



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



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ARTICLE INFO

Article history:

Received 24 October 2018

Received in revised form 13 May 2019

Accepted 15 May 2019

Available online 23 May 2019

Keywords:

[¹⁸F]florbetapir

Neurofibrillary tau tangles

Subjective cognitive decline

Amyloid beta plaques

Aging

Alzheimer's disease

[¹⁸F]florbetapir

ABSTRACT

We evaluated the associations of subjective (self-reported everyday cognition [ECog]) and objective cognitive measures with regional amyloid- β (A β) and tau accumulation in 86 clinically normal elderly subjects from the Alzheimer's Disease Neuroimaging Initiative. 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 [¹⁸F]florbetapir and [¹⁸F]flor-taucipir uptake and how these associations compared to those obtained with objective cognitive measures. A texture analysis, the weighted 2-point correlation, was used as an additional approach for estimating the whole-brain tau burden without positron emission tomography intensity normalization. Although the strongest models for ECog domains included either tau (planning and visuospatial) or A β (memory and organization), the strongest models for all objective measures included A β . In A β -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 A β and tau in clinically normal adults. Detailed characterization of ECog may render a valuable prescreening tool for pathological prediction.

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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 Alzheimer's disease (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 SCD in the clinically normal (CN) 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 (A β) plaques and neurofibrillary tangles 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 nondemented subjects. Previous research has established an association between SCD and preclinical AD pathologies (Amariglio et al., 2012, 2015, 2018; 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 A β pathology. A recent study by Buckley et al., 2017, reported that preclinical SCD is associated with both increasing entorhinal tau

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burden and (to a lesser extent) global A β burden. However, they found that tau and A β do not necessarily interact to influence preclinical SCD.

In this study, we have conducted a comprehensive examination of the associations of 2 major AD pathologies (A β , 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 CN 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 used 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 2-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 positron emission tomography (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 be affected by the background off-target binding (Baker et al., 2019).

2. Materials and 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, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Cognitive, demographic, and imaging data for this study were collected from 86 CN ADNI subjects. We did not include any early amnesic mild cognitive impairment, MCI, or AD subjects because this study focuses on associations between AD pathologies (A β 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 Clinical Dementia Rating of 0, and education-adjusted score on delayed recall of paragraph A from Wechsler Memory Scale Logical Memory II ≥ 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, 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 Alzheimer's Disease Assessment Scale-cognitive subscale, Rey Auditory Verbal Learning Test, MMSE, and Logical Memory Task. Self-reported ECog (Farias et al., 2008) scores were used as a measure of SCD. The self-rated ECog questionnaire comprised 6 subscales, including everyday memory, everyday language, everyday visuospatial abilities, everyday planning, everyday organization, and everyday divided attention.

2.3. Preprocessing of imaging data

2.3.1. 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 \pm 10% of [18 F]Flortaucipir was followed by a 30-minute (6×5 min frames) PET scan starting at 75–105 minutes after injection. The temporal frames were uploaded to University of Southern California Laboratory of Neuroimaging ADNI database 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 resolution. [18 F]Flortaucipir SUVR values from 6 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 (GM) uptake (Baker et al., 2017) and regrouped into Braak I (entorhinal), Braak III-IV (limbic), and Braak V-VI (isocortical) regions of interest (ROIs).

2.3.2. Amyloid- β positron emission tomography

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 4 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 A β -positive individuals (Landau et al., 2012).

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

We used 3 types of regression models in R (www.R-project.org) to determine individual and combined associations between A β 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 apolipoprotein (APOE) $\epsilon 4$ 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 $\epsilon 4$ 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 stepwise 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, that is, 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 A β -negative subjects of the CN group. Interactions between predictors (model 3): We tested multiple 2-way interactions between individual regional tau, regional A β , age, sex, and APOE ϵ 4 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 the individual subjects' brain. We used this metric as an alternative approach for estimating the severity of global tau burden. We downloaded the ADNI standardized uptake value (SUV) 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 volume, and the cortical GM mask was segmented and applied to flortaucipir SUV image for the subsequent wS_2 analysis (MATLAB, 2018, MathWorks, Inc, Natick, Massachusetts). The wS_2 approach captures the image texture (spatial clustering) by pairwise comparison of the SUV signal intensities between different locations in GM. 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 wS_2 are described in previous literature (Blair et al., 1996; Jiao et al., 2008; Tewari et al., 2004). The 3-step regression analyses (see Section 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 A β SUV 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 A β SUV were tested in model 3.

3. Results

Table 1 provides a summary of subject-specific information, including age, sex, number of APOE ϵ 4 carriers, objective/subjective cognitive measures, global flortaucipir SUV values, and A β -positivity status. Of 86 subjects, 39 were women. The average age at the time of the tau PET scans was 78 ± 8 years. Of 86 subjects, 24 subjects were APOE ϵ 4 carriers and 38 subjects were A β -positive.

3.1. Associations of individual regional pathologies with cognitive measures while including age, sex, and APOE- ϵ 4 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

Table 1

Subject demographics, cognitive performance measures, APOE ϵ 4 status, and A β positivity

Parameters	Values
Subjects, n	86
Females, n	39
Age, mean $y \pm SD$	78 ± 8
APOE ϵ 4 carriers, n	24
Global [^{18}F]flortaucipir uptake, mean SUV $\pm SD$	1.2 ± 0.2
A β -positive (based on 1.11 cutoff for global flortaucipir SUV)	38
Objective cognitive performance tests (mean $\pm SD$)	
MMSE	28 ± 2
ADAS-cog	8 ± 4
ADNI-MEM	0.9 ± 0.6
ADNI-EF	0.9 ± 0.8
Self-reported ECog measures (mean $\pm SD$)	
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

Key: A β , amyloid- β ; ECog, everyday cognition; SUV, standardized uptake value ratio; MMSE, Mini-Mental State Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; ADNI-MEM, ADNI composite memory; ADNI-EF, ADNI composite executive function.

SUV measures while including age, sex, and APOE ϵ 4 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 SUV 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 SUV as the predictor. Associations with objective cognitive measures: The Braak SUV 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 A β SUV measures while including age, sex, and APOE ϵ 4 as covariates. The Bonferroni-corrected p -value of 0.0125 (0.5/4) was used to adjust for multiple comparisons across regional A β 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

Table 2
Associations of regional [¹⁸F]flortaucipir SUVR values with objective cognitive performance measures and self-reported ECog measures

Assessment type	Outcome	Predictor: Regional flortaucipir SUVR	β	SE	p-value	R ²
Objective Cognitive Measures	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
	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
		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
	ADNI-MEM	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 memory	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	
Everyday language	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	
Subjective Cognitive Measures	Everyday visuospatial	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 planning	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 organization	Braak I	−0.07	0.49	0.89	0.11
		Braak III-IV	0.11	0.66	0.86	0.11
		Braak V-VI	0.52	0.89	0.56	0.12

* or . associated with numbers in the table indicating that these values are either significant * or marginally significant .

Key: ADNI-MEM, ADNI composite memory; ADNI-EF, ADNI composite executive function; ECog, everyday cognition; SUVR, standardized uptake value ratio.

All associations included age, gender, and APOE ε4 status as covariates.

Significance codes (Bonferroni-adjusted p-value 0.05/3 = 0.016): 0; *** = 0.016; . = 0.1; * = 0.05.

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 (the 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 wS₂-based tau measures

With the simple regression model, we found significant associations between wS₂-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 ($p = 0.005$; $R^2 = 0.24$). In addition, we found significant associations between wS₂-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 wS₂-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 wS₂-based tau (but not Aβ). In addition, 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 wS₂-based tau and Aβ. We found significant interactions between wS₂-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 wS₂-based tau and global Aβ. However, when including regional Aβ SUVR values, we found a significant interaction between wS₂-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 wS₂-based tau and Aβ. We found significant interaction between tau and age in predicting MMSE.

Table 3
Associations to regional [¹⁸F]florbetapir SUVR values with objective cognitive performance measures and self-reported ECog (age, sex, and APOE ε4 status included as covariates)

Assessment type	Outcome	Predictor: Regional florbetapir SUVR	B	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
	ADAS_cog	Cingulate	−3.69	1.00	0.0004*	0.25
		Parietal	7.57	2.02	0.0003*	0.33
		Frontal	7.58	2.10	0.0005*	0.32
	ADNI-EF	Temporal	8.49	2.42	0.0007*	0.32
		Cingulate	6.95	2.14	0.002*	0.30
		Parietal	−0.96	0.43	0.027*	0.20
	ADNI-MEM	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
	Everyday memory	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
	Everyday language	Cingulate	−0.68	0.36	0.06*	0.19
		Parietal	0.73	0.29	0.0126*	0.21
		Frontal	0.76	0.29	0.0125*	0.21
	Everyday planning	Temporal	0.78	0.34	0.026*	0.19
		Cingulate	0.74	0.30	0.016*	0.20
		Parietal	0.51	0.30	0.098*	0.13
Everyday organization	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
	Everyday planning	Cingulate	0.29	0.19	0.12	0.11
		Parietal	0.17	0.21	0.43	0.11
		Frontal	0.13	0.22	0.57	0.11
	Everyday organization	Temporal	0.08	0.26	0.77	0.10
		Cingulate	0.11	0.22	0.61	0.11
		Parietal	0.65	0.22	0.006*	0.13
	Everyday divided attention	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 attention	Parietal	0.05	0.34	0.86	0.11	
	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	

** or '*' associated with numbers in the table indicating that these values are either significant ** or marginally significant '*'.

Key: ADNI-MEM, ADNI composite memory; ADNI-EF, ADNI composite executive function; ECog, everyday cognition; SUVR, standardized uptake value ratio. Significance codes (Bonferroni-adjusted *p*-value 0.05/4 = 0.0125); 0; *** = 0.0125; "*" = 0.1; "*" = 1.

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 CN subjects. Previous AD biomarker studies of SCD have primarily focused on the memory complaints (Amariglio et al., 2012, 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 et al reporting that higher [¹¹C] Pittsburgh compound B -positron emission tomography 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 because of 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.

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)

Outcome	All CN subjects		A β -negative CN subjects	
	Best model	Adjusted R ²	Best model	Adjusted R ²
Objective cognitive measures				
MMSE	Aβ (temp*, par*), age*	0.34	Age*, A β (front·)	0.14
ADAS-Cog	Aβ (par*), age*	0.29	Age*, A β (temp)	0.18
ADNI-EF	Aβ (front*), age*	0.18	Age*, APOE ϵ 4, tau (Braak III-IV·), A β (par·, temp·, cing*, front*)	0.31
ADNI-MEM	<i>Aβ (front*), age*, tau (Braak III-IV, Braak V-VI)</i>	0.19	<i>Aβ (front*, cing*), sex·, age, tau (Braak III-IV)</i>	0.20
Subjective cognitive measures				
Everyday memory	Aβ (par*), age, sex	0.17	A β (cing·), age·, APOE ϵ 4	0.11
Everyday language	Age, sex, A β (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 ϵ4	0.18
Everyday organization	Aβ (par*)	0.10	<i>tau (Braak III-IV*, Braak V-VI), Aβ (cing*, temp*), APOE ϵ4</i>	0.28
Everyday divided attention	Age·, APOE ϵ 4*	0.08	Tau (Braak III-IV*, Braak V-VI*), sex·	0.16

Key: A β , amyloid- β ; CN, cognitively normal; ADNI-MEM, ADNI composite memory; ADNI-EF, ADNI composite executive function; ECog, everyday cognition; MMSE, Mini-Mental State Examination; SUVR, standardized uptake value ratio.

Bolded cells are models that included only A β with $p < 0.05$.

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

Italics presents models that included both pathologies.

Significance codes: 0; "*" = 0.05; "." = 0.1; " " = 1.

We found that the most robust models for everyday planning and everyday visuospatial included tau only. When excluding A β -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 A β load may be an early sign of primary age-related tauopathy (PART). 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. Although the strongest models for the objective cognitive measures included A β by itself or together with tau (ADNI-MEM), the strongest models for the subjective cognitive measures included either tau only (planning and visuospatial) or A β 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 because of 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 aged 78 ± 8 years and presented a more clinically advanced group in comparison with other studies, such as the CN 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 A β , 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 A β).

The post hoc analysis with the weighted 2-point correlation curves confirmed the associations of tau with everyday visuospatial and everyday planning. Moreover, and together with global A β , wS₂-based tau was present in the strongest model for predicting

everyday organization and everyday memory (without interacting with A β). 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., 2017. The overall associations between wS₂-based tau and most cognitive measures were higher than the SUVR-based estimates of tau burden, possibly because of several methodological advantages of this metric, which may be relevant to early tau characterization in normal subjects when the [¹⁸F]florotau-cing SUVR signal is low and likely to be affected by the background off-target binding (Baker et al., 2019). However, the results of wS₂-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 CN 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 ECog domains and AD pathologies and determine how they change across different clinical diagnostic groups.

5. Conclusions

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

Disclosure

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

Acknowledgements

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National

Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc; Cogstate; Eisai Inc; Elan Pharmaceuticals, Inc; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc; Fujirebio; GE Healthcare; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co, Inc; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This study was supported by NIH grants R00 EB 009106, to SS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurobiolaging.2019.05.011>.

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