathology may have subtle cognitive consequences far in advance of clinical symptoms of AD. This would be useful not only to improve our understanding of the earliest stages of AD, but also to inform the selection of our outcome measures in early intervention clinical trials targeting amyloid pathology in middle-aged and amyloid negative adults.

Reasoning, in particular, is hypothesized to be affected by amyloid at the early stage. There is evidence in support of an early effect of amyloid on reasoning from recent amyloid-cognition studies in cognitively normal adults, even before the more AD-typical declines in episodic memory. Some cross-sectional studies have found relationships between amyloid burden and reasoning in healthy older adults but no relationship between amyloid and episodic memory (Rodrigue et al, 2012; Schott et al, 2010). Likewise, Snitz et al. (2013) found that low reasoning, but not episodic memory, was predictive of amyloid deposition 7-9 years later. As mentioned above, it is hypothesized that the OFC will be amongst the earliest of those regions that exhibit early stage amyloid accumulation. While the OFC is most commonly associated with emotional decision-making (Bechara, Damasio, & Damasio, 2000), penumbral regions of the rostral inferior prefrontal cortex, including the pars orbitalis, have been strongly implicated in reasoning (Bunge, Wendelken, Badre, & Wagner, 2005; Christoff et al, 2001; Krawczyk et al, 2008). The present dissertation does not include tests of emotional decision-making, as they were not included in the DLBS. However, it is hypothesized that reasoning decline may be related to amyloid accumulation in the OFC and pars orbitalis, based on the proximity of the rostral inferior prefrontal cortex to the OFC and the soluble nature of amyloid. Furthermore, this

relationship is hypothesized to be apparent early in the disease progression (initially amyloid negative adults) and early in the lifespan (middle-aged adults).

4.1.6. Later Cognitive Consequences of Amyloid

In contrast, amyloid is hypothesized to be widespread throughout most of the neocortex later in the disease progression (initially amyloid negative adults) and in the lifespan (older adults), and associated with the more severe and AD-typical losses in episodic memory. Results from Study 1 of the present dissertation are in concordance with this, as the steepest declines were observed in episodic memory at high levels of amyloid. While the ubiquity of amyloid deposition in this stage may make detecting regionally specific effects more difficult overall, the posteromedial cortices are potentially differentiable since they tend to have the greatest amyloid deposition (Mintun et al, 2006; Rodrigue et al, 2012) and form the primary hub into which amyloid spreads after accumulating in the OFC (Sepulcre et al, 2013; Villeneuve et al, 2015). Furthermore, posteromedial regions are known to be important for episodic memory retrieval (Rugg & Vilberg, 2013). Therefore it is hypothesized that amyloid accumulation in posteromedial regions will be associated with episodic memory decline.

4.1.7. Hypotheses

In summary, Study 2 of the present dissertation utilizes longitudinal amyloid PET imaging and cognitive assessments to evaluate whether regional changes in amyloid over time are related to cognitive decline. It is hypothesized that regional differences in accumulation will be apparent, with some regions accumulating earlier while others accumulate later. Furthermore, amyloid accumulation in specific regions will relate to cognitive decline in the domain subserved by that region. Additionally, earlier regional amyloid accumulation in middle-aged adults and

initially amyloid negative adults will already be associated with cognitive decline even at this early stage.

Based on the presented evidence from autopsy and amyloid PET studies, analyses will focus on 3 hypothesized early-accumulating regions (lateral OFC, medial OFC, pars orbitalis) and 3 later-accumulating regions (precuneus, posterior cingulate, isthmus cingulate). It is hypothesized that the lateral OFC, medial OFC, and pars orbitalis will exhibit amyloid accumulation both early in the lifespan (as measured in middle-aged adults) and early in terms of AD pathological progression (as measured in initially amyloid negative adults) and relate to reasoning decline. In contrast, it is hypothesized that AD typical declines in episodic memory will be observed later (in older adults and those who were already amyloid positive at baseline) and be most strongly associated with increased amyloid accumulation over time in posteromedial cortices. Additional analyses will be performed in a second exploratory set of regions comprising most of remaining neocortex to examine whether trends in the *a priori* set of ROIs are observed elsewhere in the neocortex. Finally, analyses will be conducted in a negative control region (pericalcarine cortex) not believed to exhibit substantial amyloid accumulation until very late in AD progression (Braak & Braak, 1991), to provide support that relationships between regional amyloid accumulation and cognitive decline reflect real amyloid accumulation.

4.2. METHODS

4.2.1. Participants

This study included all DLBS participants who completed amyloid PET scans, structural MRI scans, and a cognitive battery at baseline and four-year follow-up. A total of 288 participants were eligible to return, and 178 returned (retention rate= 62%). Reasons for non-

returns included: 8 deceased, 30 poor health, 23 not interested, and 49 lost to follow-up. Of those that returned, 19 were assessed on a different PET scanner at follow-up and were not included here. In addition, 8 participants did not undergo MRI testing at follow-up, 3 participants had MRIs but the image quality was poor, and 6 were excluded for poor PET-MRI coregistration. The final sample consisted of 142 participants. Those retained did not differ significantly from those lost to follow-up as a function of age, baseline SUVR, years of education, gender or APOE carrier status (p's > .10).

Participants were screened at baseline to ensure MMSE ≥ 26, and at follow-up all participants had an MMSE ≥ 25. All participants were recruited locally from advertisements and public talks and were screened for neurological and psychiatric disorders, loss of consciousness >10 minutes, drug or alcohol abuse, major heart surgery or chemotherapy within 5 years. All were native English speakers and right-handed. This study was approved by The University of Texas Southwestern and The University of Texas at Dallas Institutional Review Boards. All participants provided written informed consent and were debriefed according to human investigations committee guidelines.

4.2.2. Cognition.

Five cognitive outcome measures were derived from the cognitive battery. Three were averaged composites: *Episodic Memory* (Hopkins Verbal Learning (Brandt, 1991); CANTAB Verbal Recognition Memory (Robbins et al, 1994)), *Processing Speed* (WAIS Digit Symbol (Wechsler, 1997); Digit Comparison (Hedden et al, 2002; Salthouse & Babcock, 1991)), and *Reasoning* (Raven's Progressive Matrices (Raven, 1996); ETS Letter Sets (Ekstrom & Harman, 1976)). Additionally, we had a single measure of vocabulary (ETS Vocabulary (Ekstrom &

Harman, 1976)). Baseline scores for each task were converted to z-scores in the 30-89 year olds, and the follow-up scores were z-transformed using the baseline mean and standard deviation. Finally, raw MMSE scores were used as an estimate of overall cognitive status. Change in cognition over time was computed as a difference score. One subject was missing data such that they had data for episodic memory and vocabulary at both time points, but were missing processing speed, reasoning and MMSE data at follow-up.

4.2.3. MRI Protocol

Participants were scanned on the same 3T Philips Achieva scanner with an 8-channel head coil at baseline and follow-up. High-resolution anatomical images were collected with a T1-weighted MP-RAGE sequence with 160 sagittal slices; FOV= 204 x 256 x 160 mm; voxel size = $1\times1\times1$ mm^3; TR = 8.1ms, TE = 3.7ms, flip-angle = 12°. Time 1 and 2 anatomical images were processed separately using the FreeSurfer v5.3 cross-sectional pipeline (http://surfer.nmr.mgh.harvard.edu/ (Dale et al, 1999; Fischl et al, 1999)) with thorough manual editing, as detailed previously (Savalia et al, 2017). Bilateral regions of interest (ROIs) were derived from FreeSurfer cortical parcellations according to the Desikan-Killiany atlas (Desikan et al, 2006) at each time point. Adjusted cortical volume was computed separately at each time point for each bilateral ROI and for total gray matter volume (sum of all cortical gray matter ROIs) using the following equation: - adjusted volume = raw volume $- b \times$ (intracranial volume − mean intracranial volume) where b is the slope of regression of an ROI volume on intracranial volume (Raz et al, 2005). Atrophy was computed for each ROI as a difference score.

4.2.4. PET Acquisition

The PET protocol was the same at baseline and follow-up. All participants were injected with a 370 MBq (10 mCi) bolus of 18F-Florbetapir. At 30 minutes post-injection, subjects were positioned on the imaging table of a Siemens ECAT HR PET scanner. Soft Velcro straps and foam wedges were used to secure the participant's head and the participant was positioned using laser guides. A 2 minute scout was acquired to ensure the participant's brain was completely in the field-of-view and there was no rotation in either plane. A 2-frame by 5-minute each dynamic emission acquisition was started 50 minutes post injection and immediately after an internal rod source transmission scan was acquired for 7 minutes. The transmission image was reconstructed using back-projection and a 6mm FWHM Gaussian filter. The emission images were processed by iterative reconstruction, with 4 iterations and 16 subsets and a 3mm FWHM ramp filter.

4.2.5. PET Preprocessing

In order to improve the measurement of change in amyloid over time, additional preprocessing steps were taken to minimize noise across time points. First, to avoid biasing the change measurement to either time point, a mean MRI was created using FreeSurfer. PET images from each time point were linearly coregistered to the MRI at the corresponding time point using FLIRT (Jenkinson & Smith, 2001) and then transformed to mean MRI space using the transformation matrix derived from coregistration of the MRI at each time point, respectively, to the mean MRI. Second, bilateral ROIs were derived from FreeSurfer cortical parcellations (Desikan-Killiany atlas; Desikan et al, 2006) at each time point (left and right ROIs were combined), and then transformed to mean MRI space. Figure 4.3 shows all regions from the Desikan-Killiany atlas.

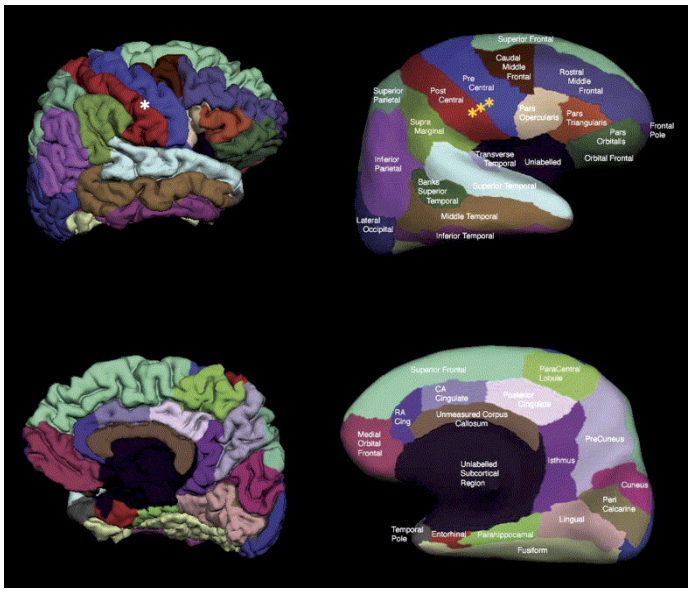

Figure 4.3. Desikan-Killiany Atlas (Desikan et al, 2006)

Due to poor parcellation in FreeSurfer resulting in unreliable ROI masks, the following cortical regions were not included in the exploratory analyses: entorhinal, parahippocampal, insula, temporal pole, frontal pole, postcentral gyrus, precentral gyrus. These regions also typically exhibit low amyloid even in amyloid positive adults (Braak et al, 2011; Mintun et al, 2006) and are thus unlikely to be sensitive to amyloid-related cognitive decline. All other regions were included.

The process of coregistering the binarized ROI masks to the mean MRI resulted in each voxel being assigned a probability (between 0 and 1) that the voxel belongs in the ROI mask. Voxels near ROI borders, including those bordering white matter and CSF, received lower probabilities. Each ROI mask was then thresholded at 0.7, thus eroding ROI borders and reducing partial volume effects (Landau et al, 2015).

Next, in order to generate a single set of ROI masks, ROIs from each time point were combined into a single conjunction mask that only included voxels present at both time points.

These conjunction masks ensured that additional error would not arise from differences in parcellations across time, including differences due to atrophy.

Finally, we used a reference region previously shown to provide the most stable reference over time: the average of both the whole cerebellum and the cerebral white matter (Schwarz, Senjem, et al, 2017). Both were derived from FreeSurfer, with whole cerebellum combining the bilateral cerebellar cortex and cerebellar white matter and cerebral white matter including all white matter in the cerebrum, as described previously (Landau et al, 2015). Both regions underwent the additional preprocessing described above to limit noise over time.

Standardized Uptake Value Ratios (SUVR) were computed for each conjunction mask ROI at each time point, normalizing to the mean counts of the whole cerebellum and the cerebral white matter. Additionally, to assess global amyloid burden, ROIs across most of the neocortex (excluding primary motor and sensory regions) were averaged to compute Mean Cortical SUVR. The following ROIs were included: superior temporal, middle temporal, superior parietal, supramarginal, inferior parietal, medial orbitofrontal, lateral orbitofrontal, superior frontal, caudal middle frontal, rostral middle frontal, pars orbitalis, pars triangularis, pars opercularis, rostral anterior cingulate, caudal anterior cingulate, posterior cingulate, posterior cingulate, isthmus cingulate and precuneus. Rate of accumulation in each ROI and Mean Cortical SUVR was computed as a difference score between baseline and follow-up SUVR.

All participants were classified as amyloid positive or -negative at baseline based on whether they fell above or below a liberal cutoff (SUVR = 0.76) of 2SD above the average Mean Cortical SUVR in young adults, as described in Section 3.3.5. The value of this cutoff is lower than that reported in Study 1 because the inclusion of cerebral white matter to improve

longitudinal stability results in lower SUVRs than using whole cerebellum alone. However, by using the same method for determining the cutoff value, the determination of amyloid status is conceptually identical. Since a major focus of the present study was to detect the earliest changes in amyloid accumulation during the four-year follow-up interval, the more liberal 2SD threshold was chosen instead of the 3SD cutoff, theoretically reducing the probability that individuals categorized as amyloid negative at baseline are false negatives.

4.2.6. Statistical Analysis

Sets of ROIs. Separate analyses were performed on 3 sets of ROIs: a) *A priori*-selected ROIs b) a negative control ROI and c) exploratory ROIs, see Table 4.1.

Table 4.1. Three Sets of ROIs

A priori-selected (n = 6)	Negative control (n = 1)	Exploratory (n = 17)
isthmus cingulate	pericalcarine	caudal anterior cingulate
lateral orbitofrontal		caudal middle frontal
medial orbitofrontal		cuneus
pars orbitalis		fusiform
posterior cingulate		inferior parietal
precuneus		inferior temporal
		lateral occipital
		lingual
		middle temporal
		pars opercularis
		pars triangularis
		rostral anterior cingulate
		rostral middle frontal
		superior frontal
		superior parietal
		superior temporal
		supramarginal

A priori analyses focused on 6 *a priori*-selected regions of interest based on evidence from autopsy (Braak and Braak, 1991) and PET studies (Villain et al, 2012, Sepulcre et al, 2013): early-stage accumulation (lateral OFC, medial OFC, pars orbitalis) and later-stage accumulation (posterior cingulate, isthmus cingulate, precuneus). The negative control analyses

sought to provide support that observed changes in SUVR over time reflect changes in amyloid rather than noise by selecting a region (pericalcarine cortex) that has been demonstrated at autopsy (Braak & Braak, 1991) to be relatively amyloid-free in cognitively-normal adults. The final set of exploratory analyses examined amyloid accumulation in the remainder of the brain, to explore general un-hypothesized trends in amyloid across the neocortex. All regions were expected to show at least some accumulation, but specific *a priori* hypotheses focus on the 6 selected regions and the negative control.

Multiple Comparisons. Since the preliminary analyses were conducted on a subset of the dataset used in the present dissertation, a *p*-value correction for interim analyses was applied, as proposed in Pocock (Pocock, 2005) and commonly used in clinical trials. Therefore, the starting significance level was $p < 0.0294$ instead of $p < 0.05$, and further corrections for multiple comparisons were applied using FDR correction. FDR-corrected *p*-values are reported along with uncorrected *p*-values where appropriate.

Analysis 1: Regional Amyloid Accumulation. The first analysis assessed regional rates of amyloid accumulation over time, and whether some regions exhibit accumulation early while others accumulate later. Early and later stages were conceptualized both in terms of age group, with individuals aged 30-59 considered to be at an earlier stage of the lifespan than 60-89 year olds, as well as baseline amyloid status, with those considered amyloid negative at baseline presumed to potentially be in an earlier disease stage than those who are already positive at baseline. To examine the question with age group as the early vs. late measure, linear mixed models were conducted to test the effects of ROI (within-subject; each ROI), age group (between-subjects; middle age: 30-59 years, older: 60-89 years) and time (repeated measure;

baseline or four-year follow-up) and their interactions on SUVR. Importantly, the age group x ROI x time interaction revealed whether the ROIs exhibited differences in the rate of change in SUVR at early vs. later stages in the adult lifespan. In the *a priori* set of analyses, a planned comparison assessed whether the three *a priori*-selected early-accumulating regions (lateral OFC, medial OFC, pars orbitalis) exhibited greater changes in amyloid early in the lifespan (age 30-59) than the *a priori*-selected later-accumulating ROIs (precuneus, posterior cingulate isthmus cingulate), while later in the lifespan (age 60-89) the rate of accumulation was similar across ROIs. The above analyses were repeated with baseline amyloid status instead of age group, to assess whether different ROIs exhibited differences in the rate of change in SUVR at early vs. later stages in the disease progression. Additionally, the main effect of time within each ROI and each subsample was computed to assess if there were significant changes in amyloid over time.

Analysis 2: Regional Amyloid Accumulation and Cognition. The next analyses addressed whether there was regional specificity in the effects of amyloid accumulation on cognitive decline. Partial correlations were computed between the rate of change in SUVR in each ROI and the rate of change in each cognitive variable, while controlling for baseline mean cortical SUVR, baseline cognitive performance, age, education, sex and APOE.

Analysis 3: Early Regional Amyloid Accumulation and Cognition. The final analyses examined whether regional amyloid accumulation in middle-aged and initially amyloid negative adults was already associated with cognitive decline. These analyses used the partial correlation approach described above, but focused on middle-aged adults and initially amyloid negative adults.

4.3. RESULTS

4.3.1. Demographics

Table 4.2 displays the sample demographics, with means and standard deviations presented for continuous variables, and counts and percentages for categorical variables.

Table 4.2. Sample Demographics. *$p < .05$

	Amyloid Negative ($n = 124$)	Amyloid Positive ($n = 18$)	30-59 year olds ($n = 49$)	60-89 year olds ($n = 93$)
Baseline Age, years	62.82 (13.36)*	74.42 (8.46)*	49.53 (8.53)*	72.07 (7.72)*
Baseline Mean Cortical SUVR	0.70 (0.03)*	0.95 (0.15)*	0.71 (0.04)*	0.75 (0.12)*
Mean Cortical SUVR Change	0.009 (0.03)*	0.07 (0.05)*	0.008 (.03)*	0.02 (.04)*
Education, years)	15.77 (3.89)	16.47 (2.33)	15.50 (1.97)	16.06 (4.38)
Years Between PET scans	3.60 (0.41)*	3.32 (0.13)*	3.56 (0.38)	3.57 (0.41)
Sex, n female (%)	72 (58.1%)	14 (77.8%)	28 (57.1%)	58 (62.4%)
APOE, n e4 carriers, (%)	27 (22.1%)	7 (41%)	16 (34.0%)	18 (19.6%)
Baseline GM volume (mm^3x10,000)	42.38 (4.72)*	39.98 (4.10)*	45.16 (4.67)*	40.45 (3.84)*
GM Atrophy (mm^3 x 10,000)	-1.39 (1.65)	-2.06 (1.49)	-1.12 (1.44)	-1.65 (1.72)
Baseline MMSE	28.48 (1.18)	28.00 (1.24)	28.47 (1.28)	28.40 (1.15)
MMSE change	0.53 (1.51)	0.22 (1.59)	0.58 (1.58)	0.44 (1.49)

Independent *t*-tests and chi square tests were used to test for differences between baseline amyloid positive and -negative adults, as well as between 30-59 year olds and 60-89 year olds. Unsurprisingly, amyloid positive adults were older than amyloid negative adults ($t = -3.57$, $p < .001$), and older adults had a greater baseline Mean Cortical SUVR than middle-aged adults ($t = -2.21$, $p = .029$). These effects also extended to change in amyloid, with amyloid positive adults exhibiting greater change in Mean Cortical SUVR than amyloid negative adults ($t = -6.901$, $p < .001$), and older adults exhibiting greater change than middle-aged adults ($t = -2.11$, $p = .037$). There were no differences between baseline amyloid negative and -positive adults or middle-aged and older adults for education years, sex, APOE ε4 carrier status, baseline MMSE or change in MMSE (Table 4.2). There was a slightly shorter follow-up interval for baseline amyloid positive than amyloid negative adults ($t = 2.891$, $p = .004$), but, given the slow rate of

change in amyloid, a difference of less than four months (Table 4.2) was considered negligible both in terms of change in amyloid and change in cognition. Finally, amyloid negative adults had higher baseline cortical gray matter (GM) volume than amyloid positive adults ($t = 2.04$, $p = .043$), and middle-aged adults had higher volume than older adults ($t = 6.43$, $p < .001$). However, there were no significant differences in the rate of cortical gray matter atrophy.

4.3.2 Regional Amyloid Accumulation

A Priori Regions. It was hypothesized that lateral orbitofrontal, medial orbitofrontal and pars orbitalis cortices would start accumulating amyloid earlier, while posteromedial regions (precuneus, posterior cingulate and isthmus cingulate) would not start accumulating until later. To test this, two complimentary linear mixed models were conducted: a Baseline Amyloid Status x ROI x Time analysis (see Table 4.3) and an Age Group x ROI x Time analysis (see Table 4.4). However, neither 3-way interaction nor the ROI x Time interactions in either analysis reached statistical significance, indicating that the mean rate of change in SUVR did not differ as a function of region, regardless of age group or amyloid status (p's > .90).

Table 4.3. Linear Mixed Model Results for Baseline Amyloid Status x ROI x Time Analysis

	F	***p***
Amyloid Status	336.913	**<0.001**
ROI	79.718	**<0.001**
Time	141.941	**<0.001**
ROI*Time	0.3	0.913
Amyloid Status*ROI	8.773	**<0.001**
Amyloid Status*Time	82.7	**<0.001**
Amyloid Status* ROI*Time	0.295	0.916

As is apparent in Figure 4.4, there are regional differences in SUVR, with the pars orbitalis exhibiting the lowest SUVR while the lateral OFC is highest. Furthermore, these

regions do significantly interact with baseline amyloid status, such that there are greater differences between amyloid positive and-negative adults in the medial OFC and precuneus than in the other four regions. Additionally, there is a significant main effect of time, and an amyloid status x time interaction, reflecting overall increases in SUVR across all regions over time that are greater in initially amyloid positive adults than in initially amyloid negative adults. However, the rate of increase in SUVR does not significantly differ between regions, as demonstrated by the non-significant ROI x Time interaction (Table 4.3). Furthermore, regional differences did not significantly interact with baseline amyloid status, thus failing to support the hypothesis that regional differences would be apparent early in disease progression (in initially amyloid negative adults), while at later stages (in initially amyloid positive adults) all regions would show similarly high rates of accumulation.

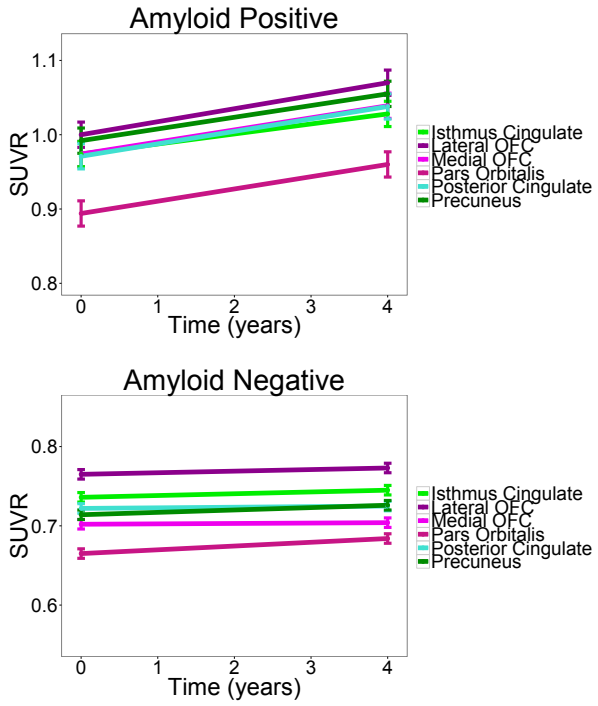

Figure 4.4. Mean Change in SUVR by Region for Amyloid Positive and Amyloid Negative Adults

Similar findings were found when grouping individuals by age, as shown in Table 4.4 and Figure 4.5. There was a significant effect of age group, such that adults aged 60-89 years exhibited greater amyloid than those aged 30-59 years, as well as an age group x time interaction, such that older adults also showed a higher rate of amyloid accumulation over time than middle-aged adults. There were also regional differences in SUVR, with the pars orbitalis again exhibiting the lowest SUVR and the largest difference between middle-aged and older adults. However, these regional differences did not extend to the rate of change in SUVR, regardless of age group.

Table 4.4. Linear Mixed Model Results for Age Group x ROI x Time Analysis

	F	*p*
Age Group	6.687	**0.011**
ROI	144.743	**<0.001**
Time	38.229	**<0.001**
ROI*Time	1.027	0.4
Age Group*ROI	4.633	**<0.001**
Age Group*Time	8.999	**0.003**
Age Group*ROI*Time	0.213	0.957

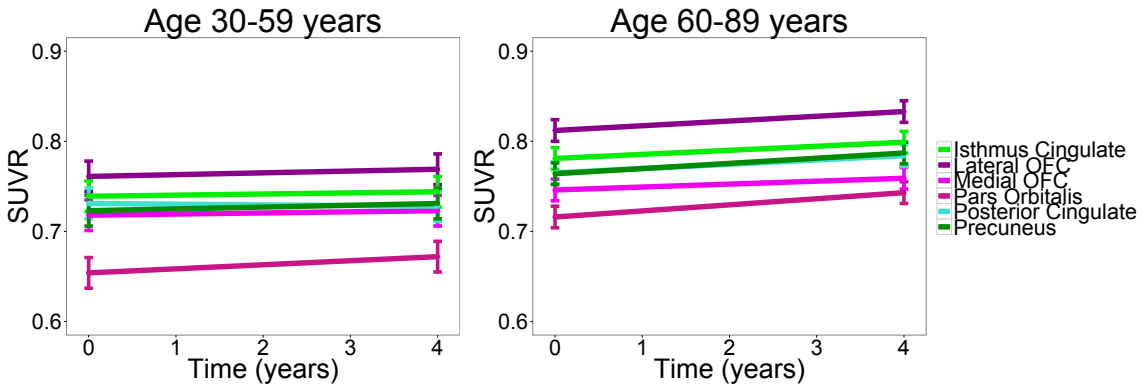

Figure 4.5. Mean Change in SUVR by Region for Middle-Aged and Older Adults

Table 4.5. Mean Changes in SUVR within Each Subgroup for *A Priori* ROIs.

	Amyloid Negative			Amyloid Positive			Age 30-59 years			Age 60-89 years		
	M_D (SE)	*p*	*p, corr*	M_D (SE)	*p*	*p, corr*	M_D (SE)	*p*	*p, corr*	M_D (SE)	*p*	*p, corr*
Pars Orbitalis	**0.018 (0.005)**	**<0.001**	**0.001**	0.067 (0.021)	**0.006**	0.008	**0.018 (0.008)**	**0.021**	0.126	**0.028 (0.007)**	**<0.001**	**<0.001**
Lateral OFC	0.008 (0.004)	0.046	0.055	0.07 (0.019)	**0.002**	0.003	0.008 (0.006)	0.191	0.382	**0.020 (0.006)**	**0.002**	**0.002**
Medial OFC	0.002 (0.003)	0.565	0.565	0.065 (0.016)	**<0.001**	0.002	0.005 (0.006)	0.394	0.473	**0.013 (0.005)**	**0.020**	**0.02**
Isthmus Cingulate	**0.008 (0.003)**	**0.018**	**0.024**	0.054 (0.014)	**0.001**	0.003	0.006 (0.005)	0.260	0.390	**0.019 (0.005)**	**<0.001**	**<0.001**
Posterior Cingulate	0.003 (0.005)	0.492	0.537	0.067 (0.016)	**<0.001**	0.002	-0.003 (0.006)	0.630	0.630	**0.019 (0.005)**	**0.005**	**0.006**
Precuneus	**0.012 (0.004)**	**0.001**	**0.003**	0.062 (0.013)	**<0.001**	0.001	0.009 (0.005)	0.095	0.285	**0.023 (0.005)**	**<0.001**	**<0.001**

While there were not regional differences in mean amyloid accumulation rates, we did however examine which regions (if any) were showing significant accumulation (a main effect of time) within each early and later subgroup. As shown in Table 4.5, the pars orbitalis, isthmus cingulate and precuneus exhibited significant mean change in SUVR over time in initially amyloid negative adults, while the medial OFC, lateral OFC and posterior cingulate did not. In middle-aged adults, only the pars orbitalis exhibited significant change in SUVR over time. In amyloid positive and older adults, all regions exhibited significant increases.

In summary, our findings do not support the hypothesis that the lateral OFC, medial OFC and pars orbitalis are "early-accumulating," while the precuneus, posterior cingulate and isthmus cingulate are "later-accumulating". In contrast, it appears that some of the posteromedial ROIs may already exhibit significant increases in initially amyloid negative adults while the OFC ROIs do not. However, it is important to note that these are mean changes in SUVR, and that does not mean that some individuals are not exhibiting increases in SUVR in these OFC ROIs as well as in the posteromedial ROIs. Figure 4.6 demonstrates that there are individuals exhibiting

high rates of increase in SUVR (in red) even at these earlier stages (younger age, lower initial SUVR) across all ROIs. These figures also demonstrate the variability in SUVR change, with declines (green), no change (yellow) and increases (red) observed. Thus, there is variance in SUVR change within each ROI that may relate to cognitive decline.

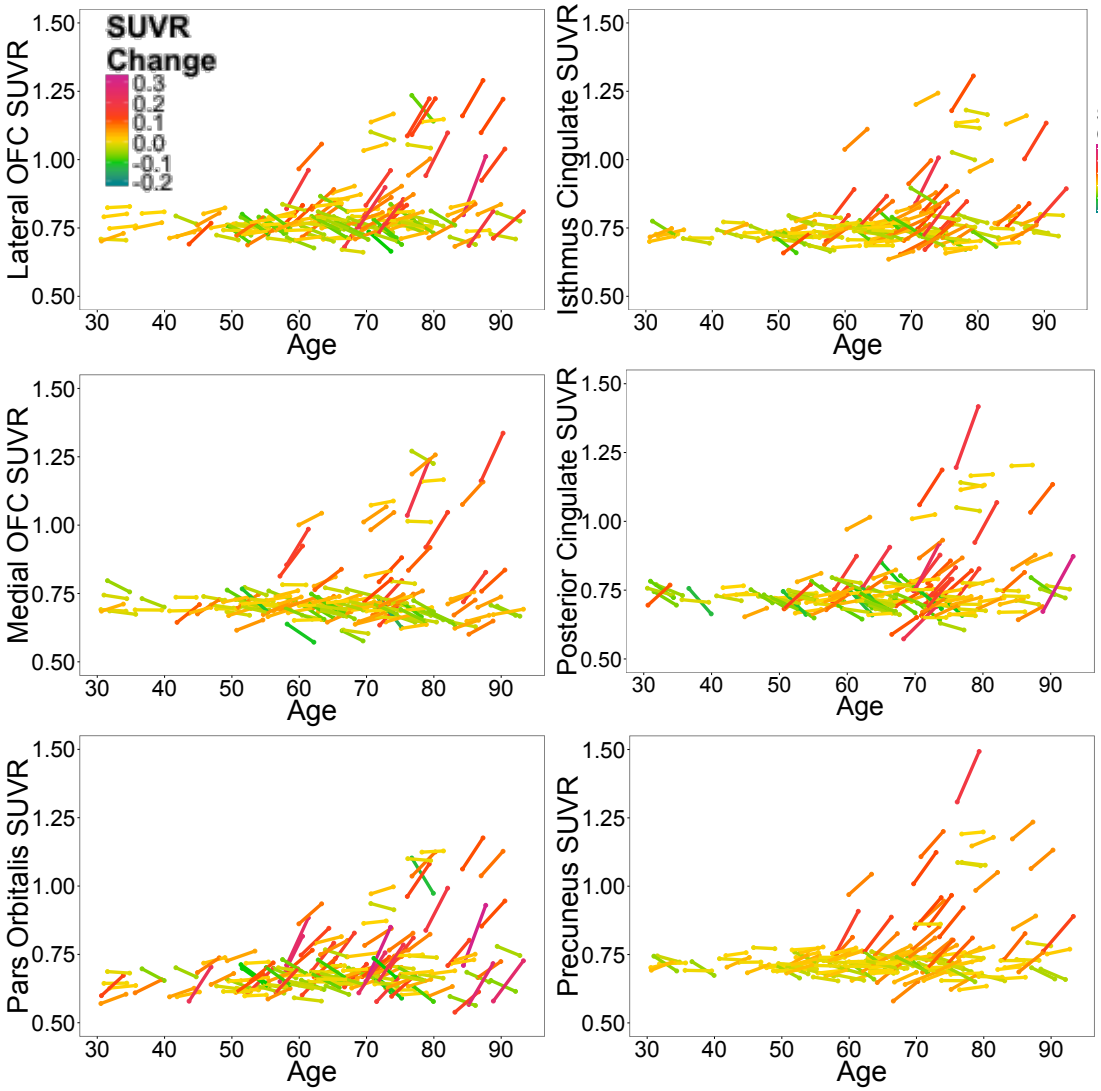

Figure 4.6. Individual Trajectories of Change in Amyloid Across the Adult Lifespan in 6 *A Priori* Regions of Interest. The rate of SUVR change within each region is depicted on a color scale, with warmer colors representing increases and cooler colors representing decreases.

Exploratory Regions. In addition to primary analyses in the *a priori* set of ROIs, the above analyses were repeated to explore changes in SUVR in most of the remaining neocortex. Table 4.6 displays the results of the linear mixed models.

Table 4.6. Linear Mixed Model Results for Exploratory ROIs. The Age Group x ROI x Time analysis is on the left, and the Amyloid Status x ROI x Time Analysis is on the right.

	F	*p*
Age Group	**6.527**	**0.012**
ROI	**127.184**	**<.001**
Time	**155.347**	**<.001**
ROI*Time	**20.717**	**<.001**
Age Group*ROI	**3.959**	**<.001**
Age Group*Time	1.571	0.068
Age Group*ROI*Time	**0.192**	**<.001**

	F	*p*
Amyloid Status	**320.399**	**<0.001**
ROI	**493.668**	**<0.001**
Time	**160.158**	**<0.001**
ROI*Time	**232.095**	**<0.001**
Amyloid Status*ROI	**62.478**	**<0.001**
Amyloid Status*Time	**2.999**	**<0.001**
Amyloid Status* ROI*Time	1.352	0.156

In contrast to the *a priori* set of ROIs, there were significant regional differences in the rate of change in SUVR in these exploratory ROIs (ROI x Time, $p < .001$ in both models), most strongly driven by less change in SUVR over time in the lingual and superior temporal cortices than in the remaining neocortical regions, see Table 4.7.

Additionally, the regional differences in change in SUVR varied significantly by age group, though not by initial amyloid status. While most ROIs exhibited greater change in SUVR over time in older adults than middle-aged adults, the lingual and superior temporal cortices did not exhibit change in either age group, see Table 4.7. The cuneus also contributed to this interaction, with a similar low but significant increase in both middle-aged and older adults.

In summary, similar rates of accumulation are apparent throughout most of the neocortex that are higher in older adults and initially amyloid positive adults than in middle-aged and initially amyloid negative adults. Regional differences in the rate of accumulation are most

apparent when contrasting most of the neocortex with regions that exhibit low accumulation, including lingual gyrus, superior temporal gyrus and the cuneus.

Table 4.7. Mean Changes in SUVR within each subgroup for Exploratory ROIs.

	Amyloid Negative			Amyloid Positive			Middle Aged			Older adults		
	M_D (SE)	*p*	*p, corr*	M_D (SE)	*p*	*p, corr*	M_D (SE)	*p*	*p, corr*	M_D (SE)	*p*	*p, corr*
Caud. Ant. Cingulate	0.006 (0.005)	0.202	0.214	**0.062 (0.016)**	**0.001**	**0.001**	0.004 (0.008)	0.639	0.679	**0.019 (0.006)**	**0.005**	**0.007**
Rost. Ant. Cingulate	0.006 (0.004)	0.113	0.136	**0.069 (0.016)**	**<0.001**	**<0.001**	0.005 (0.006)	0.373	0.453	**0.019 (0.006)**	**0.002**	**0.002**
Caud. Mid. Frontal	**0.018 (0.003)**	**<0.001**	**<0.001**	**0.083 (0.010)**	**<0.001**	**<0.001**	**0.017 (0.006)**	**0.005**	**0.022**	**0.031 (0.005)**	**<0.001**	**<0.001**
Rost. Mid. Frontal	**0.023 (0.004)**	**<0.001**	**0.005**	**0.100 (0.012)**	**<0.001**	**<0.001**	**0.022 (0.006)**	**0.001**	**0.018**	**0.038 (0.005)**	**<0.001**	**<0.001**
Pars Tri-angularis	**0.014 (0.004)**	**<0.001**	**<0.001**	**0.079 (0.015)**	**<0.001**	**<0.001**	**0.014 (0.006)**	**0.020**	0.048	**0.027 (0.005)**	**<0.001**	**<0.001**
Pars Oper-cularis	**0.013 (0.003)**	**<0.001**	**<0.001**	**0.063 (0.012)**	**<0.001**	**<0.001**	**0.013 (0.005)**	**0.009**	0.030	**0.023 (0.005)**	**<0.001**	**<0.001**
Superior Frontal	**0.010 (0.003)**	**0.004**	**<0.001**	**0.075 (0.012)**	**<0.001**	**<0.001**	0.010 (0.005)	0.059	0.091	**-0.005 (0.005)**	**<0.001**	**<0.001**
Supra-marginal	**0.018 (0.003)**	**<0.001**	**<0.001**	**0.063 (0.011)**	**<0.001**	**<0.001**	**0.015 (0.005)**	**0.002**	**0.018**	**0.028 (0.004)**	**<0.001**	**<0.001**
Superior Parietal	**0.016 (0.003)**	**<0.001**	**<0.001**	**0.069 (0.015)**	**<0.001**	**<0.001**	0.010 (0.005)	0.050	0.085	**0.029 (0.005)**	**<0.001**	**<0.001**
Inferior Parietal	**0.019 (0.003)**	**<0.001**	**<0.001**	**0.075 (0.012)**	**<0.001**	**<0.001**	**0.016 (0.005)**	**0.004**	**0.022**	**0.031 (0.005)**	**<0.001**	**<0.001**
Middle Temporal	**0.011 (0.003)**	**<0.001**	**0.002**	**0.077 (0.015)**	**<0.001**	**<0.001**	0.008 (0.006)	0.180	0.255	**0.026 (0.005)**	**<0.001**	**<0.001**
Fusiform	0.006 (0.004)	0.113	0.136	**0.044 (0.016)**	**<0.001**	**<0.001**	0.005 (0.005)	0.306	0.400	**0.014 (0.005)**	**0.006**	**0.007**
Superior Temporal	-0.002 (0.003)	0.485	0.485	**0.052 (0.013)**	**<0.001**	**<0.001**	0.000 (0.005)	0.963	0.963	0.007 (0.004)	0.065	0.069
Inferior Temporal	**0.015 (0.004)**	**<0.001**	**<0.001**	**0.065 (0.014)**	**<0.001**	**<0.001**	**0.012 (0.006)**	**0.037**	0.070	**0.026 (0.005)**	**<0.001**	**<0.001**
Lateral Occipital	**0.015 (0.003)**	**<0.001**	**<0.001**	**0.070 (0.017)**	**<0.001**	**<0.001**	**0.012 (0.005)**	**0.015**	0.044	**0.028 (0.005)**	**<0.001**	**<0.001**
Cuneus	**0.010 (0.004)**	**0.011**	**0.016**	**0.030 (0.009)**	**0.004**	**0.004**	**0.013 (0.005)**	**0.025**	0.053	**0.012 (0.005)**	**0.01**	**0.011**
Lingual	0.005 (0.003)	0.176	0.198	0.017 (0.013)	0.203	0.203	0.003 (0.005)	0.461	0.522	0.008 (0.005)	0.098	0.098

Figure 4.7 displays the individual variability in change in SUVR across the lifespan in a selected group of 6 of the 17 ROIs, again demonstrating substantial variance in change that may relate to cognitive decline.

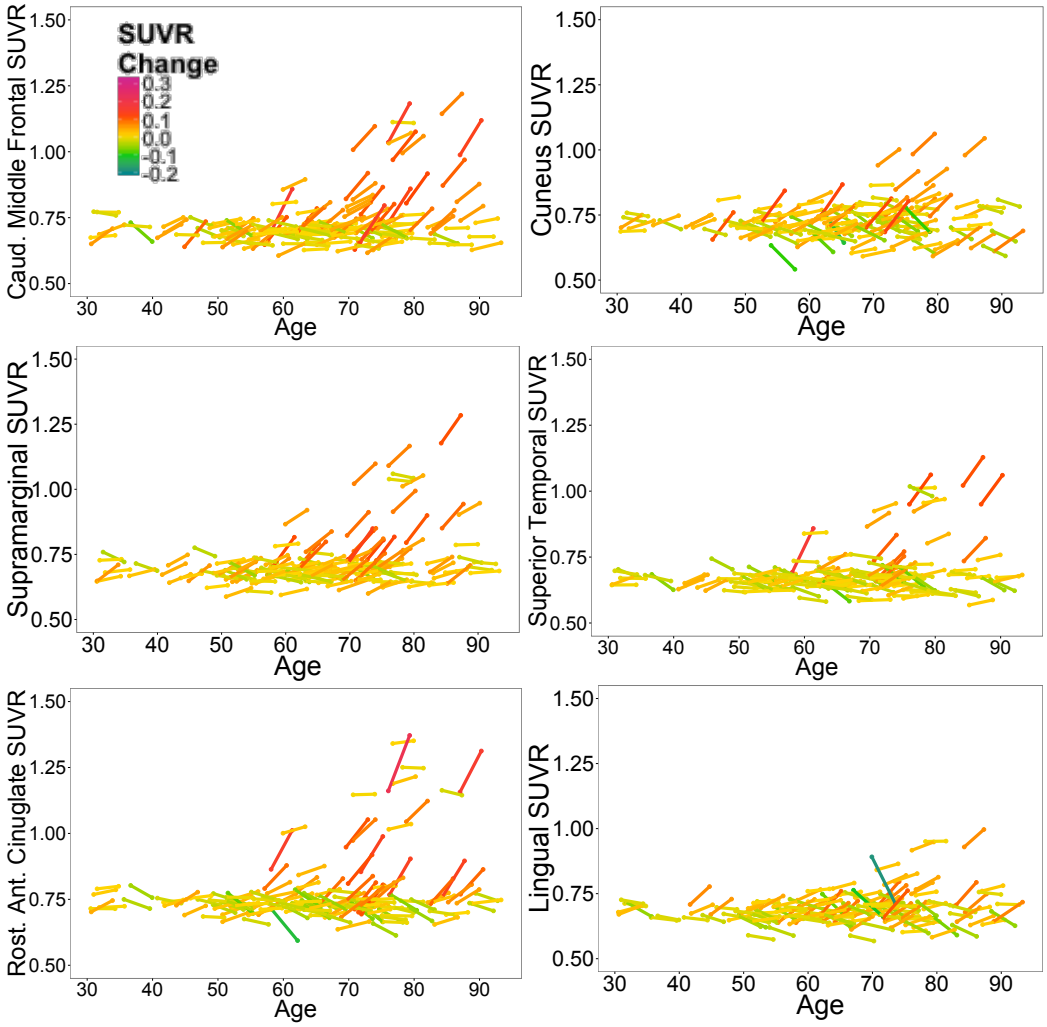

Figure 4.7. Individual Trajectories of Change in Amyloid Across the Adult Lifespan in 6 Exploratory Regions of Interest. The rate of SUVR change within each region is depicted on a color scale, with warmer colors representing increases and cooler colors representing decreases. Higher accumulating regions are shown on the left, and lower accumulating regions are shown on the right.

Negative Control Region. Finally, we also analyzed SUVR change in a negative control ROI (pericalcarine) not expected to show amyloid accumulation except in individuals already

amyloid positive at baseline. Consistent with this hypothesis, initially amyloid negative adults exhibited only marginally significant change in amyloid over time (M_D = 0.006, SE = 0.003, p = 0.055), while initially amyloid positive adults show a small but significant increase in SUVR (M_D = 0.032, SE = 0.012, p = 0.015), as seen in Figure 4.8. The rate of change in SUVR in the pericalcarine cortex was significantly higher in the initially amyloid positive adults than the initially amyloid negative adults (Amyloid Status x Time F(1,147) = 5.393, p = .022).

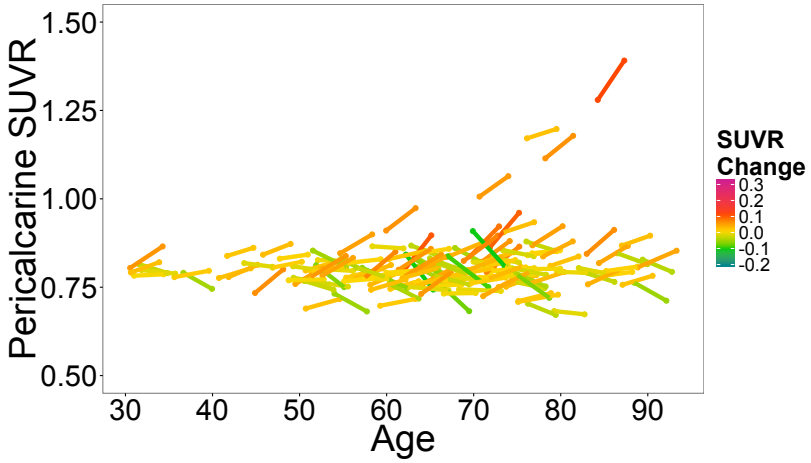

Figure 4.8. Individual Trajectories of Change in Amyloid Across the Adult Lifespan in a Negative Control Region. The rate of SUVR change is depicted on a color scale, with warmer colors representing increases and cooler colors representing decreases.

4.3.3. Regional Amyloid Accumulation and Cognitive Decline.

A priori Regions. The *a priori* hypotheses predicted that accumulation in the lateral OFC, medial OFC and pars orbitalis would be related to decline in reasoning, while accumulation in the posteromedial ROIs would be related to decline in episodic memory. As predicted, greater decline in episodic memory was related to change in SUVR in the 3 *a priori*-selected posteromedial ROIs, with significant partial correlations for the posterior cingulate (r(131) = -0.226, p = 0.009) and precuneus (r(131) =-0.238, p = 0.006), and a trend for isthmus cingulate (r(131) = -0.159, p = .068), see Figure 4.9a-c.

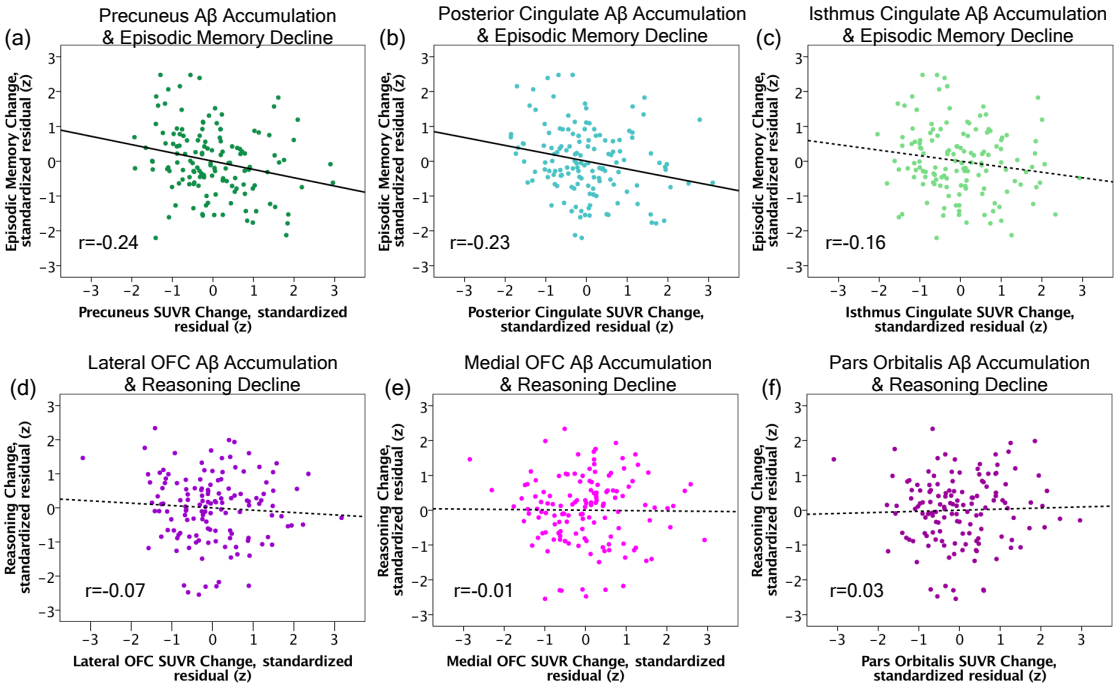

Figure 4.9. Increasing Posteromedial Amyloid Accumulation Associated with Declines in Episodic Memory, OFC Amyloid Accumulation Unrelated to Reasoning. Data are standardized residuals, after partialing out all baseline cognitive performance, age, sex, education and APOE. Increasing changes in SUVR in the precuneus (a), posterior cingulate (b) and isthmus cingulate (c) are associated with declining episodic memory. Increasing change in the lateral OFC (d), medial OFC (e) and pars orbitalis (f) are not associated with reasoning decline.

However, change in reasoning was not related to change in SUVR in the medial OFC ($r(130)=-0.011$, $p=0.901$), lateral OFC ($r(130)=-0.069$, $p=0.433$) or pars orbitalis ($r(130)=0.032$, $p=0.720$), see Figure 4.9d-f. Thus the hypothesis that accumulation in these frontal regions would be related to reasoning decline was not supported by the data, but the hypothesized relationship between episodic memory and posteriomedial ROIs was supported.

In addition to these *a priori* regional amyloid-cognition relationships, additional partial correlations were conducted to explore the relationship between changes in SUVR in these 6 ROIs and changes in each of the 5 cognitive variables. Correlation coefficients, uncorrected *p*-values, and FDR-corrected *p*-values are presented in Table 4.8.

Table 4.8. Partial Correlations between Regional SUVR Change and Cognitive Change for 6 *A Priori* Regions and 5 Cognitive Variables.

		Cognitive Change														
		Episodic Memory			Reasoning			MMSE			Vocabulary			Processing Speed		
		r	*p*	*p*, corr.	*r*	*p*	*p*, corr.	*r*	*p*	*p*, corr.	*r*	*p*	*p*, corr.	*r*	*p*	*p*, corr.
SUVR Change	Isthmus Cingulate	-0.159	0.068	-	-0.085	0.334	0.531	-0.117	0.180	0.531	-0.048	0.584	0.667	-0.059	0.504	0.637
	Posterior Cingulate	**-0.226**	**0.009**	-	**-0.190**	**0.029**	0.232	**-0.251**	**0.004**	0.096	0.012	0.895	0.939	-0.102	0.246	0.531
	Precuneus	**-0.238**	**0.006**	-	-0.105	0.231	0.531	-0.145	0.097	0.388	-0.072	0.411	0.548	-0.078	0.374	0.531
	Lateral OFC	-0.083	0.345	0.531	-0.069	0.433	-	-0.153	0.080	0.384	-0.095	0.279	0.531	-0.082	0.348	0.531
	Medial OFC	0.003	0.968	0.968	-0.011	0.901	-	**-0.194**	**0.026**	0.232	0.011	0.900	0.939	-0.078	0.376	0.531
	Pars Orbitalis	-0.055	0.531	0.637	0.032	0.720	-	-0.171	0.050	0.300	-0.083	0.344	0.531	-0.123	0.161	0.531

In addition to its relationship with episodic memory decline, amyloid accumulation in the posterior cingulate was also related to reasoning decline and MMSE decline (see Figure 4.10), highlighting the posterior cingulate as a sensitive region in the link between amyloid accumulation and cognitive decline. However, these effects do not survive correction for multiple comparisons ($p > .05$).

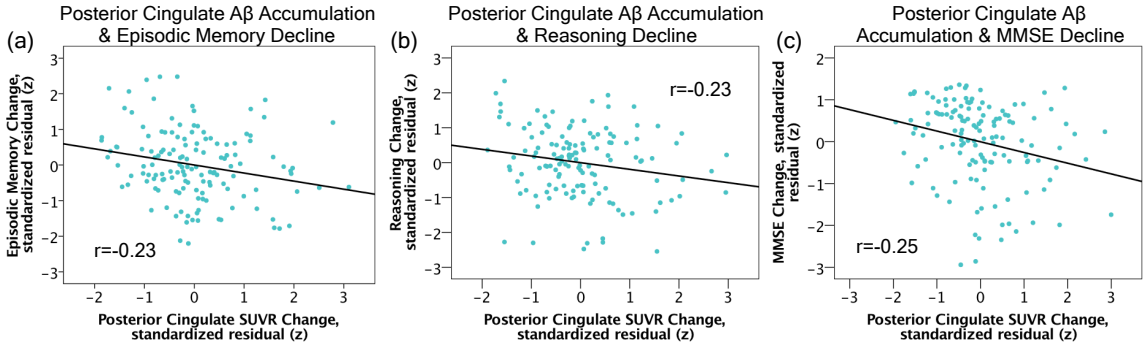

Figure 4.10. Increasing Posterior Cingulate Amyloid Accumulation Associated with Declining Episodic Memory, Reasoning and MMSE.

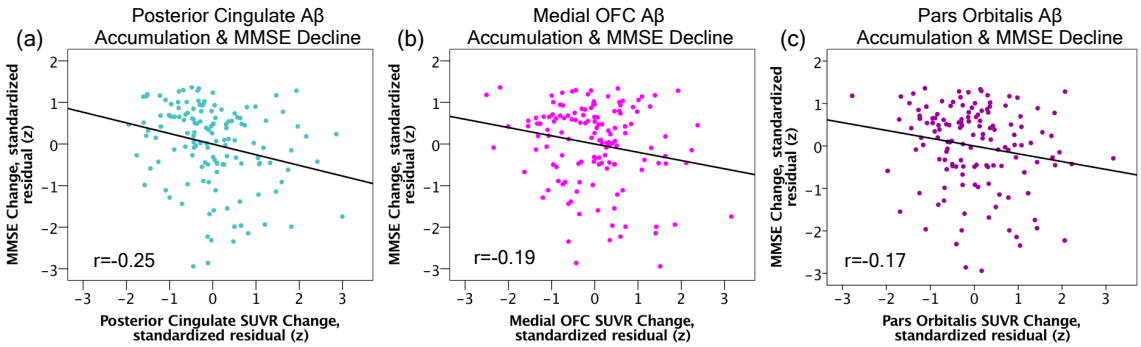

Figure 4.11. Increasing Rate of Amyloid Accumulation across Many Regions Associated with MMSE Decline

Interestingly, there was a relationship between change in SUVR and change in MMSE across multiple regions, with a significant relationship for posterior cingulate and medial OFC as well as trends for precuneus, lateral OFC and pars orbitalis (see Figure 4.11, Table 4.8). While none of the individual effects survived correction for multiple comparisons, it is notable that there was a consistent relationship across multiple regions that did not appear to be regionally specific. In comparison, the relationship between amyloid accumulation and episodic memory decline was more specific to the hypothesized posteromedial regions and was unrelated to accumulation in the OFC ROIs and pars orbitalis.

Exploratory Regions. Additional exploratory analyses were conducted to examine the relationship between amyloid accumulation and cognitive decline in 17 regions that comprise the majority of the remaining neocortex. With 17 regions and 5 cognitive domains, none of the relationships survive corrections for multiple comparisons. However, as the intention with these exploratory analyses was to observe trends in the data, the correlations with uncorrected *p*-values are presented in Table 4.9.

Table 4.9. Partial Correlations between Regional SUVR Change and Cognitive Change for Exploratory ROIs.

			Cognitive Change									
			Episodic Memory		Reasoning		MMSE		Vocabulary		Processing Speed	
			r	p	r	p	r	p	r	p	r	p
SUVR Change	Parietal	Superior	**-0.214**	**0.013**	-0.112	0.201	-0.127	0.148	-0.001	0.987	-0.035	0.69
		Inferior	**-0.247**	**0.004**	-0.074	0.398	**-0.216**	**0.013**	0.021	0.811	-0.078	0.374
		Supramarginal	**-0.252**	**0.003**	-0.018	0.837	**-0.225**	**0.01**	-0.01	0.91	-0.08	0.362
	Occipital	Lateral	**-0.202**	**0.02**	-0.022	0.801	-0.184	0.034	-0.005	0.958	-0.106	0.225
		Cuneus	**-0.235**	**0.007**	0.009	0.917	**-0.231**	**0.008**	-0.099	0.261	-0.044	0.613
		Lingual	-0.108	0.216	0.09	0.307	-0.124	0.156	-0.158	0.071	-0.027	0.762
	Temporal	Inferior	-0.156	0.072	-0.047	0.591	-0.145	0.098	-0.051	0.561	-0.106	0.227
		Middle	-0.17	0.05	0.008	0.931	**-0.239**	**0.006**	-0.024	0.785	-0.144	0.1
		Fusiform	-0.1	0.251	-0.067	0.448	-0.085	0.33	-0.071	0.421	-0.04	0.652
		Superior	-0.145	0.096	0.06	0.496	**-0.196**	**0.024**	-0.074	0.399	-0.148	0.091
	Anterior Cingulate	Rostral	-0.036	0.678	-0.013	0.886	**-0.244**	**0.005**	0.022	0.804	-0.072	0.413
		Caudal	-0.021	0.806	-0.061	0.489	**-0.258**	**0.003**	0.005	0.957	-0.086	0.329
	Frontal	Pars Triangularis	-0.096	0.27	0.08	0.36	-0.165	0.059	-0.053	0.542	-0.156	0.074
		Pars Opercularis	-0.144	0.098	0.027	0.759	-0.168	0.054	0.005	0.956	-0.121	0.168
		Caudal Middle	-0.043	0.623	-0.011	0.898	-0.101	0.249	-0.033	0.705	-0.067	0.444
		Rostral Middle	-0.105	0.23	0.009	0.918	-0.162	0.064	-0.089	0.311	-0.144	0.1
		Superior	-0.095	0.276	-0.04	0.645	-0.144	0.099	-0.004	0.961	-0.078	0.373

Interestingly, patterns similar to those observed in the *a priori* regions were found, further attesting to a more regionally specific relationship between amyloid accumulation and episodic memory decline and a global relationship between amyloid accumulation and MMSE decline.

In addition to a relationship between episodic memory decline and amyloid accumulation in the posterior cingulate and precuneus, an association was also detected for all parietal regions, lateral occipital, and cuneus cortices (Figure 4.12).

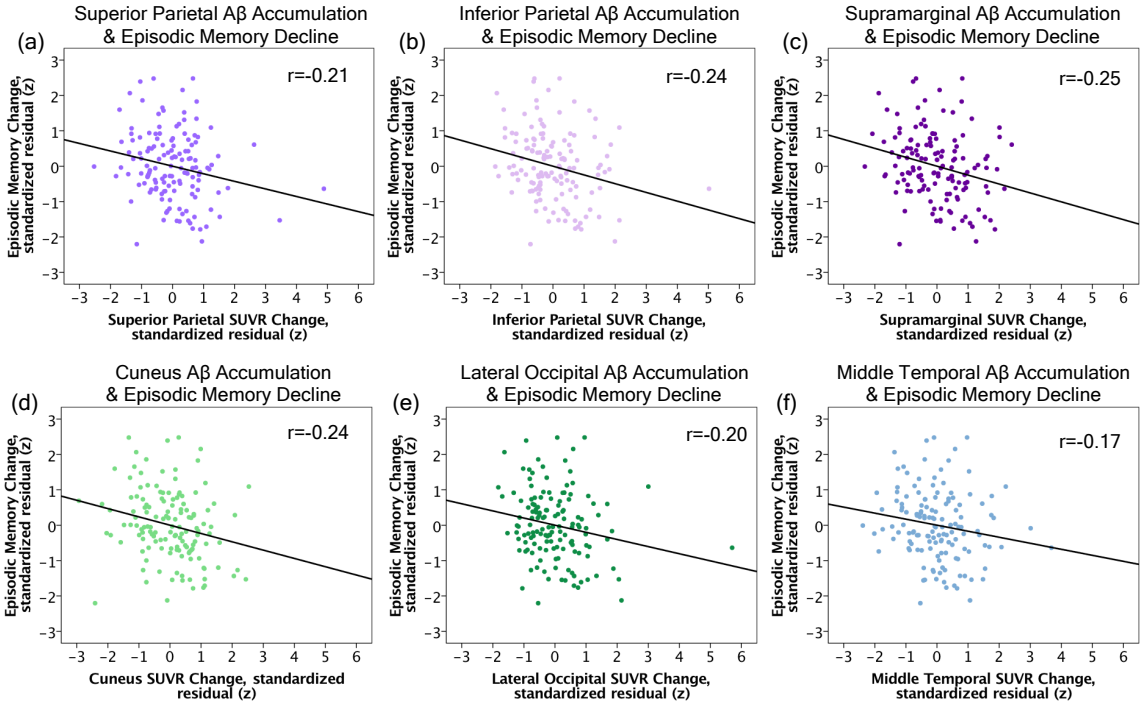

Figure 4.12. Increasing Regional Amyloid Accumulation Across Multiple Posterior Regions Associated with Declining Episodic Memory

There was not a significant association between regional amyloid accumulation and episodic memory decline for any frontal or anterior cingulate regions, despite many individuals exhibiting change in SUVR in these regions. Thus there is evidence that declining episodic memory is specifically related to increasing amyloid accumulation in predominately posterior ROIs.

In contrast, the relationship between amyloid accumulation and MMSE decline that was present across multiple regions in the *a priori* set was also present across most of the remaining neocortex in the exploratory set (see Table 4.9). This indicates that decline on MMSE, a measure of global cognition sensitive to pathological changes rather than normal aging, may be related to more global changes in amyloid. Follow-up analyses were conducted assessing the relationship between Mean Cortical SUVR change and MMSE change, and increasing amyloid

accumulation across the neocortex was associated with increasing decline in MMSE performance ($r(130)=-0.239$, $p=0.006$), see Figure 4.13.

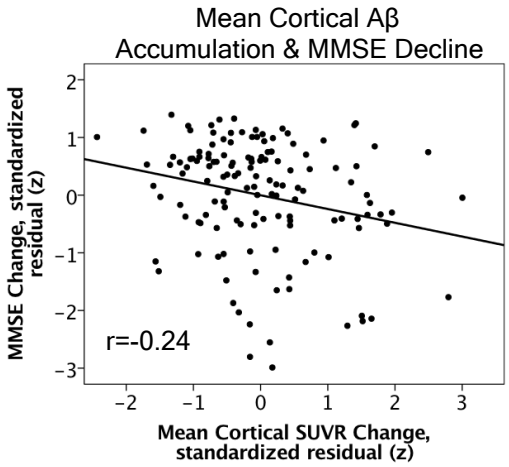

Figure 4.13. Increasing Global Amyloid Accumulation Associated with Declining MMSE

Increasing Mean Cortical SUVR change was also marginally significantly associated with episodic memory decline ($r(131)=-0.182$, $p=0.036$) at the significance level of 0.0294 (due to interim analysis), or significant at the conventional significance level of 0.05. Thus it is possible to detect a relationship between change in amyloid and episodic memory decline using a global measure of amyloid burden, but the effect is driven by accumulation in more posterior regions.

In summary, across both the *a priori* and exploratory sets of ROIs, two patterns emerge: 1) a regional-specific relationship between amyloid accumulation in predominately posterior regions and episodic memory and 2) a regionally nonspecific relationship between global changes in amyloid and declines in global cognition. Specific *a priori* hypotheses about frontal amyloid accumulation and reasoning decline were not supported by the data.

4.3.4. Early Regional Amyloid Accumulation and Cognitive Decline in Initially Amyloid Negative Adults

Next, additional analyses were conducted within initially amyloid negative adults only, to assess whether a relationship between regional amyloid accumulation and cognitive decline was already apparent at this early stage. It was hypothesized that reasoning decline may be particularly sensitive to amyloid accumulation in the OFC. However, as in the full sample analysis, there was not a significant relationship between reasoning decline and amyloid accumulation in lateral OFC ($r(113)=0.032$, $p=0.735$), medial OFC ($r(113)=0.062$, $p=0.509$), or pars orbitalis ($r(113)=0.158$, $p=0.092$) in initially amyloid negative adults.

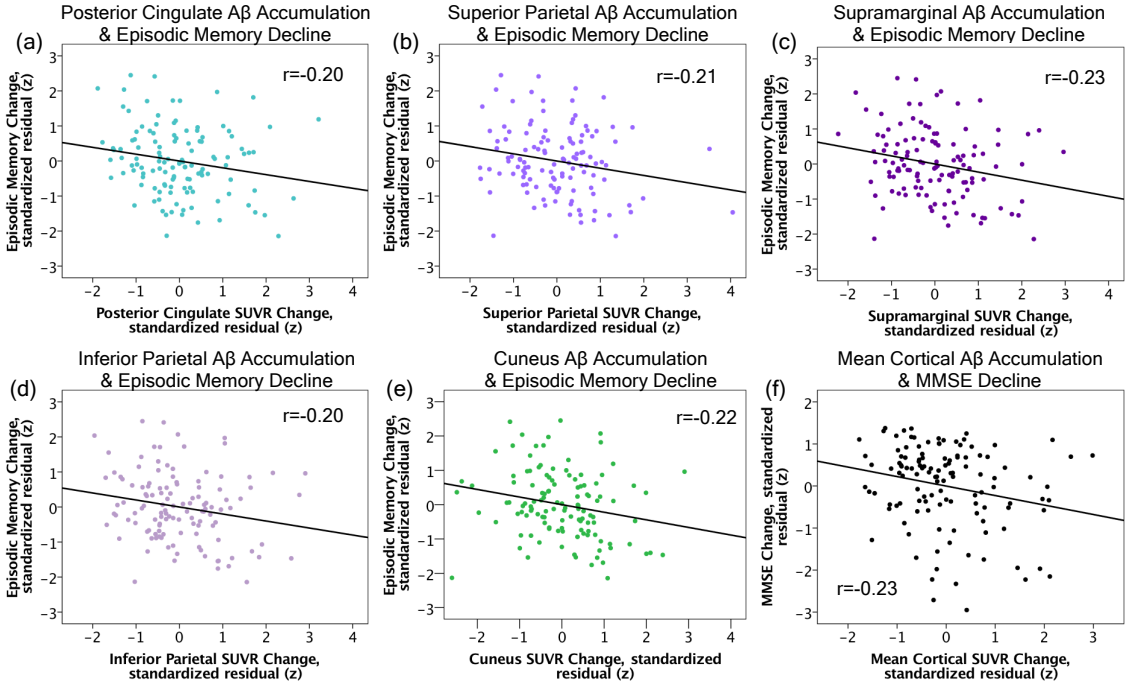

Figure 4.14. Early Relationships between Regional Amyloid Accumulation and Cognitive Decline in Initially Amyloid Negative Adults. (a-e) Increasing rate of accumulation in posterior regions relates to greater episodic memory decline in initially amyloid negative adults. (f) Increasing global amyloid accumulation associated with declining MMSE performance.

Importantly, the relationship reported in the full sample between episodic memory decline and increasing SUVR change remained significant in amyloid negative adults for posterior cingulate (r(114)=-0.195, p=0.036), superior parietal (r(114)=-0.206, p=0.027), inferior parietal (r(114)=-0.200, p=0.031), supramarginal (r(114)=-0.231, p=0.013) and cuneus (r(114)=-0.221, p=0.017), as well as a trend for precuneus (r(114)=-0.181, p=0.052), see Figure 4.14. With the adjusted significance level of 0.0294 to account for the interim analysis, the results for posterior cingulate and inferior parietal cortices were reduced to trends.

Unlike in the full sample, mean cortical SUVR change was not significantly related to episodic memory decline (r(114)=-0.149, p=0.111). Thus at this earlier stage, the relationship between amyloid accumulation and episodic memory decline is even more regionally specific, emphasizing the necessity of examining regional amyloid accumulation rather than a global measure of amyloid accumulation to assess the earliest stages of preclinical AD. However, it is notable that MMSE decline remains significantly associated with increasing Mean Cortical SUVR Change (r(113)=-0.226, p=.015), see Figure 4.14f.

4.3.6. Early Regional Amyloid Accumulation and Cognitive Decline in 30-59 Year Olds

Next, additional analyses were conducted in the group of adults aged 30-59 years selectively, to assess whether a relationship between regional amyloid accumulation and cognitive decline was already apparent at this early stage in the lifespan. As observed in previous analyses, there was not a significant relationship between reasoning decline and SUVR change in the lateral OFC (r(38)=-0.021, p=0.897), medial OFC (r(38)=0.138, p=0.397) and pars orbitalis (r(38)=-0.047, p=0.774). Importantly, some of the previously detected relationships between regional amyloid accumulation and episodic memory decline survived when focusing on middle-

aged adults, including those for the supramarginal (r(38)=-0.312, p=0.047), cuneus (r(38)=-0.310, p=0.049), and lateral occipital cortices (r(38)=-0.360, p=0.021), though only the lateral occipital cortex remained significant at the adjusted significance level of 0.0294, see Figure 4.15. Trends were also observed for the superior parietal (r(38)=-0.299, p=0.057) and inferior parietal cortices (r(38)=-0.290, p=0.066), but the posterior cingulate (r(38)=-0.210, p=0.188) and precuneus (r(38)=-0.22, p=0.164) were not significant in this smaller sample.

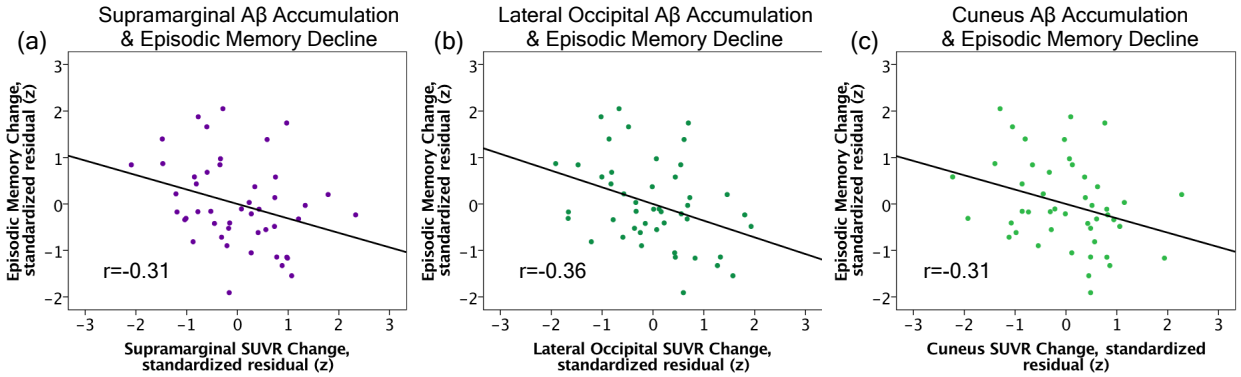

Figure 4.15. Early Relationships between Posterior Amyloid Accumulation and Episodic Memory Decline in Middle-Aged Adults

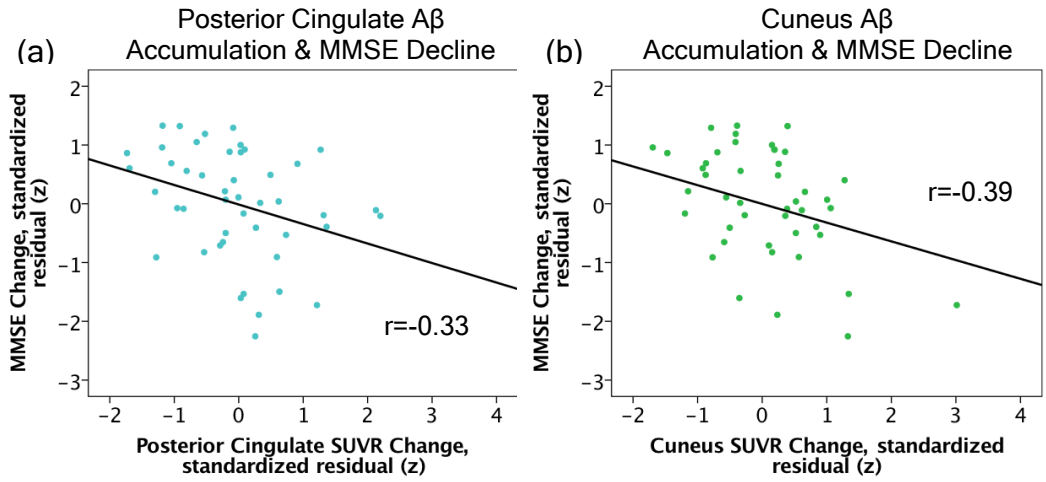

Figure 4.16. Early Relationships between Posterior Amyloid Accumulation and MMSE Decline in Middle-Aged Adults

The relationship between MMSE and amyloid accumulation was more regionally specific in middle-aged adults. The only significant relationships detected in this earlier age range was between declining performance on the MMSE and increasing SUVR change in the posterior cingulate (r(38)=-0.326, p=0.040) and cuneus (r(38)=-0.387, p=0.014), see Figure 4.16. The effect for posterior cingulate was reduced to a trend when using the adjusted significance level of 0.0294, though it should also be noted that in this smaller sample the correlation coefficient required for the effects to reach statistical significance at p=0.05 was higher (r ranges from -0.36 to -0.39) than in the full sample (r ranges from -0.19 to -0.25). The rate of change in Mean Cortical SUVR was not related to MMSE decline (r(38)=-0.170, p=0.295) or episodic memory decline (r(38)=-0.155, p=0.335) in the middle-aged sample, emphasizing the importance of utilizing regional changes in SUVR to detect relationships between amyloid and cognition at this earlier stage in the lifespan.

4.3.7. Additional Control Analyses

Negative Control Region. In order to provide evidence that the observed relationship between regional SUVR change and cognitive decline reflects amyloid pathology, additional analyses were conducted focusing on a negative control region that does not typically deposit amyloid until very late: the pericalcarine cortex. Importantly, there were no significant relationships between amyloid accumulation and any cognitive domain (episodic memory: r(131)=-0.128, p=0.141; MMSE: r(130)=-0.124, p=0.157; reasoning: r(130)=0.010, p=0.909; processing speed: r(130)=0.007, p=0.934; vocabulary r(130) =-0.145, p=0.097).

Atrophy-Correction. Due to the possibility that regional SUVR change may be confounded with regional atrophy, additional follow-up partial correlations were conducted to

test whether the relationships between regional SUVR changes and cognition reported above remained significant after controlling for regional atrophy. All previously significant correlations were rerun, and for each regional SUVR the corresponding measure of regional change in brain volume was included as a control variable. All effects remained statistically significant after controlling for changes in regional brain volume, see Table A7 in the appendix. Furthermore, the observed effects also remained significant after controlling for total cortical gray matter atrophy (see Table A8) or hippocampal atrophy (see Table A9).

Baseline Amyloid Status. Since SUVR is not normally distributed, additional analyses were also conducted with Baseline Amyloid Status (positive or negative) as a covariate in place of continuous SUVR in the full sample analyses. While the relationships between regional amyloid accumulation and cognitive decline were weaker, the pattern of significance remained the same, see table A10 in the appendix**.**

4.4. DISCUSSION

Study 2 of the present dissertation demonstrated that faster rates of amyloid accumulation are associated with faster rates of cognitive decline. Importantly, the relationship between the rate of amyloid accumulation and the rate of decline in episodic memory was regionally specific, with posterior regions including the posterior cingulate, parietal and occipital cortices driving the relationship. Additionally, a global relationship was detected between increasing amyloid accumulation throughout the neocortex and declining MMSE performance, which was also apparent in initially amyloid negative adults. Furthermore, the relationships between amyloid accumulation and declining episodic memory and MMSE were apparent early in the disease progression (in initially amyloid negative adults) and early in the lifespan (in middle-aged

adults). In these subsamples, regionally specific relationships were again detected between posterior amyloid accumulation and cognitive decline, suggesting these regions may be useful in monitoring progression of amyloid pathology and its relationship to cognitive decline from a very early stage. It was hypothesized that the OFC would be a useful regional marker of early amyloid accumulation and demonstrate an early relationship with reasoning decline, but these hypotheses were not supported in the present study.

4.4.1. The Rate of Change in Amyloid Relates to Rate of Change in Cognition

The present study demonstrated a relationship between an increasing rate of amyloid accumulation and an increasingly negative trajectory of cognitive change. To our knowledge, the only study to date to examine change in amyloid and change in cognition (Villemagne et al, 2013) found that changes in mean cortical SUVR were related to cognitive decline, but not after controlling for baseline amyloid burden. Because a higher rate of accumulation is typically observed in cognitively normal adults who start out with higher amyloid, those results suggested that change in amyloid does not provide additional information over baseline amyloid burden about episodic memory decline. However, our results indicate that, even after accounting for baseline amyloid burden, faster rates of amyloid accumulation are related to faster episodic memory decline in cognitively normal adults. Thus, the rate of amyloid accumulation provides additional information about the rate of cognitive decline that is not provided by baseline amyloid burden alone. Furthermore, this provides important evidence that amyloid and cognition are changing together. In combination with the results of Study 1, these findings provide further support for amyloid as an important marker of cognitively normal individuals on a pathological trajectory.

4.4.2. Posterior Amyloid Accumulation and Episodic Memory Decline

Importantly, the relationship between amyloid accumulation and episodic memory decline was regionally specific. While global change in amyloid, as measured by Mean Cortical SUVR, was related to episodic memory decline, it was driven by a relationship between increasing amyloid accumulation in posterior regions and greater episodic memory decline. In the *a priori* set of analyses, the hypothesized relationship between posteromedial regions and episodic memory decline was detected. Expanding the analysis into the remaining neocortex revealed a relationship between increasing amyloid accumulation and declining episodic memory for multiple regions, including all regions of the parietal lobe, and parts of the occipital lobe (cuneus and lateral occipital cortices). Interestingly, functional neuroimaging studies have identified the posterior cingulate/precuneus and the angular gyrus (inferior parietal cortex in the atlas used in the present study) as posterior nodes of a core episodic memory network (Rugg & Vilberg, 2013). Many of the remaining posterior regions have shown functional connectivity with these nodes of core memory network, or have shown activation during episodic memory in a more task-dependent manner (Park, Kennedy, Rodrigue, Hebrank, & Park, 2013; Sestieri, Corbetta, Romani, & Shulman, 2011; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009). It is also notable that amyloid accumulation among these regions is highly inter-correlated. Therefore the significance in each individual region likely reflects a more general relationship between amyloid accumulation in posterior regions and episodic memory decline.

This evidence that amyloid accumulation in regions important for episodic memory relates to episodic memory decline supports the possibility that amyloid has detrimental local effects on neural circuitry. However, because these regions in the episodic memory network are

functionally connected to the MTL, it is also possible that amyloid accumulation in these regions results in greater proliferation of tau in the MTL, and that MTL tau is actually mediating the observed relationship between amyloid accumulation and cognitive decline (discussed further in Section 4.4.8). More work is therefore needed using functional neuroimaging and tau PET imaging to more directly address the local relationships between amyloid accumulation, tau, and neural activity.

The observed regional specificity, as well as the possibility that it may reflect local effects of amyloid, is further predicated on the lack of an observed relationship between amyloid accumulation in frontal and anterior cingulate regions and episodic memory decline. Notably, the medial prefrontal cortex has also been identified as part of a core memory network, but no association between amyloid accumulation and episodic memory decline was detected. It might be predicted that if posterior regions important for memory exhibit a relationship between amyloid accumulation and episodic memory decline, that frontal regions important for memory should as well. However, previous studies have demonstrated dissociations between posterior and anterior networks supporting episodic memory (Sestieri et al, 2011; Uddin et al, 2009). Evidence also suggests that the medial prefrontal cortex is primarily involved with more autobiographical memory, while posterior regions are more closely related to the type of verbal recollection assessed in the present study (McDermott, Szpunar, & Christ, 2009; Svoboda, McKinnon, & Levine, 2006; Wagner, Shannon, Kahn, & Buckner, 2005). Thus despite evidence that frontal regions are also important for episodic memory decline, the lack of findings indicating a link between frontal amyloid accumulation and episodic memory decline does not preclude a local effect of posterior amyloid accumulation on episodic memory decline.

In summary, Study 2 found novel evidence that increasing amyloid accumulation in posterior regions is related to episodic memory decline in cognitively normal adults. These findings suggest that posterior regions, particularly the posterior cingulate and parietal cortices, are important regions to target in future studies examining the link between amyloid and episodic memory decline cognitively normal adults. Furthermore, future research incorporating both tau and functional neuroimaging will help to better understand the nature of this regionally specific relationship between posterior amyloid and episodic memory.

4.4.3. Global Amyloid Accumulation and Declining MMSE

In contrast to the regionally specific relationship between amyloid accumulation and episodic memory, a global relationship was detected between increasing amyloid accumulation across most of the neocortex and increasing MMSE decline. Paralleling the global nature of the effect of amyloid accumulation, the MMSE is a measure of global cognition, designed to detect cognitive impairment related to AD pathology. Changes on the MMSE may therefore reflect broader changes in cognitive functioning that may be a consequence of the overall increase in amyloid burden, rather than local increases in any specific region necessary to perform a specific function.

Other studies, including Study 1 of the present dissertation, have attested to the sensitivity of the MMSE to the effects of amyloid deposition, both cross-sectionally (for review, see Hedden et al, 2013) and longitudinally using baseline amyloid rather than change in amyloid (Doraiswamy et al, 2014; Farrell et al, 2017; Kawas et al, 2013; Mormino et al, 2014a; Petersen et al, 2016; Resnick et al, 2010). It is important to acknowledge, however, the limited variance in performance on the MMSE in cognitively normal adults. At baseline, performance ranged from

26 to 30, and even at follow-up the range was only 25 to 30. Importantly, change in the MMSE was normally distributed in the sample, with changes ranging from -4 to +4. The detected relationship between amyloid accumulation across the neocortex and MMSE decline resulted from improvements over time at low or negative rates of accumulations and declines at high rates of amyloid accumulation. This is consistent with the findings reported in Study 1, with less amyloid related to practice effects and greater baseline amyloid related to declines in MMSE. As mentioned in Section 3.5.5, while other measures used in the present study were designed to exhibit variance in cognitive ability in a normal population, the MMSE was designed to be specific to pathological change. Thus, even with the limited variance in change in the MMSE, it appears to be sensitive to the global effects of amyloid accumulation in cognitively normal adults.

4.4.4. Early Relationship Between Amyloid Accumulation and Cognitive Decline

Importantly, early relationships between increasing amyloid accumulation and declining cognition were apparent at early stages both in the disease progression (initially amyloid negative adults) as well as in the lifespan (middle-aged adults). In initially amyloid negative adults, increasing posterior amyloid accumulation, including the posterior cingulate, superior parietal, inferior parietal, supramarginal and cuneus cortices, was associated with an increasing rate of decline in episodic memory. Similarly, in middle-aged adults, episodic memory decline was significantly associated with amyloid accumulation in supramarginal, cuneus and lateral occipital cortices, and marginally associated with superior and inferior parietal cortices. Importantly, the rate of global amyloid accumulation was unrelated to episodic memory within both groups, attesting to the regional specificity of this relationship at earlier stages. These

results suggest that more posterior regions, particularly in posterior cingulate, parietal and occipital lobes, may be useful regions to detect amyloid pathology early in the disease progression and monitor its effects on episodic memory.

These results support other recent findings that suggested the possibility of early effects of amyloid on episodic memory. One study found marginally significant relationships between relatively high amyloid burden within the amyloid negative range at baseline and cognitive decline (Mormino et al, 2014b). Additionally, another study (Insel et al, 2016) found evidence of a relationship between cognitive decline and baseline amyloid deposition below the amyloid positivity threshold using CSF-amyloid. However, this study used a conservative threshold for positivity, and therefore sub-threshold false negatives may have driven the relationship between CSF-amyloid and cognitive decline. In Study 1, relatively high baseline amyloid burden did not predict cognitive decline in middle-aged or initially amyloid negative adults. However, by leveraging the longitudinal measurement of increasing regional amyloid burden within both initially amyloid negative adults and middle-aged adults, it was possible to detect early effects of amyloid on episodic memory decline. These results suggest that regional changes in posterior regions are important and sensitive targets for research aimed at understanding the earliest consequences of amyloid pathology.

A relationship between increasing amyloid accumulation and MMSE decline was also apparent at this early stage, though the regionally specificity of the effects are differed between amyloid negative and middle-aged adults. In initially amyloid negative adults, the relationship between MMSE and amyloid accumulation remained global, with change in mean cortical SUVR related to MMSE decline. In contrast, in middle-aged adults, the relationship between

MMSE and Mean Cortical SUVR was no longer significant, and a relationship between MMSE decline and amyloid accumulation focused on the posterior cingulate and cuneus. Since the MMSE includes tests of episodic memory, it may be that in middle-aged adults amyloid-related declines in MMSE reflects changes in memory, while in the larger amyloid negative sample the changes are more global.

Overall, this observed early relationship between amyloid accumulation and MMSE change result was surprising, given that changes in cognition severe enough to be detected by the MMSE were not expected this early in the disease progression. However, it is possible that due to the specificity of the MMSE to detecting the effects of pathology and the resulting lack of aging effects on MMSE performance, that even a very subtle change in MMSE is detectable at this early stage.

In summary, the present dissertation detected early relationships between a greater rate of regional amyloid accumulation and faster decline in episodic memory and MMSE performance over approximately four years. Furthermore, these findings highlight the importance of posterior regions, including the posterior cingulate, parietal and occipital cortices, for detecting amyloid-related changes in cognition that are already apparent both early in the lifespan as well as early in the disease course.

4.4.5. OFC Amyloid Accumulation and Reasoning Decline

While the present study found a relationship between amyloid accumulation in posterior regions and episodic memory decline even at early stages, this relationship was not hypothesized to be present early. It was hypothesized that amyloid accumulation, specifically in posteromedial regions, would relate to episodic memory decline, but that this relationship would

primarily be apparent later, in older adults and individuals who were already amyloid positive at baseline. The results, however, indicate that subtle changes in episodic memory are apparent at early stages. In contrast, the OFC and pars orbitalis that were hypothesized to start accumulating amyloid early and exhibit a relationship with reasoning decline. The present study, however, failed to detect a relationship between amyloid accumulation in OFC regions and reasoning decline. The rate of accumulation in these OFC regions was not related to any cognitive domain except MMSE, which was related to accumulation across most of the neocortex and not specific to the OFC. Thus, the present findings do not support the hypothesis that early accumulation in the OFC has subtle but detectable cognitive consequences. This lack of findings, however, may be due to difficulties reliably detecting OFC amyloid accumulation at early stages, as discussed further in Section 4.4.10. Additionally, it is possible that a cognitive measure more directly related to OFC function than reasoning, such as a measure of emotional decision-making, may be more sensitive to OFC amyloid accumulation.

The present findings also do not support the hypothesis that reasoning might decline in advance of episodic memory. While there was a weak relationship between increasing amyloid accumulation in the posterior cingulate and reasoning decline, it was not present when restricted to initially amyloid negative or middle-aged adults. These findings suggest that while reasoning may be weakly related to amyloid, declines in episodic memory may precede effects on reasoning.

4.4.6. Amyloid-Related Cognitive Decline Absent in Negative Control Region

Importantly, there was no significant relationship between SUVR change in the negative control region (pericalcarine cortex) and any cognitive domain. This helps to confirm that the

observed relationships between amyloid and cognitive decline are not driven by changes in SUVR unrelated to amyloid pathology.

4.4.7. Amyloid-Related Cognitive Decline Maintained After Atrophy-Correction

It was considered that regional changes in SUVR might be driven by local atrophy, resulting in a relationship between SUVR change and cognitive decline that is actually mediated by local atrophy. This might occur if atrophy-related discrepancies resulted in poor mapping between the regional masks at either time point and the underlying tissue. Importantly, controlling for local atrophy did not diminish the relationship between regional amyloid accumulation and cognitive decline.

4.4.8. Role of Tau in Amyloid-Related Cognitive Decline

The amyloid cascade hypothesis (Hardy & Selkoe, 2002) and the Preclinical Model of AD (Sperling et al, 2011) posit that amyloid does not directly influence cognitive decline, but acts indirectly through its effects on tau and neurodegeneration. Despite detecting regionally specific effects, particularly between amyloid accumulation in posterior regions important for episodic memory and declines in episodic memory, it is still possible that these effects are mediated by tau. Some findings from the present study, however, provide promising but inconclusive support for independent effects of amyloid on cognitive decline that are not mediated by tau.

First, since amyloid burden is still very low in the middle-aged and initially amyloid negative adults exhibiting episodic memory decline, it is less likely that tau is present in a sufficient quantity to interfere with MTL functioning. A recent tau PET study (Johnson et al, 2016) demonstrated that the spread of tau is detected only in individuals who already exhibit

high global amyloid burden, and likewise that tau is related to episodic memory decline only in individuals with high global amyloid burden. Thus while future studies that measure tau are necessary to conclude that observed effects are not driven by tau, the low amyloid burden at this early stage highlight the possibility that early episodic memory effects may be directly related to amyloid.

Second, while tau was not measured in present study, several measures of neurodegeneration were included. Importantly, neurodegeneration is hypothesized to mediate the effects of tau on cognitive decline in the Preclinical Model of AD (Sperling et al, 2011). As mentioned above, local atrophy did not mediate the relationship between amyloid change and cognitive change. Additional analyses also confirmed that the observed amyloid-related changes in cognition were maintained after accounting for hippocampal atrophy as well as broader neurodegeneration across all cortical gray matter. Together, these findings suggest that the observed amyloid-related changes in cognition are not driven by neurodegeneration. However, it is important to note that neurodegeneration is also a common feature of normal aging (Raz et al, 2005). Thus it is still possible that AD and tau-specific neurodegeneration are mediating the observed relationship between amyloid and cognition, but that the effect is obscured due to age-related neurodegeneration.

Thus while the present study presents interesting findings that raise the possibility of direct effects of amyloid on cognitive decline at early stages, it will be necessary in the future to incorporate tau to fully understand the roles of amyloid, tau and neurodegeneration in cognitive decline in cognitively normal adults.

4.4.9. Correlation not Causation

It is important to note that in the present study we are measuring change in both amyloid and cognition over the same interval. It is thus important to consider that declining cognitive performance may lead to increased deposition of amyloid, rather than amyloid leading (directly or indirectly) to cognitive change. As mentioned in Section 2.8, there is evidence suggesting that poor neural efficiency (which may result in lower cognitive performance) may lead to greater amyloid deposition (Jagust & Mormino, 2011; Lazarov et al, 2005). This is also plausible given that many of the regions found to have relationships between amyloid accumulation and episodic memory decline are part of the default mode network. Failure to suppress the default mode network is known to have negative consequences for memory related to amyloid deposition (Hedden et al, 2009; Huijbers et al, 2014; Kennedy et al, 2012; Sperling et al, 2009; Vannini et al, 2012). Thus it is possible that hyperactivity in these default mode network regions is related both to declining episodic memory and increasing amyloid deposition. Future longitudinal research incorporating functional neuroimaging may help to elucidate the nature of this relationship. However, it is notable that Study 1 of the present dissertation (Farrell et al, 2017), as well as multiple other studies (Lim et al, 2014; Petersen et al, 2016; Villemagne et al, 2013; Wirth et al, 2013), have demonstrated temporal precedence of amyloid over cognitive decline, providing support for the hypothesis that amyloid (directly or indirectly) leads to cognitive decline, rather than cognitive decline leading to amyloid.

4.4.10. Regional Differences in Amyloid Accumulation

In addition to examining the link between regional amyloid accumulation and cognitive decline, the present study also sought to determine whether some regions may start accumulating

amyloid earlier (in middle-aged and initially amyloid negative adults) while others do not start accumulating until later (in older adults and initially amyloid positive adults). Based on evidence from autopsy (Braak & Braak, 1991) and PET imaging studies (Sepulcre et al, 2013; Villain et al, 2012; Villeneuve et al, 2015), it was hypothesized that OFC regions would be early-accumulating while posteromedial regions would be later-accumulating. However, the present data do not support this pattern of findings. This disagreement with previous studies may reflect a few issues in present study, discussed further below.

First, since PET data suggest posteromedial regions begin accumulating directly after OFC regions (Sepulcre et al, 2013; Villeneuve et al, 2015), the OFC and posteromedial regions may be too closely linked in the temporal progression of amyloid pathology to detect differences with gross measures such as age group and baseline amyloid status. Indeed, the present findings indicated that the posteromedial regions qualify as early-accumulating, on the basis that they exhibit significant amyloid accumulation even in individuals who were considered amyloid negative at baseline. Furthermore, early accumulation was observed in many additional neocortical regions in the exploratory dataset that were not expected to exhibit accumulation based on previous evidence the focal nature of early amyloid accumulation. Using middle-age and initial amyloid-negativity as markers of an early stage may not be fine-grained enough to detect the earliest amyloid accumulation in the OFC and distinguish it from the subsequent steps in amyloid pathological progression. Interestingly, regional differences in amyloid accumulation were detected as a function of age group by contrasting most of the neocortex with ROIs that do not start accumulating until very late (including lingual and superior temporal cortices). Thus regional differences in early and later stages of amyloid accumulation may be more apparent

when comparing regions less closely linked in the temporal and spatial progression of amyloid pathology.

Second, the earliest amyloid deposition in the OFC may be too sparse and focal to be detected using a regional approach. Voxel-wise approaches like those used previously (Sepulcre et al, 2013; Villain et al, 2012) may be necessary to detect focal amyloid accumulation. Furthermore, autopsy studies on patients who underwent PET imaging prior to death (Clark et al, 2011; Sojkova et al, 2011) have indicated that florbetapir binds primarily in tissues with high densities of amyloid plaques, rather than in tissue with a lower density of focal deposits, as is observed at the earlierst stage of amyloid pathological progression. The observed changes in SUVR in the OFC may predominately reflect larger increases in amyloid at later stages, when posteromedial regions are also accumulating amyloid. If that is the case, then it would not be expected that regional differences in the rate of amyloid accumulation would be apparent between OFC and posteromedial ROIs.

Third, difficulty detecting small increases in amyloid burden may also reflect issues with the longitudinal reliability of florbetapir PET data. Notably, previous studies demonstrating OFC accumulation in initally amyloid negative adults used a different tracer (PIB), which has less non-specific binding than florbetapir (Klunk et al, 2004; Villemagne et al, 2012; Wong et al, 2010). The higher noise with florbetapir may result in small changes in SUVR that are due solely to changes in non-specific binding and other sources of noise. The present study incorporated multiple preprocessing steps to reduce noise associated with longitudinal PET imaging, but even with these additional steps there is still substantial noise in the data. Joshi et al. (2012) demonstrated with a retest interval of only four weeks, that percent change in SUVR using

florbetapir was 1.5% ± 0.84% in controls aged 35-55. While this test-retest variability may seem small, the magnitude of change in amyloid is low enough that differentiating between real changes in amyloid and test-retest variability can be difficult. This is particularly problematic when dealing with the small changes likely to occur in the OFC at the very earliest stages of amyloid pathology.

Finally, imprecision in the coregistration between PET and MRI (Schwarz, Jones, et al, 2017) may further contribute to poor longitudinal reliability. Importantly, a thorough visual inspection was conducted of MRI and coregistered PET images in the present sample, and individuals with poor PET-MRI coregistration were excluded. However, due to the low spatial resolution of PET, less egregious errors in coregistration are difficult to detect, and thus may contribute to variability in SUVR change that is unrelated to amyloid. As a result, mean changes in amyloid may be obscured by changes in SUVR measurement due to imprecise coregistration. Notably, mean changes in SUVR in early groups were observed primarily for lateral regions, many of which showed no association with cognitive decline in subsequent analyses. Importantly, lateral regions are known to be more susceptible to coregistration errors than medial regions (Bookstein, 2001). As a result, it is difficult to draw any strong conclusions about which regions may exhibit early amyloid accumulation in the present study. However, since the changes likely to be related to coregistration are small, this issue is of less concern when SUVR changes are large. The larger individual changes observed across multiple ROIs provide qualitative evidence that amyloid accumulation is apparent in some middle-aged and initially amyloid negative adults across multiple regions. Furthermore, the relationships between regional SUVR change and cognitive change observed in the present study are primarily driven by

cognitive declines in individuals with high SUVR change, providing confidence that these relationships reflect amyloid rather than coregistration error.

In summary, while the present study failed to detect the hypothesized early-accumulating and later-accumulating regions, this may be due to issues with the present approach as well as current limitations of PET imaging. Future research using a voxel-wise approach may help to clarify the role of the OFC in early AD pathology, especially if tools for PET-MRI coregistration can be optimized. However, the evidence does indicate the amyloid pathology has already started accumulating in posteromedial regions early in the disease progression, and that this accumulation appears to have early effects of episodic memory.

4.4.11. Limitations

In addition to those limitations already discussed, another issue pervading PET research is the lack of a normal distribution for SUVR. Due to these concerns, the amyloid-cognition correlations were repeated using baseline amyloid status instead of continuous SUVR as a control. Importantly, the pattern of findings remained the same when controlling for baseline amyloid status. Multiple comparisons are also an important consideration in the present study. With such a high number of regions, many effects do not survive correction for multiple comparisons, especially in the exploratory dataset. However, it is notable that many of the effects were observed across multiple regions. Finally, it is important to note that the participants in the present study were not evaluated clinically. It is therefore possible that some of the participants may no longer be considered cognitively normal at follow-up. However, regardless of whether some individuals have transitioned to MCI or dementia, the present study

provides important evidence that regional changes in SUVR relates to episodic memory decline in individuals who were cognitively-normal at baseline.

4.5. CONCLUSION

Study 2 of the present dissertation demonstrates a regionally specific relationship between the rate of amyloid accumulation over four years in posterior regions and episodic memory decline. Importantly, this amyloid-cognition relationship is apparent even at early stages, both in the lifespan and in Alzheimer's disease progression. These findings demonstrate the importance of assessing regional changes in amyloid, particularly posterior regions such as the posterior cingulate and parietal lobe, to monitor disease progression from an early stage. Future research is needed to assess whether amyloid may have independent effects on cognitive decline, or if these effects are mediated by tau or other pathologies.

CHAPTER 5

CONCLUDING REMARKS

Understanding the presymptomatic trajectory of Alzheimer's disease in cognitively normal adults is of utmost importance to the potential treatment and prevention of the disease. The predominant school of thought casts amyloid in a central role in the development of AD, initiating a cascade of pathological events thought to lead to dementia. Consequently, anti-amyloid therapies have been developed to remove amyloid plaques from the brain. Clinical trials, however, have repeatedly shown that while these therapies successfully remove amyloid plaques from the brains of AD patients, they do not slow cognitive decline. This result is often explained not as evidence that amyloid is unrelated to cognitive decline in AD, but rather that the critical period for interventions targeting amyloid is earlier in the disease progression, when individuals are still cognitively normal (Sperling et al, 2014). This belief is concordant with evidence (Jack et al, 2010; Jack et al, 2013) that amyloid accumulation occurs primarily in cognitively normal adults, in advance of the appearance of clinical symptoms. Clinical trials such as the A3 trial (Sperling et al, 2014) are therefore increasingly moving toward earlier intervention, testing whether the application of anti-amyloid therapies in middle-aged and amyloid negative adults may prevent the further accumulation of amyloid, as well as downstream pathological events including tau spreading, neurodegeneration and cognitive decline. Thus, it has become critically important to understand the relationship of amyloid pathology to cognitive decline in cognitively normal adults, particularly in middle-aged adults and those who are initially amyloid negative. The present dissertation contributes to our understanding of the

impact of amyloid pathology on cognitive decline in cognitively normal adults, even at this earlier stage, in a number of ways.

First, Study 1 demonstrated that the magnitude of amyloid burden at baseline predicts the rate of cognitive decline over four years, with the most robust amyloid-associated decline observed in episodic memory and more subtle declines in processing speed, vocabulary and MMSE performance. These results concur with a growing body of evidence that greater amyloid burden at baseline is predictive of greater future cognitive decline in cognitively normal adults (Lim et al, 2014; Mormino et al, 2014a; Petersen et al, 2016; Resnick et al, 2010; Villemagne et al, 2013; Wirth et al, 2013). Together, these findings provide support for amyloid as a predictor of subtle changes in cognition in advance of clinical symptoms. Importantly, Study 1 contributes novel evidence that the magnitude of amyloid at baseline provides additional information about the expected rate of future cognitive decline that is not provided by a simple positive/negative classification. Such findings may be useful both in research as well as in clinical practice to develop prognoses for future decline based on current amyloid burden.

Second, Study 2 demonstrated that the rate of change in amyloid is related to the rate of change in both episodic memory and MMSE performance. To our knowledge, this is the first study to demonstrate a relationship between change in amyloid and change in cognition after accounting for baseline amyloid burden. Thus, the present dissertation demonstrates that the rate of change in amyloid provides additional information about the rate of cognitive decline that is not provided by the magnitude of amyloid burden at baseline. Together, Study 1 and 2 demonstrate that different measures of amyloid burden (baseline amyloid positivity, baseline amyloid burden, the rate of change in amyloid burden) all play a role, together and individually,

in predicting future cognitive decline in cognitively normal adults. While continued follow-up is necessary to demonstrate that these individuals will go on to develop dementia, the present study helps to confirm the existence of subtle amyloid-related cognitive decline that may precede the onset of dementia.

Third, Study 2 provided important novel evidence of a regionally specific relationship between amyloid accumulation in posterior regions and episodic memory decline. Importantly, many of the regions for which a relationship between amyloid accumulation and episodic memory decline was detected are known to play an important role in episodic memory (Rugg & Vilberg, 2013). This supports the possibility that amyloid may have detrimental local effects on neural circuitry that results in a direct link between increasing amyloid accumulation and episodic memory decline. However, additional neuroimaging studies are necessary to demonstrate that the relationship between amyloid and episodic memory decline is mediated by impaired activity in these regions. Furthermore, the high degree functional connectivity between these regions and the MTL raises the possibility that these effects may be mediated by tau in the MTL, a common feature in early AD (Braak & Braak, 1991). Regardless of whether this regional specificity reflects direct effects of amyloid or indirect effects via tau, it emphasizes the importance of focusing on changes in amyloid in posterior regions, such as the posterior cingulate, parietal and occipital lobes, to detect amyloid-related declines in episodic memory in cognitively normal adults.

Fourth, the present dissertation provides important evidence that amyloid accumulation is already related to cognitive decline in individuals at an early stage in the disease progression. By leveraging regional changes in amyloid in initially amyloid negative adults in Study 2, we were

able to demonstrate an early relationship between a higher rate of amyloid accumulation across multiple posterior regions and more rapid decline in episodic memory. Notably, Study 1 failed to detect episodic memory decline within initially amyloid negative adults using global amyloid burden at baseline, and Study 2 demonstrated that global amyloid accumulation was also not sensitive to episodic memory decline at this early stage. Together these results indicate that regional change in these specific regions, including the posterior cingulate, parietal lobe and cuneus, provides a sensitive marker of early amyloid-related changes in episodic memory. Importantly, these posterior regions may be useful targets in both research on the early stages of AD as well as in clinical trials aimed at early intervention.

Fifth, the present dissertation yielded novel findings in a rarely studied group: middle-aged adults. As mentioned above, clinical trials are starting to turn their attention to middle-age in order to intervene at an early stage. However, very little is known about amyloid and its relationship to cognition in middle-age, as most studies have focused on older adults. Using the unique sample afforded by the Dallas Lifespan Brain Study, the present dissertation demonstrated relationships between amyloid and cognitive decline even at this early stage in the lifespan. In Study 1, higher baseline amyloid burden predicted greater decline in vocabulary, though this effect was driven by a small group of participants with a genetic vulnerability to earlier onset of AD (APOE ε4 homozygotes). Furthermore, Study 2 was able leverage longitudinal changes in amyloid in posterior regions to detect early amyloid-related changes in episodic memory and MMSE performance in middle-aged adults, while controlling for APOE. Together, these findings indicate that amyloid-related changes in cognition may be detectable at a much earlier stage in the lifespan than researchers typically examine.

Finally, the present dissertation provides an important step toward fully elucidating the progression from health to dementia in Alzheimer's disease, particularly the earliest stages. Future work will help to provide a more complete picture by incorporating tau into our understanding of the early stages of AD. The Preclinical Model of AD (Sperling et al, 2011) posits that cognitive decline is a consequence of tau and neurodegeneration rather than amyloid deposition, and thus that the relationship between amyloid and cognitive decline is mediated by tau. Importantly, Study 2 detected relationships between regional amyloid accumulation and cognitive decline at an early stage (in both middle-aged and initially amyloid negative adults), when tau is less likely to be present and driving cognitive decline. Furthermore, Study 2 demonstrated that the relationship between regional changes in amyloid and cognitive decline remained significant after controlling for measures of neurodegeneration that included local atrophy, total cortical gray matter atrophy and hippocampal atrophy. The Preclinical Model of AD posits that tau's effects on cognition are mediated by neurodegeneration, and therefore these findings provide some evidence that there may potentially be changes in cognition that are directly related to amyloid. However, neurodegeneration is not specific to AD pathology and is a common feature of normal aging (Raz et al, 2005), and thus it is not possible differentiate AD and tau-specific neurodegeneration to test whether this might mediate the amyloid and cognitive relationship. The present dissertation provides preliminary evidence that amyloid may itself have independent effects on cognitive decline. In order to understand the full picture, it will be necessary in the future to build off the present work and incorporate tau, to assess whether there are independent effects of amyloid on cognition or if cognitive decline is fully mediated by tau and neurodegeneration, even at early stages. The present study, however, demonstrates that

regardless of whether its effects are direct or indirect, amyloid provides an important marker of cognitively normal individuals on a pathological cognitive trajectory.

Table A1. Summary of Parameter Estimates from Linear Mixed Models with both Amyloid Status and SUVR. Parameter estimates and standard errors are reported for each cognitive outcome in the whole sample. p<.05 in bold.

		Effects of Time						Other Main Effects									
	Effect	**Time**		**Aβ Status x Time**		**Age x Time**		**Aβ Status**		**Age**		**Ed.**		**Sex**		**APOE**	
	Statistic	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	*p*
Episodic Memory (z)	**2SD Aβ Status**	0.35 (0.18)	0.053	**-0.29 (0.13)**	**0.028**	-	-	0.14 (0.13)	0.292	**-0.02 (0.00)**	**<0.001**	**0.07 (0.02)**	**0.001**	**0.77 (0.10)**	**<0.001**	-0.01 (0.11)	0.93
	3SD Aβ Status	**-0.35 (0.14)**	**0.011**	**-0.40 (0.15)**	**0.009**	-	-	0.19 (0.15)	0.210	-0.02 (0.00)	<0.001	0.08 (0.02)	0.001	0.78 (0.10)	<0.001	0.01 (0.11)	0.91
Processing Speed (z)	**2SD Aβ Status**	**0.49 (0.20)**	**0.017**	-0.11 (0.08)	0.161	**-0.01 (0.00)**	**0.001**	-0.09 (0.14)	0.524	**-0.04 (0.01)**	**<0.001**	0.04 (0.03)	0.147	**0.38 (0.12)**	**0.002**	-0.24 (0.14)	0.08
	3SD Aβ Status	0.22 (0.24)	0.363	-0.16 (0.09)	0.081	-0.01 (0.00)	0.001	-0.16 (0.17)	0.369	-0.04 (0.01)	<0.001	0.04 (0.03)	0.116	0.39 (0.12)	0.002	-0.23 (0.14)	0.1
Vocabulary (z)	**2SD Aβ Status**	0.18 (0.09)	0.053	**-0.14 (0.07)**	**0.044**	-	-	-0.05 (0.16)	0.772	**0.02 (0.01)**	**0.016**	**0.20 (0.03)**	**<0.001**	0.22 (0.14)	0.119	-0.08 (0.16)	0.61
	3SD Aβ Status	**-0.16 (0.07)**	**0.023**	**-0.20 (0.08)**	**0.011**	-	-	-0.29 (0.19)	0.123	0.02 (0.01)	0.004	0.21 (0.03)	<0.001	0.25 (0.14)	0.077	0.04 (0.16)	0.83
Reasoning (z)	**2SD Aβ Status**	**0.68 (0.28)**	**0.016**	-0.09 (0.11)	0.412	**-0.01 (0.00)**	**0.022**	-0.18 (0.14)	0.222	**-0.03 (0.01)**	**<0.001**	**0.09 (0.03)**	**<0.001**	0.07 (0.12)	0.575	0.14 (0.13)	0.31
	3SD Aβ Status	0.47 (0.33)	0.151	-0.12 (0.13)	0.327	**-0.01 (0.00)**	**0.019**	-0.28 (0.17)	0.099	-0.03 (0.01)	<0.001	0.10 (0.03)	<0.001	0.06 (0.12)	0.596	0.16 (0.13)	0.24
MMSE	**2SD Aβ Status**	**0.80 (0.36)**	**0.029**	-0.19 (0.27)	0.472	-	-	-0.04 (0.22)	0.856	**-0.02 (0.01)**	**0.001**	**0.08 (0.03)**	**0.023**	**0.50 (0.15)**	**0.002**	-0.33 (0.18)	0.06
	3SD Aβ Status	0.32 (0.28)	0.250	-0.28 (0.31)	0.361	-	-	-0.01 (0.26)	0.651	-0.02 (0.01)	0.001	0.08 (0.03)	0.016	0.51 (0.15)	0.001	-0.31 (0.18)	0.08

Table A2. Summary of Parameter Estimates from Linear Mixed Models with Amyloid Status instead of SUVR. Parameter estimates and standard errors are reported for each cognitive outcome in the whole sample. p<.05 in bold.

		Effects of Time						Other Main Effects									
		Time		Aβ Status x Time		Age x Time		Aβ Status		Age		Ed.		Sex		APOE	
	Statistic	*Est (SE)*	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*
Episodic Memory (z)	**2SD Aβ Status**	0.35 (0.18)	0.05	**-0.29 (0.13)**	**0.03**	-	-	0.14 (0.13)	0.29	**-0.02 (0.00)**	**<0.001**	**0.07 (0.02)**	**0.001**	**0.77 (0.10)**	**<0.001**	-0.01 (0.11)	0.93
	3SD Aβ Status	**-0.35 (0.14)**	**0.01**	**-0.40 (0.15)**	**0.01**	-	-	0.19 (0.15)	0.21	-0.02 (0.00)	<0.001	0.08 (0.02)	0.001	0.78 (0.10)	<0.001	0.01 (0.11)	0.91
Processing Speed (z)	**2SD Aβ Status**	**0.49 (0.20)**	**0.02**	-0.11 (0.08)	0.16	**-0.01 (0.00)**	**0**	-0.09 (0.14)	0.52	**-0.04 (0.01)**	**<0.001**	0.04 (0.03)	0.147	**0.38 (0.12)**	**0.002**	-0.24 (0.14)	0.08
	3SD Aβ Status	0.22 (0.24)	0.36	-0.16 (0.09)	0.08	-0.01 (0.00)	0	-0.16 (0.17)	0.37	-0.04 (0.01)	<0.001	0.04 (0.03)	0.116	0.39 (0.12)	0.002	-0.23 (0.14)	0.1
Vocabulary (z)	**2SD Aβ Status**	0.18 (0.09)	0.05	**-0.14 (0.07)**	**0.04**	-	-	-0.05 (0.16)	0.77	**0.02 (0.01)**	**0.016**	**0.20 (0.03)**	**<0.001**	0.22 (0.14)	0.119	-0.08 (0.16)	0.61
	3SD Aβ Status	**-0.16 (0.07)**	**0.02**	**-0.20 (0.08)**	**0.01**	-	-	-0.29 (0.19)	0.12	0.02 (0.01)	0.004	0.21 (0.03)	<0.001	0.25 (0.14)	0.077	0.04 (0.16)	0.83
Reasoning (z)	**2SD Aβ Status**	**0.68 (0.28)**	**0.02**	-0.09 (0.11)	0.41	**-0.01 (0.00)**	**0.02**	-0.18 (0.14)	0.22	**-0.03 (0.01)**	**<0.001**	**0.09 (0.03)**	**<0.001**	0.07 (0.12)	0.575	0.14 (0.13)	0.31
	3SD Aβ Status	0.47 (0.33)	0.15	-0.12 (0.13)	0.33	**-0.01 (0.00)**	**0.02**	-0.28 (0.17)	0.1	-0.03 (0.01)	<0.001	0.10 (0.03)	<0.001	0.06 (0.12)	0.596	0.16 (0.13)	0.24
MMSE	**2SD Aβ Status**	**0.80 (0.36)**	**0.03**	-0.19 (0.27)	0.47	-	-	-0.04 (0.22)	0.86	**-0.02 (0.01)**	**0.001**	**0.08 (0.03)**	**0.023**	**0.50 (0.15)**	**0.002**	-0.33 (0.18)	0.06
	3SD Aβ Status	0.32 (0.28)	0.25	-0.28 (0.31)	0.36	-	-	-0.01 (0.26)	0.65	-0.02 (0.01)	0.001	0.08 (0.03)	0.016	0.51 (0.15)	0.001	-0.31 (0.18)	0.08

Table A3. Summary of Parameter Estimates from Linear Mixed Models for Amyloid Positive Adults Only. Parameter estimates and standard errors are reported for each cognitive outcome in amyloid positive adults, with positivity determined for both 2SD and 3SD thresholds. <.05 in bold.

		Effects of Time						**Other Main Effects**									
		Time		**SUVR x Time**		**Age x Time**		**SUVR**		**Age**		**Ed.**		**Sex**		**APOE**	
	Statistic	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***
Episodic Memory (z)	**2SD Aβ Status**	**1.46 (0.70)**	**0.042**	**-1.33 (0.54)**	**0.018**	-	-	0.33 (0.52)	0.527	**-0.03 (0.01)**	**0.004**	0.08 (0.05)	0.108	**0.86 (0.21)**	**<0.001**	-0.03 (0.21)	0.902
	3SD Aβ Status	1.52 (0.91)	0.109	**-1.36 (0.66)**	**0.048**	-	-	0.79 (0.63)	0.216	-0.02 (0.01)	0.109	0.07 (0.07)	0.294	**0.93 (0.29)**	**0.003**	0.02 (0.27)	0.944
Processing Speed (z)	**2SD Aβ Status**	**1.88 (0.58)**	**0.002**	-0.48 (0.30)	0.115	**-0.02 (0.01)**	**0.001**	-0.52 (0.54)	0.340	**-0.04 (0.01)**	**0.001**	-0.03 (0.05)	0.581	0.48 (0.25)	0.610	-0.11 (0.58)	0.671
	3SD Aβ Status	**2.14 (0.83)**	**0.015**	-0.49 (0.42)	0.259	**-0.03 (0.01)**	**0.006**	-0.64 (0.72)	0.379	-0.03 (0.02)	0.055	-0.04 (0.09)	0.680	0.62 (0.37)	0.103	-0.05 (0.34)	0.895
Vocabulary (z)	**2SD Aβ Status**	0.52 (0.38)	0.183	-0.48 (0.30)	0.112	-	-	-1.72 (0.73)	0.022	0.01 (0.02)	0.361	**0.27 (0.08)**	**0.001**	0.16 (0.34)	0.652	0.37 (0.35)	0.288
	3SD Aβ Status	0.31 (0.60)	0.612	-0.34 (0.44)	0.438	-	-	-1.37 (1.03)	0.277	0.01 (0.24)	0.682	**0.30 (0.13)**	**0.025**	0.10 (0.54)	0.862	0.56 (0.51)	0.277
MMSE	**2SD Aβ Status**	**2.85 (1.35)**	**0.040**	-1.91 (1.05)	0.075	-	-	-0.59 (0.78)	0.454	-0.02 (0.01)	0.109	**0.15 (0.06)**	**0.020**	**0.75 (0.28)**	**0.011**	0.02 (0.28)	0.952
	3SD Aβ Status	**3.78 (2.00)**	**0.064**	**-2.52 (1.44)**	**0.086**	-	-	**-0.43 (1.04)**	**0.685**	**-0.02 (0.02)**	**0.318**	**0.10 (0.09)**	**0.294**	**0.47 (0.40)**	**0.253**	**0.16 (0.38)**	**0.684**

Table A4. Summary of Parameter Estimates from Linear Mixed Models for Amyloid Negative Adults Only. Parameter estimates and standard errors are reported for each cognitive outcome in amyloid negative adults, with negativity determined for both 2SD and 3SD thresholds. p<.05 in bold.

		Effects of Time								**Other Main Effects**									
		Time		**SUVR x Time**		**Age x Time**		**Ed. x Time**		**SUVR**		**Age**		**Ed.**		**Sex**		**APOE**	
	Statistic	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***
Episodic Memory (z)	**2SD Aβ Status**	-0.60 (2.06)	0.773	0.64 (2.00)	0.751	-	-	-	-	-0.82 (1.90)	0.668	-0.01 (0.00)	0.006	0.07 (0.03)	0.005	0.74 (0.11)	<0.001	0.02 (0.14)	0.903
	3SD Aβ Status	0.26 (1.66)	0.875	-0.21 (1.60)	0.898	-	-	-	-	-0.82 (1.52)	0.589	-0.02 (0.01)	0.001	0.08 (0.02)	0.001	0.75 (0.11)	<0.001	0.003 (0.13)	0.979
Processing Speed (z)	**2SD Aβ Status**	-1.17 (1.20)	0.331	1.27 (1.16)	0.274	-0.01 (0.00)	0.044	-	-	0.09 (2.07)	0.967	-0.04 (0.01)	<0.001	0.08 (0.03)	0.012	0.29 (0.14)	0.039	-0.39 (0.17)	0.024
	3SD Aβ Status	-0.40 (0.93)	0.671	0.61 (0.91)	0.508	-0.01 (0.00)	0.010	-	-	0.10 (1.64)	0.950	-0.04 (0.01)	<0.001	0.06 (0.03)	0.029	0.30 (0.13)	0.022	-0.34 (0.16)	0.033
Vocabulary (z)	**2SD Aβ Status**	1.54 (1.02)	0.132	-1.46 (0.99)	0.142	-	-	-	-	4.32 (2.18)	0.049	0.02 (0.01)	0.011	0.18 (0.03)	<0.001	0.26 (0.15)	0.080	-0.18 (0.18)	0.330
	3SD Aβ Status	1.04 (0.78)	0.184	-0.97 (0.76)	0.201	-	-	-	-	3.89 (1.80)	0.024	0.02 (0.01)	0.005	0.19 (0.03)	<0.001	0.26 (0.14)	0.066	-0.19 (0.17)	0.251
Reasoning (z)	**2SD Aβ Status**	0.15 (1.26)	0.906	-0.19 (1.23)	0.876	-	-	-	-	5.23 (1.99)	0.009	-0.04 (0.01)	<0.001	0.10 (0.03)	0.001	0.03 (0.13)	0.800	0.11 (0.16)	0.483
	3SD Aβ Status	0.82 (1.24)	0.512	-0.32 (1.22)	0.791	-0.01 (0.00)	0.059	-	-	3.41 (1.59)	0.034	-0.04 (0.01)	<0.001	0.10 (0.03)	0.001	-0.02 (0.12)	0.866	0.12 (0.15)	0.415
MMSE	**2SD Aβ Status**	2.95 (4.23)	0.487	-4.31 (4.15)	0.302	-	-	0.14 (0.06)	0.039	6.37 (3.36)	0.059	-0.02 (0.01)	0.004	-0.00 (0.05)	0.932	0.43 (0.18)	0.021	-0.41 (0.23)	0.073
	3SD Aβ Status	1.69 (3.26)	0.605	-2.80 (3.14)	0.375	-	-	0.12 (0.06)	0.040	4.24 (2.60)	0.105	-0.02 (0.01)	0.002	0.02 (0.05)	0.687	0.49 (0.17)	0.006	-0.45 (0.21)	0.034

Table A5. Summary of Parameter Estimates from Linear Mixed Models for Middle-Aged Adults Only. Parameter estimates and standard errors are reported for each cognitive outcome in the middle-aged subsample (n=51). p<.05 in bold.

		Episodic Memory (z)		Processing Speed (z)		Vocabulary (z)		Reasoning (z)		MMSE	
		Est (SE)	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*	*Est (SE)*	*p*
Effects of Time	Time	2.87 (1.73)	0.103	-1.34 (1.00)	0.188	2.18 (0.89)	0.019	-0.40 (1.04)	0.704	-3.83 (3.35)	0.26
	SUVR x Time	-2.63 (1.65)	0.118	1.08 (0.96)	0.263	-2.05 (0.86)	0.021	0.38 (1.00)	0.705	4.32 (3.20)	0.184
Other Main Effects	SUVR	-0.54 (1.72)	0.754	1.28 (2.05)	0.537	1.74 (2.24)	0.441	0.06 (1.93)	0.974	-0.04 (2.96)	0.988
	Age	0.02 (0.02)	0.315	-0.03 (0.02)	0.263	0.03 (0.03)	0.239	-0.04 (0.02)	0.117	-0.04 (0.03)	0.224
	Ed.	0.10 (0.04)	0.038	0.06 (0.06)	0.281	0.17 (0.06)	0.009	0.07 (0.05)	0.181	0.10 (0.07)	0.148
	Sex	0.83 (0.19)	<0.001	0.03 (0.25)	0.903	0.43 (0.27)	0.122	0.23 (0.23)	0.324	0.29 (0.31)	0.352
	APOE	-0.10 (0.19)	0.579	0.14 (0.24)	0.575	-0.22 (0.27)	0.413	0.01 (0.29)	0.95	-0.61 (0.30)	0.051

Table A6. Summary of Parameter Estimates from Linear Mixed Models for Older Adults. Parameter estimates and standard errors are reported for each cognitive outcome in the older adult subsample (n=123). p<.05 in bold.

		Episodic Memory (z)		**Processing Speed (z)**		**Vocabulary (z)**		**Reasoning (z)**		**MMSE**	
		Est (SE)	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***	***Est (SE)***	***p***
Effects of Time	**Time**	**1.06 (0.43)**	**0.016**	**1.26 (0.42)**	**0.003**	**0.50 (0.22)**	**0.024**	**1.72 (0.63)**	**0.007**	**2.33 (0.89)**	**0.01**
	SUVR x Time	**-1.03 (0.38)**	**0.008**	**-0.53 (0.22)**	**0.019**	**-0.46 (0.19)**	**0.019**	-0.29 (0.33)	0.389	**-1.63 (0.79)**	**0.041**
	Age x Time	-	-	**-0.02 (0.01)**	**0.005**	-	-	**-0.02 (0.01)**	**0.009**	-	-
Other Main Effects	**SUVR**	-0.25 (0.38)	0.509	-0.56 (0.40)	0.173	**-0.92 (0.47)**	**0.049**	-0.82 (0.42)	0.053	-0.19 (0.64)	0.77
	Age	**-0.02 (0.01)**	**0.017**	**-0.04 (0.01)**	**<0.001**	0.001 (0.01)	0.912	**-0.02 (0.01)**	**0.017**	**-0.03 (0.01)**	**0.012**
	Ed.	**0.07 (0.03)**	**0.005**	0.05 (0.03)	0.137	**0.22 (0.04)**	**<0.001**	**0.10 (0.03)**	**0.001**	**0.08 (0.03)**	**0.04**
	Sex	**0.73 (0.12)**	**<0.001**	**0.46 (0.14)**	**0.002**	0.17 (0.17)	0.312	0.01 (0.14)	0.969	**0.58 (0.19)**	**0.002**
	APOE	-0.05 (0.15)	0.729	0.29 (0.17)	0.104	-0.11 (0.20)	0.58	-0.23 (0.17)	0.193	0.09 (0.23)	0.682

Table A7. Partial Correlations between Regional SUVR Change and Episodic Memory Change after Correcting for Regional Atrophy. p<.05 in bold.

		Episodic Memory Change					
		Whole Sample		Amyloid Negative		Middle Age	
		r	*p*	*r*	*p*	*r*	*p*
SUVR Change	Posterior Cingulate	**-0.228**	**0.009**	**-0.209**	**0.024**	-0.256	0.106
	Precuneus	**-0.248**	**0.004**	**-0.192**	**0.039**	**-0.333**	**0.036**
	Superior Parietal	**-0.227**	**0.009**	**-0.22**	**0.018**	-0.265	0.099
	Inferior Parietal	**-0.235**	**0.006**	**-0.203**	**0.029**	-0.295	0.064
	Supramarginal	**-0.253**	**0.003**	**-0.234**	**0.012**	**-0.344**	**0.03**
	Cuneus	**-0.248**	**0.004**	**-0.235**	**0.011**	**-0.392**	**0.012**
	Lateral Occipital	**-0.235**	**0.007**	-0.182	0.05	**-0.337**	**0.034**

Table A8. Partial Correlations between Regional SUVR Change and Episodic Memory Change after Correcting for Total Grey Matter Atrophy. p<.05 in bold.

		Episodic Memory Change					
		Whole Sample		Amyloid Negative		Middle Age	
		r	*p*	*r*	*p*	*r*	*p*
SUVR Change	Posterior Cingulate	**-0.207**	**0.017**	**-0.19**	**0.042**	-0.231	0.152
	Precuneus	**-0.211**	**0.015**	-0.175	0.061	-0.298	0.062
	Superior Parietal	**-0.194**	**0.026**	**-0.202**	**0.031**	-0.282	0.078
	Inferior Parietal	**-0.219**	**0.011**	**-0.195**	**0.037**	-0.281	0.079
	Supramarginal	**-0.228**	**0.009**	**-0.226**	**0.015**	-0.303	0.058
	Cuneus	**-0.213**	**0.014**	**-0.217**	**0.02**	**-0.343**	**0.03**
	Lateral Occipital	**-0.191**	**0.028**	-0.152	0.104	**-0.313**	**0.049**

Table A9. Partial Correlations between Regional SUVR Change and Episodic Memory Change after Correcting for Hippocampal Atrophy. p<.05 in bold.

		Episodic Memory Change					
		Whole Sample		Amyloid Negative		Middle Age	
		r	*p*	*r*	*p*	*r*	*p*
SUVR Change	Posterior Cingulate	**-0.239**	**0.006**	**-0.214**	**0.022**	-0.254	0.114
	Precuneus	**-0.246**	**0.004**	**-0.196**	**0.036**	-0.26	0.105
	Superior Parietal	**-0.22**	**0.011**	**-0.219**	**0.019**	**-0.314**	**0.048**
	Inferior Parietal	**-0.254**	**0.003**	**-0.214**	**0.022**	-0.31	0.052
	Supramarginal	**-0.254**	**0.003**	**-0.237**	**0.011**	**-0.326**	**0.04**
	Cuneus	**-0.241**	**0.005**	**-0.236**	**0.011**	**-0.329**	**0.038**
	Lateral Occipital	**-0.206**	**0.018**	-0.161	0.086	**-0.377**	**0.016**

Table A10. Partial Correlations between Regional SUVR Change and Episodic Memory Change after Correcting for Baseline Amyloid Status Instead of Mean Cortical SUVR.
p<.05 in bold.

		Cognitive Change									
		Episodic Memory		Reasoning		MMSE		Vocabulary		Processing Speed	
		r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
SUVR Change	Isthmus Cingulate	-0.128	0.141	-0.063	0.47	-0.088	0.316	-0.006	0.949	-0.02	0.818
	Posterior Cingulate	-0.198	**0.022**	-0.172	**0.049**	-0.226	**0.009**	0.059	0.501	-0.063	0.473
	Precuneus	-0.213	**0.014**	-0.085	0.334	-0.12	0.169	-0.038	0.665	-0.046	0.6
	Lateral OFC	-0.05	0.569	-0.047	0.593	-0.127	0.147	-0.058	0.505	-0.05	0.57
	Medial OFC	0.034	0.695	0.011	0.897	-0.179	**0.04**	0.033	0.704	-0.059	0.503
	Pars Orbitalis	-0.021	0.808	0.055	0.534	-0.139	0.112	-0.034	0.698	-0.082	0.349
	Superior Parietal	-0.181	**0.037**	-0.088	0.313	-0.091	0.301	0.054	0.542	0.013	0.885
	Inferior Parietal	-0.214	**0.013**	-0.046	0.6	-0.183	**0.036**	0.082	0.348	-0.028	0.749
	Supramarginal	-0.226	**0.009**	0.007	0.937	-0.201	**0.021**	0.031	0.722	-0.045	0.609
	Rostral Anterior Cingulate	-0.003	0.969	0.011	0.9	-0.223	**0.01**	0.058	0.512	-0.043	0.628
	Caudal Anterior Cingulate	-0.004	0.963	-0.049	0.578	-0.247	**0.004**	0.02	0.821	-0.072	0.41
	Pars Triangularis	-0.063	0.475	0.112	0.199	-0.14	0.109	-0.017	0.843	-0.129	0.142
	Pars Opercularis	-0.124	0.155	0.046	0.597	-0.155	0.076	0.02	0.824	-0.108	0.217
	Caudal Middle Frontal	-0.01	0.912	0.014	0.872	-0.079	0.365	-0.009	0.917	-0.044	0.613
	Rostral Middle Frontal	-0.07	0.42	0.04	0.648	-0.14	0.11	-0.06	0.492	-0.12	0.17
	Superior Frontal	-0.06	0.493	-0.014	0.874	-0.118	0.177	0.035	0.694	-0.046	0.6
	Fusiform	-0.079	0.364	-0.051	0.56	-0.069	0.433	-0.053	0.547	-0.021	0.809
	Inferior Temporal	-0.127	0.144	-0.024	0.783	-0.119	0.174	-0.015	0.862	-0.075	0.391
	Middle Temporal	-0.133	0.127	0.043	0.622	-0.211	**0.015**	0.032	0.715	-0.102	0.243
	Superior Temporal	-0.112	0.199	0.095	0.278	-0.174	**0.046**	-0.039	0.66	-0.12	0.169
	Lateral Occipital	-0.173	**0.047**	0.004	0.965	-0.158	0.07	0.038	0.665	-0.072	0.414
	Cuneus	-0.223	**0.01**	0.02	0.82	-0.221	**0.011**	-0.086	0.325	-0.032	0.713
	Lingual	-0.109	0.213	0.09	0.304	-0.128	0.143	-0.166	0.056	-0.034	0.696
	Pericalcarine	-0.115	0.189	0.022	0.8	-0.115	0.191	-0.138	0.114	0.017	0.848
	Mean Cortical	-0.146	0.093	-0.039	0.654	-0.214	**0.014**	0.017	0.848	-0.072	0.415

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BIOGRAPHICAL SKETCH

Michelle E. Farrell was born in Stockton, California. After completing her schoolwork at Lincoln High School in Stockton in 2003, Michelle entered the University of California, Berkeley. While at Berkeley, she worked with Rebecca Spencer and Rich Ivry, studying the impact of aging on sleep-dependent memory consolidation. She received a bachelor's degree from the University of California Berkeley in 2007, with a double major in Molecular and Cell Biology and Integrative Biology. After college, she worked as a research assistant to Joy Taylor and Jerome Yesavage at the Stanford/VA Aging Clinical Research Center in Palo Alto, California, examining how aging affects expertise in older pilots and coordinating Stanford's chapter of the Alzheimer's Disease Neuroimaging Initiative. In 2012, she joined the Park Aging Mind Lab as a PhD student at The University of Texas at Dallas in Cognition and Neuroscience, investigating the impact of amyloid deposition on cognition in cognitively normal adults.

CURRICULUM VITAE

Michelle E. Farrell

EDUCATION

The University of Texas at Dallas (2012-present)
M.S. Applied Cognition and Neuroscience May 2017
Ph.D. Cognition and Neuroscience, in progress

University of California Berkeley (2003-2007)
B.A., double major: Molecular and Cell Biology, emphasis in Neurobiology;
Integrative Biology, emphasis in Systems Biology; Celtic Studies (minor)

RESEARCH INTERESTS

- Understanding the impact of Alzheimer's disease pathology on the progression from cognitive health to dementia.
- Determining what individual difference factors, including education and genetics, prevent or limit the formation of amyloid and tau deposits, or protect individuals from exhibiting deleterious effects of these deposits.

PUBLICATIONS

Farrell, M.E., Kennedy, K.M., Rodrigue, K.M., Wig, G.S., Bischof, G.N., Rieck, J.R., Chen, X., Festini, S.B., Devous, M.D. Sr, Park, D.C. (2017). Association of Longitudinal Cognitive Decline with Amyloid Burden in Middle-Aged and Older Adults: Evidence for a Dose-Response Relationship. *JAMA Neurol.* Published online May 30, 2017. doi:10.1001/jamaneurol.2017.0892

McDonough, I.M., Bischof, G.N., Kennedy, K.M., Rodrigue, K.M.; **Farrell, M.E.**, Park, D.C. (2016)between fluid and crystallized ability in healthy adults: a behavioral marker of preclinical Alzheimer's disease. *Neurobiology of Aging,* 46, 68-75.

Park, D.C., **& Farrell, M.E.** (2015) . Amyloid deposition and progression toward Alzheimer's disease. Warner K. Schaie and Sherry Willis (Eds.) Handbook of the Psychology of Aging: Eighth Edition. New York: Elsevier.

Taylor J.L., Scanlon, B.K., **Farrell, M.E**., Hernandez, B., Adamson, M.M., Ashford, J.W., Noda, A., Murphy, G.M. Jr, Weiner, M.W. (2014) APOE-ε4 and aging of medial temporal lobe gray matter in healthy adults older than 50 years. *Neurobiology of Aging;* 35(11):2479-85.

Adamson, M.M., Bayley, P.B., Scanlon, B.K., **Farrell, M.E**., Weiner, M.E, Yesavage, J., Taylor J.L. (2013) Impact of hippocampal size on longitudinal flight simulator performance varies with pilot expertise. *Aviat Space Environ Med*; 83(9):850-7.

PRESENTATIONS and POSTERS

Farrell, M.E., Chen, X., Park, D.C. (2017, July 19). Early Amyloid Accumulation and its Cognitive Consequences in Healthy Adults. Alzheimer's Association International Conference. London, UK. (oral presentation)

Chen, X., **Farrell, M.E.**, Park, D.C. (2017, July 18). Actual memory decline mediates the effect of amyloid burden on subjective memory in cognitively-normal adults. Alzheimer's Association International Conference. London, UK. (oral presentation)

Farrell, M.E., Bischof, G.N., Park, D.C. (2017, January 29). Cognitive Reserve and Amyloid Status: Are Protective Effects Limited by Age? Dallas Aging Cognition Conference. Dallas, TX. (poster)

Festini, S.B., **Farrell, M.E.,** Chen, X., Park, D.C. (2017, January 29). Relative contributions of lifestyle and health factors to cognition across the adult lifespan. Dallas Aging Cognition Conference. Dallas, TX. (poster)

Parker, A.N., **Farrell, M.E.,** Rundle, M.M., Park, D.C. (2017, January 29). A lifespan approach to understanding the relationship of Amyloid Beta deposition to obesity: Results from the Dallas Lifespan Brain Study. Dallas Aging Cognition Conference. Dallas, TX. (poster)

Farrell, M.E., Kennedy, K.M., Rodrigue, K.M., Wig, G.S., Bischof, G.N., Rieck, J.R., Chen, X., Festini, S.B., Devous, M.D. Sr, Park, D.C. (2017, January 13). Baseline amyloid burden predicts cognitive decline four years later in healthy adults: The value of a dose-response analysis. Human Amyloid Imaging Conference. Miami, FL. (Oral presentation)

Parker, A.N., Festini, S.B., **Farrell, M.E.,** Park, D.C. (2017, January 13). Does high baseline amyloid predict declines in activity participation and need for cognition over four years? Results from the Dallas Lifespan Brain Study. Human Amyloid Imaging Conference. Miami, FL. (poster)

Farrell, M.E., Festini, S.B., Park, D.C. (2016, November 26). Scaffolding of the Aging Mind: How Neural Depletion and Neural Enrichment Factors Affect Cognition. Australasian Cognitive Neuroscience Society Conference. Shoal Bay, Australia. (Keynote on behalf of Denise Park)

Farrell, M.E., Kennedy, K.M., Rodrigue, K.M., Wig, G.S., Bischof, G.N., Rieck, J.R., Chen, X., Festini, S.B., Park, D.C. (2016, July 25). Differentiating Preclinical Alzheimer's Disease from Normal Aging: The Effects of Age and Amyloid on Cognitive Decline over 3.5 Years. Alzheimer's Association International Conference. Toronto, Canada. (poster)

Farrell, M.E., Bischof, G.N., Park, D.C. (2016, July 22). Cognitive Reserve and Amyloid Status: Are Protective Effects Limited by Age? Professional Interest Area Day: Alzheimer's Association International Conference. Toronto, Canada. (Invited Talk)

Farrell, M.E., Chen, X., Festini, S.B., Park, D.C. (2016, April 15). What predicts cognitive decline over 3.5 Years in healthy adults? Age or Amyloid? Cognitive Aging Conference. Atlanta, GA. (poster)

Farrell, M.E., Festini, S.B., Chen, X., Park, D.C. (2016, January 15). Regional differences in the progression of amyloid accumulation and cognitive consequences in healthy adults across the lifespan. Human Amyloid Imaging Conference. Miami, Fl. (poster)

Parker, A., **Farrell, M.E.**, Rundle, M., Park, D.C. (2016, January 15). A lifespan approach to understanding the relationship of amyloid beta deposition to obesity: Results from The Dallas Lifespan Brain Study. Human Amyloid Imaging Conference. Miami, Fl. (poster)

Song, Z., **Farrell, M.E.**, Chen, X., Park, D.C. (2016, January 15). Longitudinal accrual of amyloid is associated with degradation of white matter tracts connected to the hippocampus in cognitively-normal adults. Human Amyloid Imaging Conference. Miami, Fl. (poster)

McDonough, I.M., Bischof, G.N., Kennedy, K.M., Rodrigue, K.M., **Farrell, M.E.**, Denise C. Park (2016, January 15). Discrepancies between Fluid and Crystallized Ability in Healthy Adults: A Behavioral Marker of Preclinical Alzheimer's Disease. Human Amyloid Imaging Conference. Miami, Fl. (poster)

Festini, S.B., **Farrell, M.E.**, Chen, X., Park, D.C. (2016, April 16). What underlying lifestyle and health factors predict cognition? A principal component analysis on the Dallas Lifespan Brain Study. Cognitive Aging Conference. Atlanta, GA. (poster)

Farrell, M.E., Bischof, G.N., Kennedy, K.M., Rodrigue, K.M., Devous, M.D. Sr, Park, D.C. (2015, January 26). The importance of frontal and temporal amyloid deposition in middle adulthood: The predictive value of APOE ε4 and lifetime cognitive engagement. Dallas Aging and Cognition Conference, Dallas, TX. (poster)

Chen, X., **Farrell, M.E.**, Festini, S.B., McDonough, I., Rieck, J.R., & Park, D.C. (2015, January 25). Cognitive predictors of everyday problem solving across the lifespan. Dallas Aging and Cognition Conference, Dallas, TX. (poster)

Park, D.C., **Farrell, M.E.,** Rodrigue, K.M., Kennedy, K.M., Bischof, G.N., Devous, M.D. Sr, (2015, January 15) Longitudinal Effects of Amyloid Accumulation on Cognition in a Healthy Adult Cohort Aged 30-89: Results from the Dallas Lifespan Brain. Human Amyloid Imaging, Miami, FL. (poster)

Farrell, M.E., Bischof, G.N., Kennedy, K.M., Rodrigue, K.M., Devous, M.D. Sr, Park, D.C. (2015, January 16) The importance of frontal and temporal amyloid deposition in middle adulthood: The predictive value of APOE ε4 and lifetime cognitive engagement. Human Amyloid Imaging, Miami, FL. (poster)

Farrell, M.E., Bischof, G.N., Kennedy, K.M., Rodrigue, K.M., Devous, M.D. Sr, Park, D.C. (2014, July 15) Amyloid accumulation in early and middle adulthood: The impact of life experience. Alzheimer's Association International Conference, Copenhagen, Denmark. (poster)

Farrell, M.E., Bischof, G.N., Kennedy, K.M., Rodrigue, K.M., Devous, M.D. Sr, Park, D.C. (2014, July 17) Amyloid accumulation in early and middle adulthood: The impact of life experience. Alzheimer's Imaging Consortium, Copenhagen, Denmark. (oral presentation)

Park, D.C., Devous, M.D. Sr., **Farrell, M.E.,** Bischof, G.N., Rieck, J.R., Rodrigue, K.M., Kennedy, K.M. (2014, July 19) Effect of *in vivo* amyloid burden on cognition in healthy adults aged 30 to 89: Initial longitudinal results across 3.5 years from the Dallas Lifespan Brain Study. Alzheimer's Association International Conference, Copenhagen, Denmark. (poster)

Farrell, M.E., Bischof, G.N., Rodrigue, K.M., Kennedy, K.M., Park, D.C. (2014, April 4) Advanced education mediates the impact of amyloid burden on reasoning in healthy older adults. Cognitive Aging Conference, Atlanta, GA. (poster)

Farrell, M.E., Bischof, G.N., Rodrigue, K.M., Kennedy, K.M., Park, D.C. (2014, January 15) Advanced education attenuates the impact of amyloid burden on reasoning in healthy older adults. Human Amyloid Imaging, Miami, FL. (poster)

RESEARCH EXPERIENCE

Center for Vital Longevity, 2012 – 2017
The University of Texas at Dallas
Graduate Research Assistant

Advisor:	Dr. Denise C. Park
Project:	Dallas Lifespan Brain Study. Large-scale, longitudinal study of healthy aging, including cognitive, genetics, MRI, fMRI, DTI, and amyloid PET data.
Responsibilities:	PET preprocessing, data management and analysis; Cognitive assessment and data-vetting; DNA extraction for genotyping

Alzheimer's Disease Neuroimaging Initiative 2009-2012
Department of Psychiatry
Stanford University
Study Coordinator

Research Advisor:	Jerome Yesavage, MD; Joy Taylor, PhD
Project:	Establishing standardized biomarkers to define the rate of progression of MCI and AD, including structural MRI, FDG PET, amyloid PET, lumbar puncture, genetics and neuropsychological assessment.
Responsibilities:	Data collection, scheduling, lab management, manuscript preparation

Aviation MRI Laboratory 2009-2012
Stanford/VA Aging Clinical Research Center
Research Assistant

Research Advisor: Joy Taylor, PhD; Maheen Adamson, PhD

Project:	Longitudinal MRI study exploring impact of age, expertise, APOE, brain volumes on episodic memory and flight simulator performance; fMRI study exploring effect of age, expertise, APOE, brain volumes on memory encoding and default mode network
Responsibilities:	MRI data acquisition, Cognitive assessment, lab management, manuscript preparation

War-Related Illness and Injury Study Center 2010-2012
VA Palo Alto Health Care System
Research Assistant

Research Advisor:	J.Wesson Ashford, MD, PhD; Maheen Adamson, PhD
Project:	Collect task-related and resting state fMRI pilot data on working memory, emotional-regulation and memory tasks in Veterans with PTSD, TBI and other war-related illnesses.
Responsibilities:	Cognitive and psychosocial assessment

Cognition and Action Lab Aug 2007-Dec 2007
Department of Psychology
University of California, Berkeley
Undergraduate Research Assistant

Research Advisor:	Rebecca Spencer, PhD; Rich Ivry, PhD
Project:	Age-related decline in sleep-dependent memory consolidation on reward-motivated learning and implicit learning.
Responsibilities:	Cognitive assessment, scheduling

RESEARCH GRANTS AND AWARDS

2017	Graduate Student Travel Scholarship
2017	Human Amyloid Imaging Conference Travel Scholarship
2014	University of Michigan Training Course in fMRI Travel Scholarship
2014	Human Amyloid Imaging Conference Travel Scholarship
2012-2017	Graduate Tuition Scholarship, The University of Texas at Dallas
2003-2007	Cal Grant
2003	Governor's Scholarship: Exemplary Standardized Testing Award

PROFESSIONAL SKILLS

SPSS, R, MATLAB, SPM, FSL, FreeSurfer, bash