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The relationship between domain-specific subjective cognitive decline and Alzheimer's pathology in normal elderly adults

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Abstract

We evaluated the associations of subjective (self-reported Everyday Cognition, ECog) and objective cognitive measures with regional amyloid-β (Aβ) and tau accumulation in 86 clinically normal (CN) elderly subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Regression analyses were conducted to identify whether individual ECog domains (Memory, Language, Organization, Planning, Visuospatial, and Divided Attention) were equally or differentially associated with regional [^{18}F]florbetapir and [^{18}F]flortaucipir uptake and how these associations compared to those obtained with objective cognitive measures. A texture analysis, the weighted two-point correlation, was used as an additional approach for estimating the whole-brain tau burden without PET intensity normalization. While the strongest models for ECog domains included either tau (Planning and Visuospatial) or Aβ (Memory and Organization), the strongest models for all objective measures included Aβ. In Aβ-negative participants, the strongest models for all ECog domains of executive functioning included tau. Our results indicate differential associations of individual subjective cognitive domains with Aβ and tau in CN. Detailed characterization of ECog may render a valuable pre-screening tool for pathological prediction.

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Disclosure statement

The authors report no actual or potential conflicts of interest relevant to this article.

Keywords

[^{18}F]flortaucipir; neurofibrillary tau tangles; subjective cognitive decline; amyloid beta plaques; Aging; Alzheimer's disease; [^{18}F]florbetapir

1- Introduction

Subjective cognitive decline (SCD) is increasingly recognized as a precursor to mild cognitive impairment (MCI). Older individuals with SCD are at higher likelihood of converting to MCI and dementia than those without SCD (Dufouil et al., 2005; Glodzik-Sobanska et al., 2007; Mitchell et al., 2014; Reisberg et al., 2010). However, SCD is etiologically heterogeneous and complex. Biomarker studies may help clarify the biological basis of SCD and pinpoint the most AD-predictive SCD characteristics as early as possible and help rule out other conditions that can lead to self-perceptions of cognitive alterations. Identifying the pathological pathways that influence subjective cognitive decline in the clinically normal elderly population is also critical for the identification and recruitment of at-risk participants in prevention trials before the onset of dementia. Self-recognized deficiencies can pertain to one or more cognitive domains, including memory, attention/processing speed, language, executive function, orientation, and visuospatial skills. Understanding how biological factors influence individual SCD domains would provide valuable early diagnosis and prognosis information.

Amyloid-β (Aβ) plaques and Neurofibrillary tangles (NFTs) of misfolded hyperphosphorylated tau proteins begin to accumulate decades before the onset of clinical dementia, which raises the question of how they influence the manifestation of SCD in non-demented subjects. Previous research has established an association between SCD and preclinical AD pathologies (Amariglio et al., 2012; Amariglio et al., 2018; Amariglio et al., 2015; Barnes et al., 2006; Buckley et al., 2017; Jorm et al., 2004; La Joie et al., 2016; Perrotin et al., 2012; Snitz et al., 2015; Vogel et al., 2017). Most of these studies have focused on associations between subjective deficits within the memory domain and Aβ pathology. A recent study by Buckley and colleagues (Buckley et al., 2017) reported that preclinical subjective cognitive decline is associated with both increasing entorhinal tau burden and (to a lesser extent) global Aβ burden. However, they found that tau and Aβ do not necessarily interact to influence preclinical subjective cognitive decline.

In this study, we have conducted a comprehensive examination of the associations of two major AD pathologies (Aβ, tau) with objective and subjective cognitive measures to gain a more in-depth understanding of the pathological basis of SCD, measured with the Everyday Cognition (ECog) instrument (Farias et al., 2008) in clinically normal subjects. Specifically, we have addressed the central question of whether individual ECog domains (memory, language, executive functioning, and visuospatial processing) are equally or differentially linked with regional [^{18}F]flortaucipir and [^{18}F] florbetapir standardized uptake value ratios (SUVRs). We have utilized multiple regression models to (1) determine associations between individual pathologies (predictors) and each ECog domain (outcomes), (2)

construct the strongest prediction model (best combination of predictors) for each ECog domain, and (3) identify interactions between key predictors in the strongest models.

In addition to the regional tau SUVR values, we have conducted a post hoc whole brain texture analysis approach, the weighted two-point correlation function (wS_2), as an additional approach for estimating the severity of tau burden. One of the main advantages of this technique is the elimination of the reference region normalization of PET image intensity, which may be relevant to early tau characterization in normal subjects when the [^{18}F]flortaucipir SUVR signal is low and likely to affected by the background off-target binding (Baker SL, 2019).

2- Materials & Methods

2.1- Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). This study was approved by the Institutional Review Board of Vanderbilt University Medical Center (IRB#181429). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner MD, with the primary goal 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). Cognitive, demographic, and imaging data for this study were collected from 86 clinically normal (CN) ADNI subjects. We did not include any EMCI, MCI or AD subjects because this study focuses on associations between AD pathologies (Aβ and tau burden) and the earliest self-reported cognitive symptoms. The ADNI CN group has a Mini-Mental State Examination, MMSE (Folstein et al., 1983) memory scores of 24–30 (inclusive), a CDR of 0, and education-adjusted score on delayed recall of paragraph A from Wechsler Memory Scale Logical Memory II (E-WMS) ≥ 9 for 16 or more years of education, ≥5 for 8–15 years of education, ≥3 for 0–7 years of education. CN subjects are not diagnosed with MCI or dementia (based on the absence of significant impairment in cognitive functions and daily activity).

2.2- Cognitive and neuropsychological measures

Participants' global cognitive measures were obtained from their MMSE, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog), composite executive function (ADNI-EF), and composite memory (ADNI-MEM) scores (Crane et al., 2012; Gibbons et al., 2012). The ADNI-EF is a composite executive function score derived from the baseline scores of a number of tasks including Category Fluency, Clock Drawing, Digit Span Backwards, Digit Symbol Substitution, as well as Trails A and B. The ADNI-MEM is a composite score combining recognition and recall scores from a number of tasks including the ADAS-Cog, Rey Auditory Verbal Learning Test (RAVLT), MMSE and Logical Memory Task. Self-reported ECog (Farias et al., 2008) scores were used as a measure of subjective cognitive decline. The self-rated ECog questionnaire comprised six subscales, including Everyday Memory, Everyday Language, Everyday Visuospatial abilities, Everyday Planning, Everyday Organization, and Everyday Divided Attention.

2.3- Pre-processing of imaging data

Tau PET—All ADNI [^{18}F]Flortaucipir scans were acquired at participating sites following the standardized ADNI protocol for [^{18}F]Flortaucipir (adni.loni.usc.edu). In brief, the injection of 370 MBq ± 10% of [^{18}F]Flortaucipir was followed by a 30 min (6X5min frames) PET scan starting at 75–105 minutes post-injection. The temporal frames were uploaded to USC's Laboratory of Neuroimaging ADNI database (LONI) where they were coregistered, averaged, and smoothed with a scanner-specific filter derived from each site's Hoffman brain phantom to obtain a common isotropic resolution of 8 mm full width at half maximum (FWHM) resolution. [^{18}F]Flortaucipir SUVR values from six regions (Braak I-IV) (Schöll et al., 2016) were directly downloaded from the ADNI PET imaging archive. The regional SUVR values were normalized by the inferior cerebellar gray matter uptake (Baker et al., 2017) and re-grouped into Braak I (entorhinal), BraakIII-IV (limbic), and Braak V-VI (isocortical) regions of interest (ROIs).

Aβ PET—All ADNI [^{18}F]Florbetapir scans were acquired at participating sites following the standardized ADNI protocol for [^{18}F]Florbetapir (Jagust et al., 2015). Regional [^{18}F]Florbetapir SUVR values (normalized by the whole cerebellum) were directly downloaded from the ADNI PET imaging archive. We used SUVR values from four ROIs, the anterior-posterior cingulate, lateral parietal (including precuneus), frontal, and lateral temporal cortices (Farrell et al., 2018; Landau et al., 2014; Palmqvist et al., 2017; Perrotin et al., 2012; Villeneuve et al., 2015) for the subsequent statistical analyses. In addition to individual regional SUVR values, a mean composite ROI SUVR was calculated, and a threshold of 1.11 was applied to identify the Aβ-positive individuals (Landau et al., 2012).

2.4- Statistical analysis of the associations between tau-PET measures and cognitive and behavioral measures

We utilized three types of regression models in R (www.R-project.org) to determine individual and combined associations between Aβ and tau pathologies and cognitive measures. Multiple simple linear regression models (model 1) were used as the first step to determine the associations of individual cognitive measures (outcomes) with individual regional pathologies (predictors). The regional [^{18}F] florbetapir and [^{18}F] flortaucipir values were included separately as predictors. All models included age, gender, and APOE-Ɛ4 status (dichotomous variable) as covariates. We performed the Bonferroni correction whenever we needed to adjust for multiple comparisons. Backward-elimination regression analyses (model 2) were run for each objective and subjective (self-reported ECog) cognitive measure as outcome but included all regional [^{18}F]florbetapir and [^{18}F]flortaucipir SUVR values, age, sex, and APOE-Ɛ4 status as initial predictors. The backward-elimination procedure starts with an initial model that includes all predictors, followed by testing the deletion of each predictor using a chosen model fit criterion, and step-wise deleting predictors with the most statistically insignificant deterioration of the model fit. This process was used to determine which combination of predictors built the strongest model to fit a specific cognitive measure. Step-down method, i.e., backward-elimination, is usually better than the forward method (Mantel, 1970) and is also recommended over stepwise method (Harrell, 2015). The Akaike Information Criterion was used as a model selection criterion for a given set of data. The backward-elimination regression analyses were conducted first

for all CN subjects and then repeated for the Aβ-negative subjects of the CN group. Interactions between predictors (model 3): We tested multiple two-way interactions between individual regional tau, regional Aβ, age, sex, and APOE-Ɛ4 status. Due to a large number of predictors (10 variables) and outcomes (10 cognitive measures), we primarily focused on pairwise interactions between variables that were included in the strongest models (from step 2, backward elimination) for each subjective cognitive test.

2.5- Post hoc wS_2 Analysis

Applied to a flortaucipir image, the wS_2 analysis provides a quantitative characterization of spatial clustering of image intensity values in individual subjects' brain. We used this metric as an alternative approach for estimating the severity of global tau burden. We downloaded the ADNI SUV (standardized uptake value) images that were not intensity-normalized by any reference region, meaning that the uptake of the individual voxels had not been divided by the mean uptake of a reference region. Using SPM 12 (Ashburner, 2012), each tau PET SUV image was aligned with the subject's T1-weighted magnetic resonance imaging (MRI) volume and the cortical gray matter (GM) mask was segmented and applied to flortaucipir SUV image for the subsequent wS_2 analysis (MATLAB 2018, MathWorks, Inc., Natick, Massachusetts, United States). The wS_2 approach captures the image texture (spatial clustering) by pairwise comparison of the SUV signal intensities between different locations in gray matter. The outcome of this analysis is a single measure per subject that quantifies the (global) severity of spatial clustering of image intensity values as an estimate of the tau burden in the individual subject's brain. Detailed steps of this analysis are provided in the supplement section (supplement A). Applications of two-point correlation functions are described in previous literature (Blair et al., 1996; Jiao et al., 2008; Tewari et al., 2004). The three-step regression analyses (see 2.4) were repeated with the wS_2-based global measure of tau burden. The wS_2-based tau burden was combined with the global Aβ SUVR measures in the backward-elimination regression analysis (model 2) to find the strongest model for predicting each cognitive measure. Pairwise interactions between wS_2-based tau and global Aβ SUVR were tested in model 3.

3- Results

Table 1 provides a summary of subject-specific information, including age, sex, number of APOE-Ɛ4 carriers, objective/subjective cognitive measures, global florbetapir SUVR values, and Aβ-positivity status. Out of 86 subjects, 39 were women. The average age at the time of the tau-PET scans was 78±8. Out of 86 subjects, 24 subjects were APOE-Ɛ4 carriers, and 38 subjects were Aβ-positive.

3.1- Associations of individual regional pathologies with cognitive measures while including age, sex, and APOE-Ɛ4 status as covariates

Tables 2 summarizes the results of the simple regression analyses for finding associations of each objective cognitive measure and each domain of the self-reported ECog with regional tau SUVR measures while including age, sex, and APOE-Ɛ4 as covariates. The Bonferroni-corrected P-value of 0.016 (0.05/3) was used to adjust for multiple comparisons across regional tau measures (Braak I, Braak III-IV, Braak V-VI). Associations with self-reported

ECog measures: The Braak SUVR values significantly predicted Everyday Planning (Braak I). Other, marginally significant ($p<0.09$) associations were found in models for predicting Everyday Visuospatial and Everyday Organization with Braak I SUVR as the predictor. Associations with objective cognitive measures: The Braak SUVR values significantly predicted the MMSE scores. Other, marginally significant associations were found for predicting ADNI-EF ($p<0.1$).

Table 3 summarizes the results of the simple regression analyses for associations of each objective cognitive measure and each domain of the self-reported ECog with the regional Aβ SUVR measures while including age, sex, and APOE-Ɛ4 as covariates. The Bonferroni-corrected P-value of 0.0125 (0.5/4) was used to adjust for multiple comparisons across regional Aβ measures (parietal, frontal, temporal, cingulate). Associations with self-reported ECog measures: Significant associations were found in models for predicting Everyday Organization (all regions) and Everyday Memory (frontal lobe). Other, marginally significant associations ($p<0.098$) were found in Everyday Visuospatial (frontal lobe), and Everyday Language (parietal lobe). Associations with objective cognitive measures: Significant associations were found in models for predicting MMSE and ADAS_cog. Other, marginally significant associations ($p<0.07$) were found in models for predicting ADNI-MEM and ADNI-EF.

3.2- Backward-elimination regression analysis

Table 4 summarizes the results of the backward-elimination regression analyses for each objective cognitive performance test (MMSE, ADAS_cog, ADNI-EF, ADNI-MEM) and each subjective cognitive measure (self-reported ECog domains: Everyday Memory, Everyday Language, Everyday Visuospatial, Everyday Planning, Everyday Organization, Everyday Divided Attention) as outcomes. Strongest models for self-reported ECog measures: The backward-elimination regression analysis indicated that the strongest models to predict ECog measures included either only Aβ (Everyday Memory, Everyday Language, Everyday Organization), only tau (Everyday Planning, Everyday Visuospatial), or none (Everyday Divided Attention). When applied to Aβ-negative CN subjects, the strongest models for Everyday Visuospatial and Everyday Planning continued to include tau only (Braak I) whereas the model for Everyday Memory continued to include Aβ only (cingulate cortex with marginal significance). In Aβ-negative subjects, both tau and Aβ were included in the strongest model for predicting Everyday Organization. The strongest model for predicting Everyday Divided Attention in Aβ-negative CN subjects included tau. Strongest models for objective cognitive measures: The strongest models for predicting the objective cognitive measures included Aβ, mostly without tau (MMSE, ADAS_cog, ADNI-EF). The best model for predicting ADNI-MEM included both tau and Aβ. When excluding Aβ-positive CN subjects, the strongest models for ADNI-EF and ADNI-MEM included both pathologies.

3.3- Interactions between predictors

Interactions with age—We found significant interactions between tau and age when predicting Everyday Visuospatial ($p = 0.027$ for Braak I SUVR), Everyday Planning ($p= 0.002$ for Braak I SUVR and $p = 0.04$ for Braak III-IV SUVR) and ADNI-MEM ($p = 0.034$

for Braak III-IV SUVR). We found significant interactions between Aβ (temporal lobe) and age when predicting Everyday Organization (p = 0.03). Interactions between AD pathologies: When including all CN subjects, no interactions were found between the pathologies to predict the ECog domains. However, we found a significant interaction between Aβ (cingulate cortex) and tau (Braak III-IV) when predicting Everyday Organization (p = 0.017) only in Aβ-negative subjects.

3.4- Analysis with wS_2-based tau measures

With the simple regression model, we found significant associations between wS_2-based tau and several objective cognitive measures, including MMSE ($p<0.0001$, $R^2= 0.30$), ADAS_cog ($p = 0.006$, $R^2= 0.28$), and ADNI-EF ($p =0.005$, $R^2= 0.24$). Also, we found significant associations between wS_2-based tau and individual self-reported ECog measures, including Everyday Planning ($p=0.04$, $R^2= 0.16$), Everyday Organization ($p=0.01$, $R^2 = 0.11$), and Everyday Memory ($p=0.006$, $R^2= 0.22$). The associations between wS_2-based tau and Everyday Visuospatial ($p = 0.06$) and Everyday Language ($p = 0.07$) were marginal. Backward elimination regression analysis of self-reported ECog measures and interactions between predictors: Similar to the SUVR-based results, the backward elimination regression analysis confirmed that the strongest models for Everyday Visuospatial and Everyday Planning included wS_2-based tau (but not Aβ). Also, the strongest model for predicting Everyday Divided Attention did not include tau or Aβ. The strongest models for Everyday Organization and Everyday Memory included both wS_2-based tau and Aβ. We found significant interactions between wS_2-based tau and age when predicting Everyday Visuospatial ($p = 0.0001$), Everyday Planning ($p = 0.0008$), and Everyday Organization ($p = 0.03$). We found no interactions between wS_2-based tau and global Aβ. However, when including regional Aβ SUVR values, we found a significant interaction between wS_2-based tau and cingulate cortex Aβ for predicting Everyday Language ($p=0.03$). Backward elimination regression analysis of objective cognitive measures and interactions between predictors: The strongest models for ADAS_cog and ADNI-MEM included Aβ only. The strongest model for MMSE and ADNI-EF included wS_2-based tau and Aβ. We found significant interaction between tau and age in predicting MMSE.

4- Discussion

Developing accessible screening tools that can predict the Alzheimer's-related pathological profile before a person begins to show more severe signs of cognitive and/or functional decline would provide an early opportunity to set apart a 'vulnerable' population for which preventive measures could be instituted and monitored. A growing body of research suggests that the presence of SCD in older normal adults predicts future decline and conversion to MCI and AD (Mitchell et al., 2014; Reisberg et al., 2010). However, SCD is etiologically heterogeneous and complex. Biomarker studies may help disentangle the biological basis of SCD and pinpoint the most AD-predictive characteristics in clinically normal subjects. Previous AD biomarker studies of SCD have primarily focused on the memory complaints (Amariglio et al., 2012; Amariglio et al., 2015; Barnes et al., 2006; Jorm et al., 2004; Kryscio et al., 2014; Snitz et al., 2015) by using either simple memory questions or constructing composite memory scores from different instruments, such as Everyday

Memory or Memory Functioning Questionnaire (Gilewski et al., 1990). Although recent evidence suggests that the associations between SCD and AD pathology (La Joie et al., 2016) are not restricted to the memory, it is not fully understood how individual SCD domains relate to Aβ and tau.

The objective of this study was to gain an in-depth understanding of the early pathological bases of objective and subjective cognitive alterations with specific focus on individual domains of the self-reported ECog test. We found preliminary evidence in support of differential associations of ECog domains with Aβ and tau pathologies. Our findings suggest that a detailed characterization of self-reported cognitive complaints may provide useful diagnosis and prognosis information. For instance, difficulties in thinking ahead or in developing schedules in advance of anticipated events (Everyday Planning) may be an important sign of progressing tauopathy. Regarding the associations of SCD with Aβ, our findings are consistent with those from a study by Amariglio and colleagues reporting that higher [^{11}C]PiB-PET binding in normal individuals was primarily associated with both subjective complaints related to memory and Everyday Organization (Amariglio et al., 2012). Given that the episodic memory is among the earliest cognitive domains reported in preclinical AD, it is plausible to assume that initial self-reported memory concerns are influenced by Aβ, which is the earliest known AD biomarker (Jack et al., 2013). However, these relationships may change across the disease severity (Barnes et al., 2006), possibly due to the diminished self-perception of cognitive decline in MCI and AD patients with advanced neurodegeneration (Carr et al., 2000), or the plateauing of Aβ accumulation at advanced disease stages.

We found that the most robust models for Everyday Planning and Everyday Visuospatial included tau only. When excluding Aβ-positive participants, the strongest model for all ECog domains related to executive functioning (Everyday Planning, Everyday Organization, and Everyday Divided Attention) and visuospatial skills included tau. It is possible that subjective decline of the executive function and visuospatial skills in the absence of substantial Aβ load may be an early sign of primary age-related tauopathy (PART). Josephs and colleagues (Josephs et al., 2017) analyzed 52 pathologically definite PART cases and found, after accounting for age at clinical examination, a significant association between tau burden and executive function and visuospatial skills. While the strongest models for the objective cognitive measures included Aβ by itself or together with tau (ADNI-MEM), the strongest models for the subjective cognitive measures included either tau only (Planning and Visuospatial) or Aβ only (Memory and Organization). These associations remained significant after adjusting each subjective cognitive model of table 4 with objective cognitive measures such as MMSE ($p<0.021$) and ADNI-MEM ($p<0.027$). If further validated, our findings may lay a conceptual foundation for an early prediction of neuropathological designations (e.g., PART and AD trajectories) based on domain-specific SCD characterization. A direct comparison of our finding with previous studies is not straightforward due to the heterogeneity in the selected SCD instruments and age differences across these studies. Currently, there is a lack of a standardized framework to assess SCD across different research groups (Rabin et al., 2015). Consequently, different SCD instruments may not have the same relationships with AD pathologies. Our ADNI CN subjects were 78±8 years of age and presented a more clinically advanced group in

comparison with other studies, such as the clinically normal group of the Harvard Aging Brain Study (Buckley et al., 2017). Future research should include younger subjects (and other cohorts) to help establish the validity of SCD as a prescreening tool for predicting individual pathological profiles (prevalence of Aβ, tau, or both) before conducting PET scans or lumbar punctures to determine evidence of biomarker positivity, thus reducing the costs associated with the selection of appropriate candidates for clinical trials that target a specific pathology (tau or Aβ).

The post hoc analysis with the weighted two-point correlation curves confirmed the associations of tau with Everyday Visuospatial and Everyday Planning. Moreover, and together with global Aβ, wS_2-based tau was present in the strongest model for predicting Everyday Organization and Everyday Memory (without interacting with Aβ). There is no reason to assume that tau should not be associated with subjective memory complaints in normal subjects. However, these associations may have gone undetected with SUVR-based tau measures, particularly when using Everyday Memory instead of more sensitive composite memory scores similar to Buckley et al. (Buckley et al., 2017). The overall associations between wS_2-based tau and most cognitive measures were higher than the SUVR-based estimates of tau burden, possibly due to several methodological advantages of this metric which may be relevant to early tau characterization in normal subjects when the [^{18}F]flortaucipir SUVR signal is low and likely to affected by the background off-target binding (Baker SL, 2019). However, the results of wS_2-based texture analysis should be interpreted with caution until future investigations can validate this technique with pathological data.

In summary, this study shows the significance of the subjective cognitive concept in normal and pathological aging using data from clinically normal ADNI subjects. Our analyses did not include longitudinal data. However, as ADNI is an ongoing database, more follow-up scans will be available in the upcoming years to evaluate longitudinal associations between Everyday Cognition domains and AD pathologies and determine how they change across different clinical diagnostic groups.

Conclusions

In clinically normal subjects, individual domains of subjective cognitive decline have differential associations with Aβ and tau. Unlike subjective cognitive measures, the best prediction models of objective cognitive measures include Aβ. Detailed characterization of subjective cognitive decline may render a valuable tool for pathological prediction (presence of Aβ, tau, or both) and has the potential to improve the identification of individuals with the greatest risk of future dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The best models for predicting SCD domains of memory and organization include Aβ.
- The best models for SCD domains of planning and visuospatial skills include tau.
- Detailed characterization of SCD may help predict the AD pathological designations.

TABLE 1.

Subject demographics, cognitive performance measures, APOE-Ɛ4 status, and Aβ-positivity

Parameters	Values
Subjects, n	86
Females, n	39
Age, mean yr ± SD	78 ± 8
APOE-Ɛ4 carriers, n	24
Global [^{18}F]florbetapir uptake, mean SUVR ± SD	1.2 ± 0.2
Aβ-positive (based on 1.11 cutoff for global florbetapir SUVR)	38
Objective cognitive performance tests (mean ± SD)	
MMSE	28± 2
ADAS-cog	8±4
ADNI-MEM	0.9 ±0.6
ADNI-EF	0.9±0.8
Self-reported ECog measures (mean ± SD)	
Everyday Memory	1.7±0.5
Everyday Language	1.5± 0.5
Everyday Visuospatial Abilities	1.0 ±0.3
Everyday Planning	1.2 ±0.4
Everyday Organization	1.3± 0.4
Everyday Divided Attention	1.5 ±0.6

Table 2.

Associations of regional [^{18}F]flortaucipir SUVR values with objective cognitive performance measures and self-reported ECog measures. All associations included age, gender, and APOE-Ɛ4 status as covariates.

	Outcome	Predictor: Regional flortaucipir SUVR	β	SE	P-value	R^2
	MMSE	Braak I	−3.9	1.45	**0.008***	0.20
		Braak III-IV	−4.7	1.93	**0.018·**	0.18
		Braak V-VI	−4.9	2.67	**0.07·**	0.15
	ADAS_cog	Braak I	4.70	3.14	0.14	0.22
		Braak III-IV	2.72	4.21	0.52	0.21
		Braak V-VI	2.73	5.71	0.63	0.21
Objective Cognitive Measures	**ADNI-EF**	Braak I	−1.08	0.63	**0.09·**	0.18
		Braak III-IV	−1.48	0.83	**0.08·**	0.18
		Braak V-VI	−1.90	1.13	**0.10·**	0.18
	ADNI-MEM	Braak I	−0.38	0.52	0.45	0.16
		Braak III-IV	−0.23	0.68	0.73	0.16
		Braak V-VI	−0.95	0.92	0.31	0.17
	Everyday Memory	Braak I	0.63	0.43	0.14	0.16
		Braak III-IV	0.42	0.57	0.46	0.14
		Braak V-VI	0.69	0.77	0.37	0.15
	Everyday Language	Braak I	0.36	0.44	0.42	0.11
		Braak III-IV	0.33	0.59	0.58	0.10
		Braak V-VI	0.58	0.79	0.47	0.11
Subjective Cognitive Measures	**Everyday Visuospatial**	Braak I	0.43	0.26	**0.09·**	0.11
		Braak III-IV	0.25	0.34	0.47	0.09
		Braak V-VI	0.45	0.46	0.33	0.10
	Everyday Planning	Braak I	0.78	0.30	**0.011***	0.19
		Braak III-IV	0.76	0.41	**0.07·**	0.15
		Braak V-VI	1.30	0.54	**0.018·**	0.17
	Everyday Organization	Braak I	0.64	0.34	**0.06·**	0.08
		Braak III-IV	0.47	0.46	0.30	0.05
		Braak V-VI	0.47	0.62	0.45	0.04
	Everyday Divided	Braak I	−0.07	0.49	0.89	0.11
	Attention	Braak III-IV	0.11	0.66	0.86	0.11
		Braak V-VI	0.52	0.89	0.56	0.12

Significance codes (Bonferroni-adjusted P-value 0.05/3= 0.016): 0

‘*’ 0.016

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TABLE 3.

Associations of regional tau accumulation with objective cognitive performance measures and self-reported ECog (age, sex, and APOE-Ɛ4 status included as covariates).

	Outcome	Predictor: Regional florbetapir SUVR	β	SE	P-value	R^2
Objective Cognitive Measures	**MMSE**	Parietal	−4.45	0.91	**<0.0001***	0.33
		Frontal	−3.95	0.99	**0.0001***	0.27
		Temporal	−4.25	1.15	**0.0004***	0.25
		Cingulate	−3.69	1.00	**0.0004***	0.25
	ADAS cog	Parietal	7.57	2.02	**0.0003***	0.33
		Frontal	7.58	2.10	**0.0005***	0.32
		Temporal	8.49	2.42	**0.0007***	0.32
		Cingulate	6.95	2.14	**0.002***	0.30
	ADNI-EF	Parietal	−0.96	0.43	**0.027·**	0.20
		Frontal	−1.08	0.44	**0.016·**	0.21
		Temporal	−0.93	0.51	**0.07·**	0.18
		Cingulate	−0.90	0.45	**0.05·**	0.19
	ADNI-MEM	Parietal	−0.74	0.35	**0.03·**	0.21
		Frontal	−0.80	0.36	**0.03·**	0.21
		Temporal	−0.85	0.42	**0.04·**	0.20
		Cingulate	−0.68	0.36	**0.06·**	0.19
	Everyday Memory	Parietal	0.73	0.29	**0.0126·**	0.21
		Frontal	0.76	0.29	**0.0125***	0.21
		Temporal	0.78	0.34	**0.026·**	0.19
		Cingulate	0.74	0.30	**0.016·**	0.20
	Everyday Language	Parietal	0.51	0.30	**0.098·**	0.13
		Frontal	0.49	0.31	0.12	0.13
		Temporal	0.59	0.36	0.11	0.13
		Cingulate	0.44	0.32	0.17	0.12
Subjective Cognitive Measures	**Everyday Visuospatial**	Parietal	0.27	0.18	0.13	0.11
		Frontal	0.33	0.18	**0.07·**	0.12
		Temporal	0.25	0.21	0.24	0.10
		Cingulate	0.29	0.19	0.12	0.11
	Everyday Planning	Parietal	0.17	0.21	0.43	0.11
		Frontal	0.13	0.22	0.57	0.11
		Temporal	0.08	0.26	0.77	0.10
		Cingulate	0.11	0.22	0.61	0.11

Outcome	Predictor: Regional florbetapir SUVR	β	SE	P-value	R^2
Everyday	Parietal	0.65	0.22	**0.006***	0.13
Organization	Frontal	0.65	0.24	**0.008***	0.12
	Temporal	0.74	0.27	**0.008***	0.12
	Cingulate	0.67	0.23	**0.007***	0.13
Everyday Divided	Parietal	0.05	0.34	0.86	0.11
Attention	Frontal	0.07	0.34	0.85	0.11
	Temporal	0.04	0.41	0.91	0.11
	Cingulate	0.05	0.35	0.89	0.11

Significance codes (Bonferroni-adjusted P-value 0.05/4= 0.0125): 0

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0.0125

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0.1

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TABLE 4:

The strongest models for predicting each objective cognitive measure (MMSE, ADAS_Cog, ADNI-EF, ADNI-MEM) and each ECog domain (Memory, Language, Visuospatial, Planning, Organization, Divided Attention).

	All CN subjects		**Aβ-negative CN subjects**	
Outcome	Best model	Adjusted R^2	Best model	Adjusted R^2
Objective Cognitive Measures				
MMSE	Aβ(temp *, par *), Age *	0.34	Age *, Aβ(front ˙)	0.14
ADAS-Cog	Aβ(par *), Age *	0.29	Age *, Aβ(temp)	0.18
ADNI-EF	Aβ(front *), Age *	0.18	Age *, APOE-Ɛ4, Tau(Braak III-IV ˙), Aβ(par ˙, temp ˙, cing *, front *)	0.31
ADNI-MEM	Aβ(front *), Age *, Tau(Braak III-IV, Braak V-VI)	0.19	Aβ(front *, cing *), Sex ˙, Age, Tau(Braak III-IV)	0.20
Subjective Cognitive Measures				
Everyday Memory	Aβ (par *), Age, Sex	0.17	Aβ (cing ˙), Age ˙, APOE-Ɛ4	0.11
Everyday Language	Age, Sex, Aβ (par ˙)	0.09	None	
Everyday Visuospatial	Age-, Tau(Braak I *, Braak III-IV *, Braak V-VI)	0.11	Age, Tau (Braak I *)	0.07
Everyday Planning	Age *, Tau(Braak I *, Braak III-IV *, Braak V-VI *)	0.19	Age-, Tau (Braak I *), APOE-Ɛ4	0.18
Everyday Organization	Aβ(par *)	0.10	Tau (Braak III-IV *, Braak V-VI), Aβ (cing *, temp *), APOE-Ɛ4	0.28
Everyday Divided Attention	Age-, APOE-Ɛ4 *	0.08	Tau(Braak III-IV *, Braak V-VI *), Sex ˙	0.16

Blue Cells are models that included only Aβ with $p<0.05$.

Green cells are models that included only tau ($p<0.05$).

Red color present models that included both pathologies.

Significance codes: 0

‘*’ 0.05

‘.’ 0.1

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