Title

Exploration of Subthreshold Beta-Amyloid Levels and Effects on Longitudinal Cognitive Function

Authors

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http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

While there have been previous studies linking beta-amyloid accumulation in the positive range and cognitive decline, there has yet to be substantial research focusing on the significance of beta-amyloid accumulation in the negative range. The present study aims to replicate the findings of the original paper by Landau et al. 2018 which investigated potential associations between subthreshold levels of beta-amyloid accumulation and decreased executive or memory function. Utilizing data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), longitudinal beta-amyloid accumulation from florbetapir-18 PET scan measurements in cognitively normal individuals and mild cognitively impaired was compared with longitudinal executive and memory function measurements. These findings will provide implications as to whether beta-amyloid accumulation in healthy, cognitively normal individuals may be an earlier indicator of cognitive decline.

Keywords: Alzheimer's disease, beta-amyloid, executive function, florbetapir-18, memory, subthreshold, mild cognitive impairment

Introduction

Beta-amyloid (Aβ) holds great potential as a diagnostic biomarker for diagnosing Alzheimer's disease with some studies showing its diagnostic capability in blood (Nabers et al., 2018), while other studies have found mixed results within cerebrospinal fluid (Grimmer et al., 2009; Ritchie et al., 2014). Prior studies found that the accumulation of beta-amyloid in transgenic mice caused reduced cognitive abilities (Manczak et al., 2018). Other studies demonstrated that while a low dosage of beta-amyloid protein injected in mice has little effect on short-term working memory, higher dosages, through repeat injections, decreased memory performance (Cleary et al., 1995). In humans, studies have found that beta-amyloid causes age-related tangle formation in the brain, which has also been linked to Alzheimer's disease, to accelerate (Price & Morris, 1999). Researchers have also found that in Alzheimer's Disease patients and patients with mild cognitive impairment (MCI), beta-amyloid levels increased at a continuous rate compared to healthy controls (Villemagne, 2013). Greater memory decline has been seen in cognitively normal beta-amyloid positive individuals compared to beta-amyloid negative controls (Lim et al., 2014). Subtle episodic memory impairment was also related to beta-amyloid deposition,

especially in the temporal neocortex, and independently from hippocampal atrophy (Chetelat et al., 2011). However, this study is limited by the cross-sectional nature of the investigations, which may have limited sensitivity because of potential sample effects. In vivo measures of beta-amyloid deposition below a threshold indicative of beta-amyloid positivity carry critical information on future cognitive decline and accumulation of Alzheimer's Disease pathology (Bischof et al., 2019). However, the exact relationship between clinical progression and each of these beta-amyloid negative and beta-amyloid positive ranges is not well established, which is demonstrated by mixed results in studies. For example, individuals from the Australian Imaging, Biomarkers and Lifestyle study showed no decline in non-memory functions in amyloid-positive healthy older adults, compared to amyloid-negative healthy older adults (Lim et al., 2014). However these results were not reflected in amyloid-positive compared to amyloid-negative individuals with either mild cognitive impairment, or Alzheimer's Disease (Lim et al., 2014). Amyloid-negative individuals with mild cognitive impairment still showed no cognitive decline, but amyloid-positive individuals with mild cognitive impairment showed moderate decline in language, attention, and visuospatial function (Lim et al., 2014). Even given these varied findings, overall there have been few studies on longitudinal memory decline and beta-amyloid subthreshold accumulation. Our study aims to examine these longitudinal cognitive changes in baseline beta-amyloid negative individuals. Though research specifically regarding beta-amyloid accumulation in the negative range has typically been less abundant and conclusive, we expect the extensive longitudinal data of this experiment to remedy the inconclusiveness of prior studies.

The purpose of this study is to replicate the findings of Landau and colleagues' published paper which found that subthreshold beta-amyloid accumulation was associated with decline in longitudinal memory scores (Landau et al., 2018). The paper found that a high cortical beta-amyloid has been linked to cognitive decline; however, the clinical significance is unknown. The study examined amyloid and cognitive trajectories in 142 cognitively normal order individuals. The results of the paper demonstrated that among baseline negative individuals, florbetapir slope was not related to age, sex, and education. Instead, the slope was related to higher baseline cortical florbetapir. For this replication, we analyzed longitudinal beta-amyloid accumulation from florbetapir-18 PET scan data among initially cognitively normal individuals, along with the data of executive and memory function testing recorded for the original published study. As an extension, we analyzed longitudinal beta-amyloid accumulation in conjunction with executive and memory function testing in individuals with mild cognitive impairment.

Materials and Methods

We hypothesize a decrease in longitudinal cognitive function over time associated with an increase in beta-amyloid accumulation for baseline negative patients with beta-amyloid accumulation. Our replication's principal objective is to recreate prior primary statistical findings in hopes of confirming this hypothesis using data drawn from the Alzheimer's Disease Neuroimaging Initiative's (ADNI's) extensive database. We wrote our code in R, which was used along with our dataset from ADNI to generate the corresponding statistical diagrams and plots found in the initial study. In doing so, we were looking to confirm both the statistical and conceptual findings observed in the original study's outcomes. We used demographic data as well as standardized uptake value ratio of beta-amyloid with PET scan data using the radiotracer Florbetapir-18, which has been shown to be a reliable indicator of the amount of beta-amyloid in

brain scans of patients with Alzheimer's Disease and mild cognitive impairment (Johnson et al., 2013).

Data used in the preparation of this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

We first defined our sample from the ADNI dataset to include baseline cognitively normal individuals who received at least 2 PET scans, and for our extension the sample included individuals with mild cognitive impairment (MCI) who received at least 2 PET scans. We defined baseline amyloid status based on florbetapir standardized uptake value ratio (SUVR). Individuals were considered baseline beta-amyloid negative if their cortical summary SUVR values were below previously validated thresholds of 0.79 (composite reference for longitudinal comparisons) and 1.11 (whole cerebellum reference for cross sectional comparisons) (Landau et al., 2012). These threshold values have been validated by past research widely used in determining whether someone is considered baseline beta-amyloid positive or negative, and is an important biomarker as subthreshold beta-amyloid accumulation has been previously associated with decline in longitudinal memory (Landau et al., 2018).

Using our subsetted data, we recreated the spaghetti plots exhibiting the original paper's discrete trends of florbetapir accumulation in baseline positive versus baseline negative patients. Furthermore, we generated a linear mixed-effects model (LME) that offers a definite statistical representation of our findings. The LME takes into account cross sectional variables as well as longitudinal variables, and their effects on memory and executive function. The LME examines the relationship between the variables over time, controlling for within- and between-subjects effects. The independent variables used for the LME model were sex, *APOE4* status, education, age, time, baseline florbetapir measurements, annualized florbetapir change, time × baseline florebetapir measurements, and time × annualized florbetapir change. A p-value significance cutoff of less than a=0.05 was used to determine whether various independent variables were significant predictors for memory and executive function.

To express our results as a concise confirmation or refutation of our hypothesis, we recreated Figure 3 from the original study. This figure uses scatter plots to demonstrate the relationship between memory function and annualized florbetapir accumulation in baseline negative individuals through a linear regression model. We expect to see a negative correlation between memory slope and annualized beta-amyloid change, and no significant relationship between executive function slope and annualized beta-amyloid change, as seen in Landau's original paper.

Results

Defining our Sample

Our sample was defined to include individuals who were classified as cognitively normal at their initial diagnosis, and who also had at least 2 PET scans. There were 241 individuals in our data

set who were cognitively normal subjects at their baseline scan, and had 2 or more PET scans. Of these 241 subjects, 157 (65%) had a baseline negative florbetapir status, 61 (25%) had a baseline positive florbetapir status, and 23 (10%) were discordant. Subjects were categorized as baseline negative if their global cortical SUVR whole cerebellum reference was below the cross-sectional threshold of 1.11, and if the global cortical SUVR composite reference was below the longitudinal threshold of 0.79. Subjects were categorized as baseline positive if they were above both of those thresholds. Finally, subjects were categorized as discordant if their whole cerebellum and composite references had conflicting results; for example if an individual was above the threshold for one reference region, and below the threshold for the other reference region.

For our extension, we additionally defined a sample to include individuals who were classified as baseline mild cognitive impairment (MCI), and who had at least 2 PET scans. In this sample, there were 165 individuals. Of these 165 subjects, 53 (32%) had a baseline negative florbetapir status, 102 (62%) had a baseline positive florbetapir status, and 10 (6%) were discordant.

Table 1: Demographics and biomarkers for cognitively normal participants

Cognitively Normal Individuals	**Values**
Demographics	
Total	157
Age at baseline, y	74.2 ± 7.0
Female	68 (43)
APOE4+	30 (19)
Education, y	16.7 ± 2.7
Converted to MCI/AD	18/2 (12.7)
Cognition	
Memory Composite	1.14 ± 0.56
Executive Function Composite	1.12 ± 0.75

Values are n (%) or mean ± standard deviation.

Table 1 is a collection of summary statistics which describes not only demographics and test results of participants, but also quantifies changes throughout the study. There were 157 individuals, who were baseline amyloid negative, included in the experiment. Of those individuals, the mean age at the start of the experiment was 74.2 years with a standard deviation of 7.0 years. There were 68 female-identifying participants, making up 43.41 percent of the baseline negative participants. 30 participants were positive for APOE4 status, totaling 19 percent of baseline negative participants. The mean years of education among the baseline

negative participants at the start of the experiment was 16.7 years with a standard deviation of 2.7 years. The number of participants who converted from cognitively normal to having mild cognitive impairment at some point during the study was 18, while 2 individuals became clinically diagnosed with Alzheimer's Disease at some point during the study. These individuals constitute the 12.7 percent of baseline negative participants who had a change in cognitive status within the duration of the study. The mean memory cognitive assessment score at baseline was 1.14 with a standard deviation of 0.56, while the mean executive function cognitive assessment score at baseline was 1.12 with a standard deviation of 0.75.

Table 2: Demographics and biomarkers for participants with mild cognitive impairment

MCI Individuals	**Values**
Demographics	
Total	53
Age at baseline, y	73.6 ± 9.4
Female	24 (45)
APOE4+	6 (11)
Education, y	16.0 ± 2.8
Converted to AD	8 (15.1)
Converted to N	8 (15.1)
Cognition	
Memory Composite	0.22 ± 0.63
Executive Function Composite	0.39 ± 0.82

Values are n (%) or mean ± standard deviation.

Running analysis on the individuals who were baseline amyloid negative, but instead had mild cognitive impairment at the start of the experiment, created a group of just 53 individuals with summary statistics displayed in Table 2. The mean age at the start of the experiment was 73.6 years with a standard deviation of 9.4 years. There were 24 female-identifying participants, making up 45 percent of the baseline negative participants. 60 participants were positive for APOE4 status, totaling 11 percent of baseline negative participants. The mean years of education among these participants at the start of the experiment was 16.0 years with a standard deviation of 2.8 years. The number of participants who converted to Alzheimer's Disease at some point during the study was 8. 8 other individuals also converted to cognitively normal during the duration of the study. These individuals constitute the 15.1 percent of baseline negative participants with mild cognitive impairment who had a change in cognitive status within the duration of the study. The mean memory cognitive assessment score at baseline was 0.22 with a

standard deviation of 0.63, while the mean executive function cognitive assessment score at baseline was 0.39 with a standard deviation of 0.82.

Figure 1A: Florbetapir change in baseline negative cognitively normal individuals

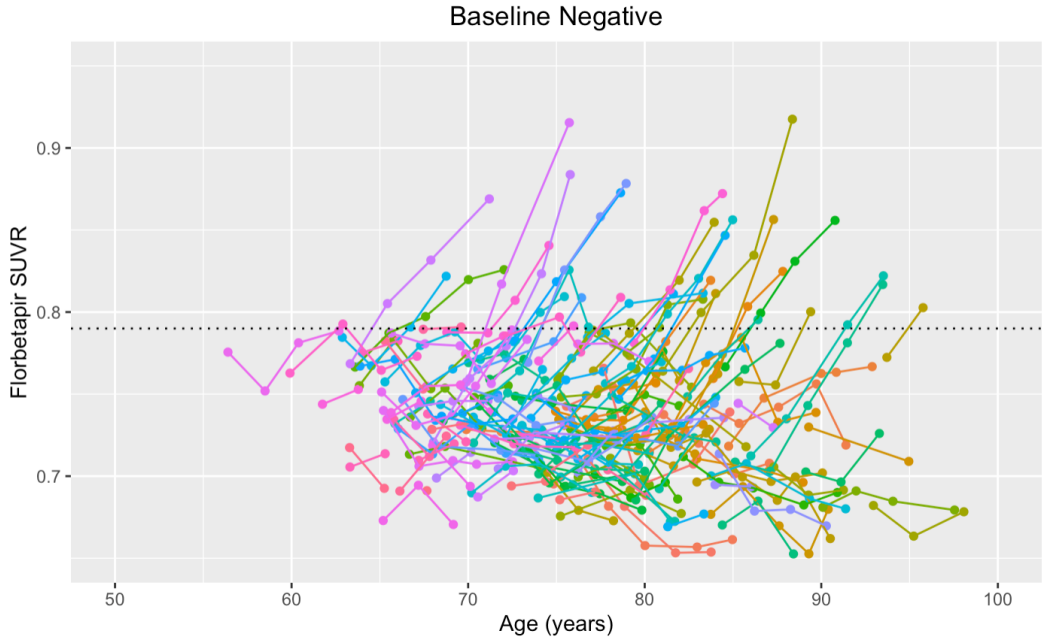


Figure 1B: Florbetapir change in baseline positive cognitively normal individuals

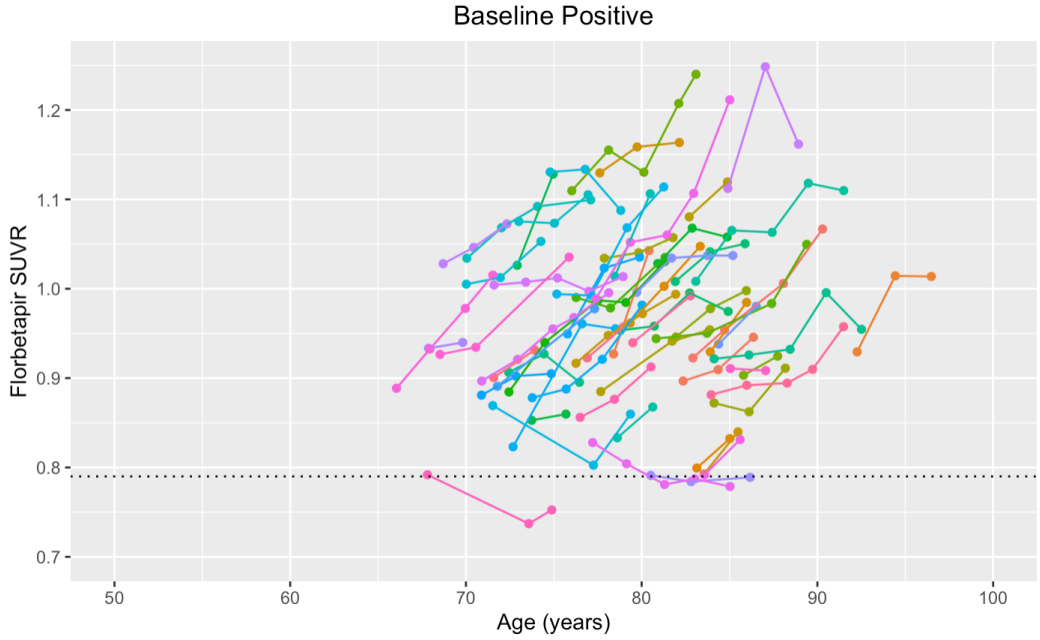


Figure 1C: Florbetapir change in baseline negative MCI individuals

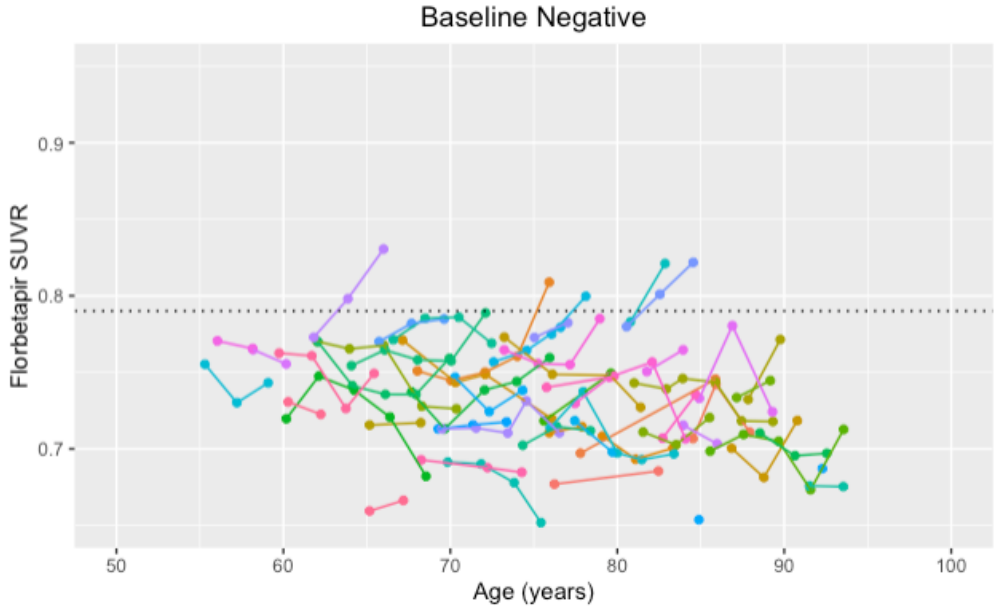


Figure 1D: Florbetapir change in baseline positive MCI individuals

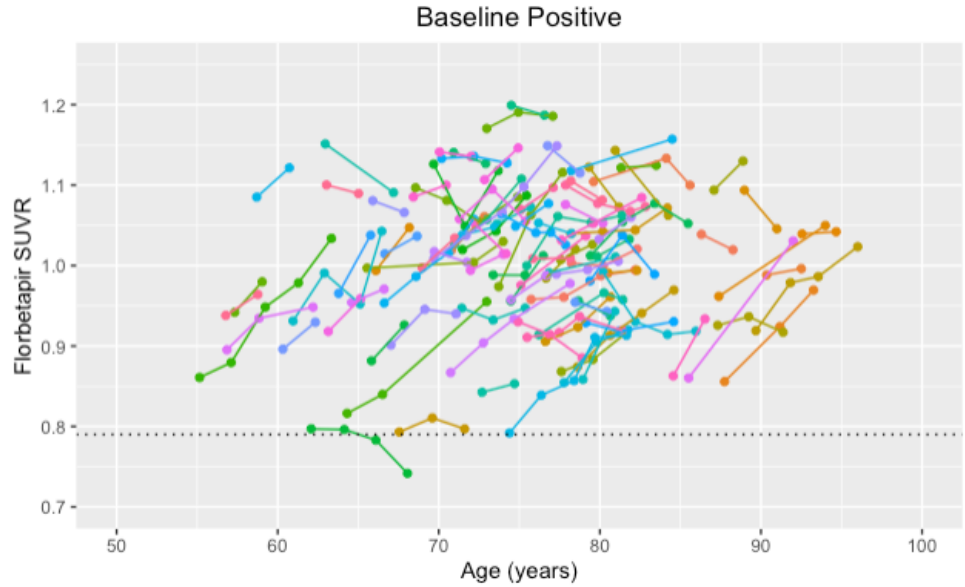


Figure 1A, 1B, 1C, and 1D depict the florbetapir standardized uptake value ratio (florbetapir SUVR) as a function of time for each individual subject with at least two PET scans. Individuals were separated between those who were baseline positive (Figures 1B and 1D) and those who were baseline negative for amyloid accumulation (Figures 1A and 1C). Of the participants who were cognitively normal at the start of the study, represented by Figures 1A and 1B, most of the participants in Figure 1B, who were baseline positive, remained florbetapir-positive throughout the study. Likewise, many of the participants in Figure 1A, who were baseline negative, remained florbetapir-negative throughout the study. However, many of the participants in Figure 1A also became florbetapir-positive at some point during the study. These individuals'

florbetapir SUVR over time slopes were about as steep as, or steeper than those of the individuals in Figure 1B, who were baseline positive.

Figures 1C and 1D display the florbetapir SUVR as a function of time for individuals with at least two PET scans and who displayed mild cognitive impairment at the start of the study. Of those who were baseline positive at the start of the experiment, depicted in Figure 1D, almost all of the participants remained florbetapir-positive for the duration of the study. Participants in Figure 1C were baseline negative at the start of the study and most remained florbetapir-negative. However, some participants in Figure 1C also converted to florbetapir-positive and displayed florbetapir SUVR over time slopes similar to those of the individuals in Figure 1D, who were baseline positive. These slopes were generally less steep compared to the cognitively normal individuals in Figure 1A displaying a similar baseline negative to florbetapir-positive conversion.

Linear Mixed Effects Model

Among 157 total individuals who were baseline cognitively normal and AB-, we wanted to predict longitudinal effects on memory and executive function. We excluded one individual from linear mixed effects modeling due to lack of data at the APOE4 variable. Among the remaining 156 individuals who all had at least 2 scans, male gender, education, and age were significant predictors of longitudinal memory score (Table 3, Model A). When decreasing the dataset to individuals with at least 3 scans (114), male gender and education were still significant predictors of longitudinal memory, but not age. Education and age were also significant predictors of longitudinal executive function and these effects did not change when reducing individuals from those with at least 2 scans to those with at least 3 scans (Table 3, Model B).

Table 3: Results of Linear Mixed Effects Models Predicting Cognitive Function Among Baseline Cognitively Normal

	At least 2 florbetapir scans			At least 3 florbetapir scans		
Model A: Longitudinal memory as dependent variable	Estimate	SE	P Value	Estimate	SE	P Value
Intercept	-0.725	1.276	0.5707	0.431	1.763	0.807
Male Sex	0.320	0.082	0.000***	0.330	0.099	0.001***
APOE4 Noncarrier	-0.006	0.088	0.9468	0.009	0.107	0.936
Education	0.055	0.015	0.000***	0.064	0.018	0.000***
Age	-0.017	0.006	0.006*	-0.014	0.008	0.067
Time	0.174	0.152	0.255	0.084	0.158	0.598
Baseline florbetapir SUVR	2.488	1.463	0.091	0.455	1.994	0.820
Time x baseline florbetapir SUVR	-0.263	0.208	0.206	-0.150	0.216	0.488
Florbetapir change	-5.793	5.523	0.296	-5.973	7.430	0.423

Time x florbetapir change	0.924	0.806	0.252	1.049	0.838	0.211
Model B: Longitudinal executive function as dependent variable						
Intercept	3.984	1.648	0.016	6.116	2.218	0.006
Male Sex	0.137	0.103	0.186	0.161	0120	0.182
APOE4 Noncarrier	-0.000	0.110	0.993	-0.177	0.130	0.175
Education	0.084	0.019	0.000***	0.095	0.021	0.000***
Age	-0.045	0.007	0.000***	-0.051	0.009	0.000***
Time	-0.090	0.250	0.718	-0.150	0.267	0.572
Baseline florbetapir SUVR	-1.502	1.915	0.434	-4.084	2.548	0.112
Time x baseline florbetapir SUVR	0.153	0.342	0.654	0.246	0.364	0.060
Florbetapir change	4.644	7.250	0.523	18.115	9.537	0.500
Time x florbetapir change	-0.849	1.323	0.521	-1.205	1.412	0.394

Significance levels denoted by: p-value<0.05 = *, p-value <0.005 = **, p-value < 0.001 = ***

SUVR in these tables refers to standardized uptake value ratio. Measure estimates are in units of aggregate cognitive test score.

Among baseline beta-amyloid negative individuals with mild cognitive impairment (53), male sex, age, and interaction between time and annualized florbetapir change were significant predictors of longitudinal memory function in individuals with at least 2 florbetapir scans. When we reduced the data set to individuals with 3 scans (33), male sex and time x florbetapir change interaction were still significant predictors, but not age (Table 4, Model C). For longitudinal executive function, education was the only significant predictor, and reducing to individuals with 3 scans still had education as a significant predictor, but also included annualized florbetapir change as well.

Table 3: Results of Linear Mixed Effects Models Predicting Cognitive Function Among Baseline Mild Cognitively Impaired

	At least 2 florbetapir scans			At least 3 florbetapir scans		
Model C: Longitudinal memory as dependent variable	Estimate	SE	P Value	Estimate	SE	P Value
Intercept	3.520	2.871	0.223	-0.865	3.543	0.808
Male Sex	0.502	0.192	0.012*	0.472	0.204	0.029*
APOE4 Noncarrier	-0.143	0.278	0.609	-0.030	0.255	0.905

Education	0.030	0.032	0.355	0.0556	0.034	0.117
Age	-0.033	0.011	0.004**	-0.011	0.014	0.413
Time	-0.274	0.218	0.213	-0.266	0.240	0.270
Baseline florbetapir SUVR	-2.787	3.279	0.400	0.605	3.756	0.873
Time x baseline florbetapir SUVR	0.416	0.297	0.164	0.375	0.324	0.250
Florbetapir change	14.189	15.106	0.352	27.302	20.170	0.187
Time x florbetapir change	-6.767	2.017	0.001**	-6.143	2.385	0.012*
Model D: Longitudinal executive function as dependent variable						
Intercept	2.574	3.667	0.484	-6.775	4.639	0.148
Male Sex	0.255	0.246	0.305	0.125	0.266	0.643
APOE4 Noncarrier	0.358	0.360	0.325	0.410	0.333	0.229
Education	0.166	0.040	0.000***	0.227	0.045	0.000***
Age	-0.015	0.143	0.288	0.019	0.018	0.302
Time	-0.403	0.347	0.247	-0.593	0.388	0.130
Baseline florbetapir SUVR	-5.628	4.192	0.186	2.925	4.913	0.557
Time x baseline florbetapir SUVR	0.551	0.472	0.245	0.757	0.526	0.154
Florbetapir change	15.260	19.320	0.434	55.532	26.312	0.044*
Time x florbetapir change	-3.5427	3.288	0.286	-4.293	3.892	0.273

Significance levels denoted by: p-value<0.05 = *, p-value <0.005 = **, p-value < 0.001 = ***

SUVR in these tables refers to standardized uptake value ratio. Measure estimates are in units of aggregate cognitive test score.

We generated two separate scatter plots each for both cognitively normal individuals, as well as MCI individuals: one plot compares the slope of concurrent longitudinal memory against annualized florbetapir change, and the other plot compares the slope of longitudinal executive function against annualized florbetapir change. This visual representation allowed us to examine the effects of florbetapir on executive function and memory.

Figure 2A: Scatter plots of longitudinal memory function slopes and executive function vs. annualized florbetapir change in cognitively normal individuals.

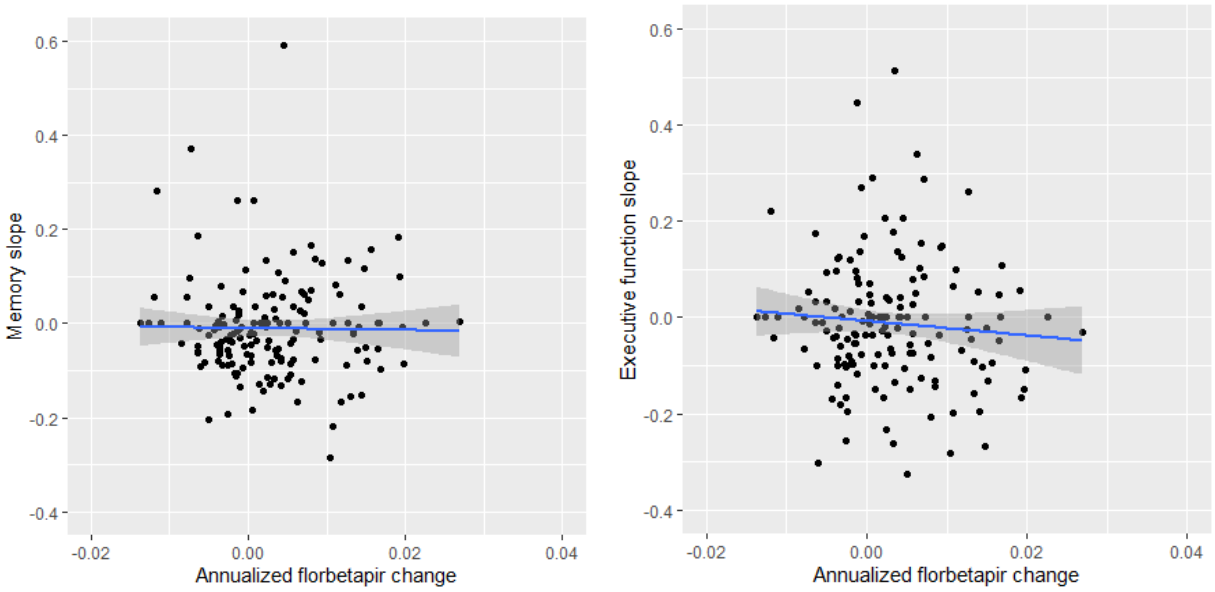
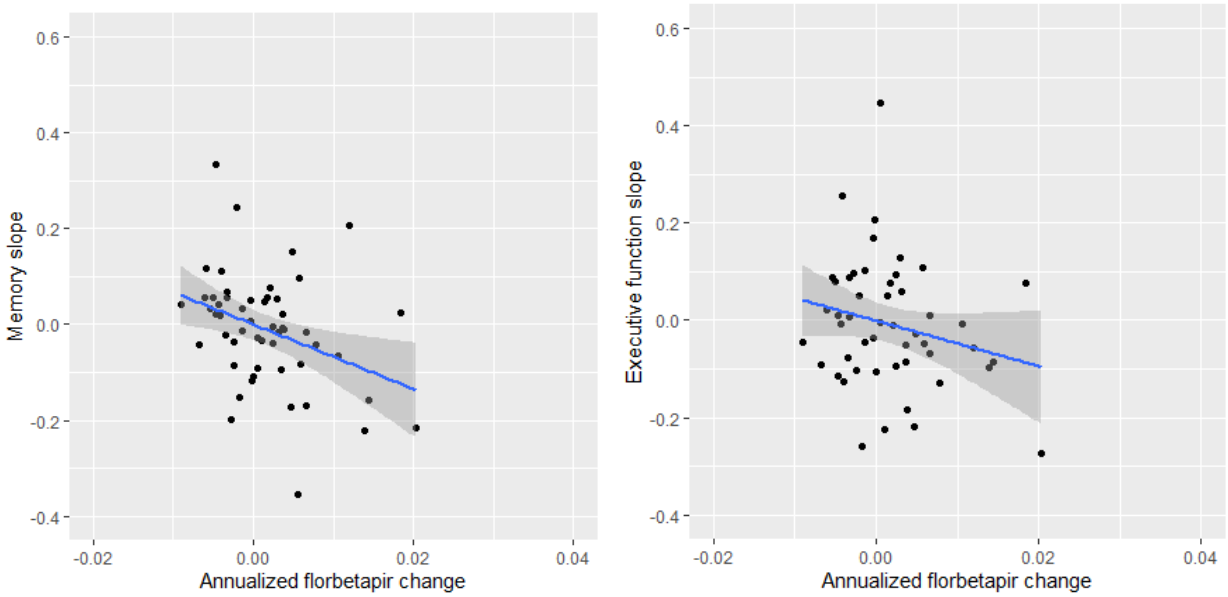


Figure 2B: Scatter plots of longitudinal memory function slopes and executive function vs. annualized florbetapir change in MCI individuals.



We observed a slight decline in executive function (slope = -1.452) and minimal decline in longitudinal memory (slope = -0.2061) with increased florbetapir amounts in baseline negative cognitively normal individuals (n=142) (Figure 2A). For individuals diagnosed as MCI (n=165), we found a much stronger association between the increase of florbetapir and a decline in both longitudinal memory (slope = -6.722) and executive function (slope = -3.677) (Figure 2B).

Discussion

Through analysis of the Figure 1 spaghetti plots, we see similar trends in both groups (cognitively normal and MCI) even though the sample size of individuals with mild cognitive impairment is significantly smaller. The majority of individuals who were originally baseline negative remained florbetapir-negative. However, many of the baseline negative individuals also converted to florbetapir-positive at some point during the study. These individuals displayed florbetapir SUVR over time slopes with similar steepness to baseline positive individuals'. In accordance with prior studies, the random fluctuations in the florbetapir SUVR of Figures 1A, 1B, 1C, and 1D can most likely be attributed to noise, while the steep baseline negative to florbetapir-positive SUVR slopes over time likely reflects amyloid accumulation (Farrell et. al, 2018). In both of the two sample set groups (Figures 1A and 1B and Figures 1C and 1D) individuals with steep baseline negative to florbetapir-positive slopes were present at an age as young as the early 60s and these individuals did not cross the threshold for positive amyloid accumulation for multiple years. However, while this may be a key finding for Figures 1A and 1B, in terms of evidence of preclinical Alzheimer's Disease, the same cannot be said for the participants in Figures 1C and 1D. This preclinical stage is defined as participants exhibiting a rate of amyloid accumulation which is similar to individuals with Alzheimer's Disease, however the accumulation is still below a threshold which is clinically diagnosable (Farrell et. al, 2018). Participants in Figures 1A and 1B were cognitively normal at baseline and therefore, this similarity in the baseline positive and baseline negative to florbetapir-positive conversion slopes provides evidence of this preclinical stage of Alzheimer's Disease. However, since individuals in Figures 1C and 1D originally had mild cognitive impairment, it is probable that these individuals will not progress toward Alzheimer's Disease and are instead classifiable as having vascular dementia (Lewis et. al, 2006). Though these individuals' subthreshold beta-amyloid accumulation may not be directly applicable to preclinical Alzheimer's Disease, understanding subthreshold amyloid accumulation for individuals with similar pathologies provides the opportunity to compare and learn in order to potentially impact Alzheimer's patients' clinical outcomes.

The scatter plots from Figure 2A and 2B depict the correlation between annualized florbetapir change and the slopes of both concurrent longitudinal memory and change in executive function for cognitively normal individuals. We observed a weak correlation between florbetapir slope and longitudinal memory decline among cognitively normal individuals (Figure 2A), and although a decline in executive function with the increase of florbetapir was more prominent, the correlation was still insignificant.

The same two scatter plots were also run on individuals classified as having mild cognitive impairment (MCI) (Figure 2B). These plots showed a much stronger correlation between florbetapir change and a decline in longitudinal memory. Similarly, the correlation between florbetapir change and executive function decline was also much stronger this time around, but not quite as drastic as the slope for memory decline.

This data suggests that for cognitively normal individuals, there is no clear association between subthreshold beta-accumulation and change in executive function, nor change in longitudinal memory scores. These results differ from the findings of Landau and colleagues' published paper as they found an association between subthreshold beta-amyloid accumulation and a decline in

longitudinal memory scores (Landau et al., 2018). There could be numerous factors impacting our results, causing them to differ slightly from the findings of Landau and colleagues' paper. For instance, this study defined the sample to include more individuals compared to the original paper. These extra individuals could have affected the results. Additionally, calculating the various data points and figures for this study was done using different coding methods compared to the original study which also could have impacted the results. Moreover, there have been a variety of findings from past studies on the subject of beta-amyloid accumulation and resulting impacts on memory/executive function. While Landau's paper did find a relationship between beta-amyloid accumulation and changes in longitudinal memory, a study done by Hedden and colleagues provides evidence of no significant relationships between the domains of working memory and semantic memory, and amyloid (Hedden et al., 2013).

As for MCI individuals, we found an association between an increase in annualized florbetapir and a significant decrease in both longitudinal memory and executive function. As beta-amyloid accumulation was already greater at baseline in these individuals, it makes sense that over the course of the study, with continued beta-amyloid accumulation, that longitudinal memory and executive function would continue to decline drastically.

Based on this replication, we did not detect a noteworthy decline in cognitive function among cognitively normal individuals based on subthreshold beta amyloid levels, which differs from the findings of the Landau et al. 2018 study. We did however, find evidence for associations between longitudinal cognitive decline and increased annualized beta-amyloid levels among individuals with mild cognitive impairment, which confirm findings from previous studies (Villemagne, 2013). Our study did identify significant predictors of longitudinal cognitive function, and future research should elucidate on the relationship between these variables of longitudinal cognitive function and Alzheimer's Disease progression.

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