

Region-Specific Association of Subjective Cognitive Decline With Tauopathy Independent of Global β -Amyloid Burden

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IMPORTANCE The ability to explore associations between reports of subjective cognitive decline (SCD) and biomarkers of early Alzheimer disease (AD) pathophysiologic processes (accumulation of neocortical β -amyloid [$A\beta$] and tau) provides an important opportunity to understand the basis of SCD and AD risk.

OBJECTIVE To examine associations between SCD and global $A\beta$ and tau burdens in regions of interest in clinically healthy older adults.

DESIGN, SETTING, AND PARTICIPANTS This imaging substudy of the Harvard Aging Brain Study included 133 clinically healthy older participants (Clinical Dementia Rating Scale global scores of 0) participating in the Harvard Aging Brain Study who underwent cross-sectional flortaucipir F 18 (previously known as AV 1451, T807) positron emission tomography (FTP-PET) imaging for tau and Pittsburgh compound B carbon 11-labeled PET (PiB-PET) imaging for $A\beta$. The following 2 regions for tau burden were identified: the entorhinal cortex, which exhibits early signs of tauopathy, and the inferior temporal region, which is more closely associated with AD-related pathologic mechanisms. Data were collected from June 11, 2012, through April 7, 2016.

MAIN OUTCOMES AND MEASURES Subjective cognitive decline was measured using a previously published method of z-transforming subscales from the Memory Functioning Questionnaire, the Everyday Cognition battery, and a 7-item questionnaire. The $A\beta$ level was measured according to a summary distribution volume ratio of frontal, lateral temporal and parietal, and retrosplenial PiB-PET tracer uptake. The FTP-PET measures were computed as standardized uptake value ratios. Linear regression models focused on main and interactive effects of $A\beta$, entorhinal cortical, and inferior temporal tau on SCD, controlling for age, sex, educational attainment, and Geriatric Depression Scale score.

RESULTS Of the 133 participants, 75 (56.3%) were women and 58 (43.6%) were men; mean (SD) age was 76 (6.9) years (range, 55-90 years). Thirty-nine participants (29.3%) exhibited a high $A\beta$ burden. Greater SCD was associated with increasing entorhinal cortical tau burden ($\beta = 0.35$; 95% CI, 0.19-.52; $P < .001$) and $A\beta$ burden ($\beta = 0.24$; 95% CI, 0.08-.40; $P = .005$), but not inferior temporal tau burden ($\beta = 0.10$; 95% CI, -0.08 to 0.28; $P = .27$). This association between entorhinal cortical tau burden and SCD was largely unchanged after accounting for $A\beta$ burden ($\beta = 0.36$; 95% CI, 0.15-.58; $P = .001$), and no interaction influenced SCD ($\beta = -0.36$; 95% CI, -0.34 to 0.09; $P = .25$). An exploratory post hoc whole-brain analysis also indicated that SCD was predominantly associated with greater tau burden in the entorhinal cortex.

CONCLUSIONS AND RELEVANCE Subjective cognitive decline is indicative of accumulation of early tauopathy in the medial temporal lobe, specifically in the entorhinal cortex, and to a lesser extent, elevated global levels of $A\beta$. Our findings suggest multiple underlying pathways that motivate SCD that do not necessarily interact to influence SCD endorsement. As such, multiple biological factors must be considered when assessing SCD in clinically healthy older adults.

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Report of subjective cognitive decline (SCD) represents a known risk factor for future progression to Alzheimer disease (AD) dementia,¹ particularly in individuals with high β -amyloid ($A\beta$) levels.² Current preclinical staging criteria argue for the appearance of SCD in stage 3 of the preclinical trajectory after the presence of abnormal levels of $A\beta$ and neurodegeneration are evident.³ In clinically healthy adults, SCD is associated with abnormal levels of AD biomarkers of $A\beta$ and neurodegeneration, such as cerebrospinal fluid⁴ and neuroimaging markers of $A\beta$ burden,⁵ smaller entorhinal cortical⁶ and hippocampal⁷ volumes, and reduced brain glucose metabolism in AD regions of interest.⁸ Supporting evidence from postmortem studies also indicates that increased neuritic plaques,⁹ diffuse plaques, and neurofibrillary tangles are present in clinically healthy older adults with endorsement of SCD symptoms proximate to death.¹⁰ Building on previous observations relating SCD to $A\beta$ levels,⁵ we sought to clarify whether the anatomical distribution of tauopathy seen with positron emission tomography (PET) can lend explanatory power to the development of SCD in clinically healthy older adults. Early signs of tauopathy are apparent in the entorhinal cortices, regardless of the presence of $A\beta$ according to in vivo neuroimaging¹¹⁻¹⁴ and postmortem studies.¹⁵⁻¹⁷ In AD, tau deposits expand into adjacent neocortical regions as $A\beta$ burden increases, and an increasing $A\beta$ level is associated with greater tau burden in the entorhinal and neocortical regions.¹¹ We sought to identify the context of successive tau deposition that is associated with SCD.

Specifically, we related the development of SCD to the specific anatomy of tau deposition revealed with flortaucipir F 18 (previously known as AV 1451, T807) PET (FTP-PET) in clinically healthy older adults. Our hypothesis was that associations between SCD and tau-specific anatomy (ie, with one or both of the entorhinal or inferior temporal FTP-PET regions) could inform the earliest appearance of SCD. We also investigated how tau deposition in these regions might interact with $A\beta$, as measured with carbon 11-labeled Pittsburgh compound B PET (PiB-PET), to influence SCD and found that greater $A\beta$ level was not associated with stronger associations between SCD and tau deposition.

Methods

Study Description

A total of 133 clinically healthy participants from the Harvard Aging Brain Study (HABS) underwent $A\beta$ imaging with PiB-PET and FTP-PET from June 11, 2012, through April 7, 2016. To be enrolled in the HABS study, participants needed to score 0 on the Clinical Dementia Rating Scale (CDR) global score (range, 0-0.5, with higher scores indicating greater dementia),¹⁸ greater than 25 on the Mini-Mental State Examination (range, 25-30, with higher scores indicating poorer cognitive performance),¹⁹ and less than 11 on the Geriatric Depression Scale (GDS; range, 0-11 for our study, with higher scores indicating greater endorsement of depression)²⁰ and perform within validated educational attainment-adjusted norms on Logical Memory II delayed recall.²¹ To be included in this study, participants were also required to have FTP-PET imaging within 18 months of

Key Points

Question How do concerns about subjective cognitive decline in clinically healthy older adults relate to tau burden in brain regions of interest and global β -amyloid burden?

Findings In this imaging study of 133 clinically healthy adults, subjective cognitive decline was associated with greater tau burden only in the entorhinal cortical region and, to a lesser extent, greater global β -amyloid levels; however, neither pathologic factor exerted an interactive influence on subjective cognitive decline.

Meaning Subjective cognitive decline is an important early indicator of abnormal tau and β -amyloid burden in clinically healthy adults with multiple underlying pathways; as such, multiple Alzheimer disease pathologic factors must be examined when considering the appearance of subjective cognitive decline in clinically healthy older adults.

neuropsychological testing. Median delay between PET and neuropsychological testing was 111 days (range, -5 to 536 days). Baseline demographic characteristics can be found in **Table 1**. Participants provided written informed consent and underwent investigation under protocols approved by the Partners Human Research Committee at Massachusetts General Hospital, Boston.

Development of the SCD composite has been published previously.²⁴ In brief, the composite was created by calculating the mean z-transformed subscales from the Memory Functioning Questionnaire²² (the first 18 items of the General Frequency of Forgetting), the Everyday Cognition battery²³ (the Memory section from the self-report version), and a 7-item questionnaire adapted from the Structured Telephone Interview for Dementia Assessment (using the present sample as the reference group).²⁴ The Memory Functioning Questionnaire was reversed before calculating the mean with the other measures. To account for the potential confounding of poor mood related to SCD, we used the GDS score to measure depressive symptoms. The GDS was adjusted for the present analyses to remove 4 items that featured elements of cognitive concern (Do you feel you have more problems with memory than most [question 14]? Do you have trouble concentrating [question 26]? Is it easy for you to make decisions [question 29]? and Is your mind as clear as it used to be [question 30]?), which resulted in a total score of 26.

For $A\beta$ PET imaging, acquisition of PiB-PET data in the HABS has previously been described in detail.²⁵ In brief, PiB-PET images were acquired with an 8.5- to 15.0-mCi bolus injection, followed by a 60-minute dynamic acquisition in 69 volumes (12 \times 15 seconds and 57 \times 60 seconds). For tau PET imaging, FTP-PET (also known as ¹⁸F-labeled AV1451 or T807) was prepared at Massachusetts General Hospital as previously described.²⁶ Images were acquired from 80 to 100 minutes in 4 \times 5-minute frames after a mean (SD) bolus injection of 10.0 (1.0) mCi. All PET data were reconstructed, attenuation corrected, evaluated for head motion, and coregistered to the corresponding T1 image for each patient using 6 *df* rigid body registration. For PiB-PET and FTP-PET, cerebellar gray matter was used as the reference region from the FreeSurfer

Table 1. Baseline Demographic Characteristics According to A β Status

Characteristic	Study Group ^a			P Value
	All (n = 133)	A β Negative (n = 94)	A β Positive (n = 39) ^b	
Age, y	75.9 (7.0)	74.9 (7.2)	78.4 (5.7)	.003
Educational attainment, y	15.8 (3.0)	15.8 (3.1)	15.7 (2.9)	.94
Female, No. (%)	75 (56.4)	54 (57.4)	21 (53.8)	.85
SCD composite ^c	0.01 (0.8)	-0.09 (0.7)	0.11 (0.9)	.15
GDS ^d	3.33 (2.8)	3.31 (2.8)	3.38 (2.9)	.90
A β FLR DVR (PVC)	1.42 (0.4)	1.18 (0.1)	2.00 (0.4)	<.001
EC FTP-PET SUVR (PVC)	1.33 (0.3)	1.22 (0.2)	1.43 (0.4)	<.001
IT FTP-PET SUVR (PVC)	1.45 (0.2)	1.41 (0.1)	1.48 (0.2)	.02
High A β burden, No. (%)	39 (29.3)	NA	NA	NA
APOE ϵ 4 carrier, No. (%)	35 (26.3)	14 (14.9)	23 (59.0)	<.001

Abbreviations: A β , β -amyloid; APOE ϵ 4, apolipoprotein E ϵ 4 allele; DVR, distribution volume ratio; EC, entorhinal cortex; FLR, frontal, lateral, and retrosplenial tracer; FTP, flortaucipir F 18; GDS, Geriatric Depression Score; IT, inferior temporal cortex; NA, not applicable; PVC, partial volume correction; SCD, subjective cognitive decline; SUVR, standardized uptake value ratio.

^a Unless otherwise indicated, data are expressed as mean (SD).

^b Indicates cutoff of Pittsburgh compound B PVC DVR FLR of greater than 1.34 using gaussian mixture modeling A β .

^c Calculated as the mean z-transformed subscales from the Memory Functioning Questionnaire,²² the Everyday Cognition battery,²³ and a 7-item questionnaire adapted from the Structured Telephone Interview for Dementia Assessment. Scores represent a z-score composite ranging from -1.15 to 2.81, with higher scores indicating greater subjective concern.

^d Scores range from 0 to 11, with higher scores indicating greater development of depression.

aseg atlas as previously described,^{11,27} with FTP-PET measures computed as standardized uptake value ratios (SUVRs), whereas for PiB-PET, a summary distribution volume ratio (DVR) was used. For PiB-PET and FTP-PET, we performed partial volume correction by using the geometric transform matrix method^{28,29} as implemented in FreeSurfer software (version 6.0; <https://surfer.nmr.mgh.harvard.edu/>) and described by Greve and colleagues.³⁰ We used a slightly modified FreeSurfer atlas mapped to each participant's native structural space that included regions of interest for cerebrospinal fluid, white matter, and extracerebral structures. The partial volume correction processing was performed assuming a uniform 6-mm point spread function.

A composite PiB-PET DVR measure of cortical A β burden consisting of frontal, lateral, and retrosplenial tracer (FLR) uptake³¹ was determined for each participant by calculating the median PiB uptake value across voxels in the precuneus, rostral anterior cingulate, medial orbitofrontal, superior frontal, rostral middle frontal, inferior parietal, inferior temporal, and middle temporal regions of interest from both hemispheres divided by the median PiB-PET DVR from cerebellar gray matter. The regions constituting the FLR are known to show elevated PiB binding in patients with AD dementia.³²

For FTP-PET, we focused our analyses on 2 structurally defined regions of interest, the entorhinal and inferior temporal cortices. The entorhinal cortex was chosen because it is among the first regions to develop tau pathologic changes, even in the absence of A β . The inferior temporal cortex was used as the current best choice of a surrogate marker of early AD-related tauopathy in the neocortex; inferior temporal cortex FTP-PET shows the largest effect size between impaired and nonimpaired individuals as reported by Johnson and colleagues.¹¹

Whole-brain maps were also used for post hoc analyses to determine SCD-associated tau and A β maps; these maps were created by taking the participants' image-mapping native PET images to fsaverage surface in FreeSurfer and smoothing with

the equivalent of an 8-mm Gaussian kernel. Uncorrected thresholds ($P < .025$, 1-tailed test) were used for the purposes of exploratory analysis for the general linear model of FTP-PET SUVR approximated as SCD + age. Analyses were conducted using MATLAB (generalized linear model scripts can be accessed at <http://mrtools.mgh.harvard.edu/>). For the whole-brain PiB analysis, the generalized linear model was conducted with A β FLR DVR approximated as SCD + age.

Statistical Analysis

We used statistical package R (version 3.2.2; <https://cran.r-project.org/bin/windows/base/old/3.2.2/>), along with the QuantPsyc, car, MASS, relaimpo, sjPlot, lm.ridge, npreg, and sjmisc extension packages. Demographic comparisons were made using independent-sample and 2-tailed t tests and χ^2 tests of independence. A series of linear hierarchical regressions were conducted to determine the influence of tau and A β on SCD after accounting for covariates (age, educational attainment, sex, depressive symptoms [adjusted GDS score], and delay from neuropsychological testing to FTP-PET scanning) and subsequently within the context of an interaction between tau and A β . Multiple comparisons for these 8 linear models were accounted for using a Šidák-corrected α of $1 - (1 - 0.05)^{1/8} = 0.006$. Because A β FLR data are positively skewed, comparison nonparametric analyses for robustness were run using rigid local linear kernel-based estimation analyses³³ and bootstrapped with 399 independently identically distributed draws (with bootstrapped P values included in Table 2). Model 1 approximated SCD with covariates; model 2a, SCD with entorhinal cortex FTP-PET + covariates; model 2b, SCD with inferior temporal cortex FTP-PET + covariates; model 3, SCD with A β FLR + covariates; model 4a, SCD with entorhinal cortex FTP-PET \times A β FLR + covariates; and model 4b, SCD with inferior temporal cortex FTP-PET \times A β FLR + covariates, where SCD is defined as described above and covariates included age, educational attainment, sex, depressive symptoms, and delay time from neuropsychological testing to FTP-PET scan.

Table 2. Regression Coefficients Estimating SCD From EC and IT Tau and Covariates^a

Covariate by Model (R ² Value)	β (95% CI)	P Value	Bootstrapped P Value ^b	Relative Importance (% Explained of R ² Value) ^c
Model 2a (0.24)				
EC tau	0.35 (0.19 to 0.52)	<.001	<.001	47
Age	0.06 (-0.11 to 0.23)	.49	.36	11
Male	0.11 (-0.04 to 0.27)	.15	.69	4
Educational attainment	-0.06 (-0.21 to 0.10)	.48	.59	0
Adjusted GDS score	0.30 (0.14 to 0.45)	<.002	<.001	36
Time from NP to FTP-PET	0.05 (-0.10 to 0.20)	.53	.53	0
Model 2b (0.14)				
IT tau	0.10 (-0.08 to 0.28)	.27	.32	10
Age	0.14 (-0.04 to 0.32)	.13	.10	25
Male	0.08 (-0.08 to 0.25)	.34	.42	5
Educational attainment	-0.02 (-0.19 to 0.14)	.79	.91	0
Adjusted GDS	0.28 (0.11 to 0.44)	.001	<.001	58
Time from NP to FTP-PET	0.05 (-0.11 to 0.22)	.53	.53	1
Model 3 (0.18)				
Aβ FLR	0.24 (0.08 to 0.40)	.005	.005	29
Age	0.13 (-0.04 to 0.30)	.13	.11	19
Male	0.08 (0.14 to 0.46)	.31	.39	4
Educational attainment	-0.03 (-0.20 to 0.13)	.67	.77	0
Adjusted GDS	0.30 (0.14 to 0.46)	<.001	<.001	47
Time from NP to FTP-PET	0.05 (-0.11 to 0.21)	.56	.56	0
Post hoc EC tau and IT tau model (0.25)				
EC tau	0.45 (0.24 to 0.65)	<.001	<.001	45
IT tau	-0.16 (-0.37 to 0.04)	.12	.03	6
Age	0.09 (-0.08 to 0.27)	.29	.18	10
Male	0.10 (-0.05 to 0.26)	.20	.40	4
Educational attainment	-0.04 (-0.20 to 0.12)	.61	.87	0
Adjusted GDS	0.29 (0.14 to 0.45)	<.001	<.001	33
Time from NP to FTP-PET	0.04 (-0.11 to 0.20)	.59	.59	0
Model 4a (0.25)				
EC tau	0.36 (0.15 to 0.58)	.001	<.001	35
Age	0.04 (-0.13 to 0.21)	.66	.58	8
Male	0.10 (-0.05 to 0.26)	.20	.09	4
Educational attainment	-0.06 (-0.21 to 0.10)	.48	.54	0
Adjusted GDS	0.30 (0.14 to 0.46)	<.01	<.001	35
Aβ FLR	0.13 (-0.06 to 0.33)	.18	0.05	11
EC tau × Aβ FLR	-0.36 (-0.34 to 0.09)	.25	.18	4
Time from NP to FTP-PET	0.03 (-0.12 to 0.19)	.67	.67	0
Model 4b (0.19)				
IT tau	-0.14 (-0.76 to 0.47)	.65	.79	5
Age	0.14 (-0.05 to 0.32)	.15	.11	16
Male	0.08 (-0.08 to 0.25)	.31	.53	4
Educational attainment	-0.04 (-0.20 to 0.13)	.66	.78	0
Adjusted GDS	0.30 (0.14 to 0.46)	<.001	<.001	48
Aβ FLR	0.22 (0.03 to 0.41)	.03	.02	25
IT tau × Aβ FLR	0.16 (-0.47 to 0.79)	.61	.64	0
Time from NP to FTP-PET	0.05 (-0.11 to 0.21)	.53	.53	0

Abbreviations: Aβ, β-amyloid; APOEε4, apolipoprotein E ε4 allele; DVR, distribution volume ratio; EC, entorhinal cortex; FLR, frontal, lateral, and retrosplenial; FTP-PET, flortaucipir F 18 positron emission tomography; GDS, Geriatric Depression Score; IT, inferior temporal cortex; NA, not applicable; NP, neuropsychological testing; PVC, partial volume correction; SCD, subjective cognitive decline; SUVR, standardized uptake value ratios.

^a All variables are centered. Models are described in the Statistical Analysis subsection of the Methods section.

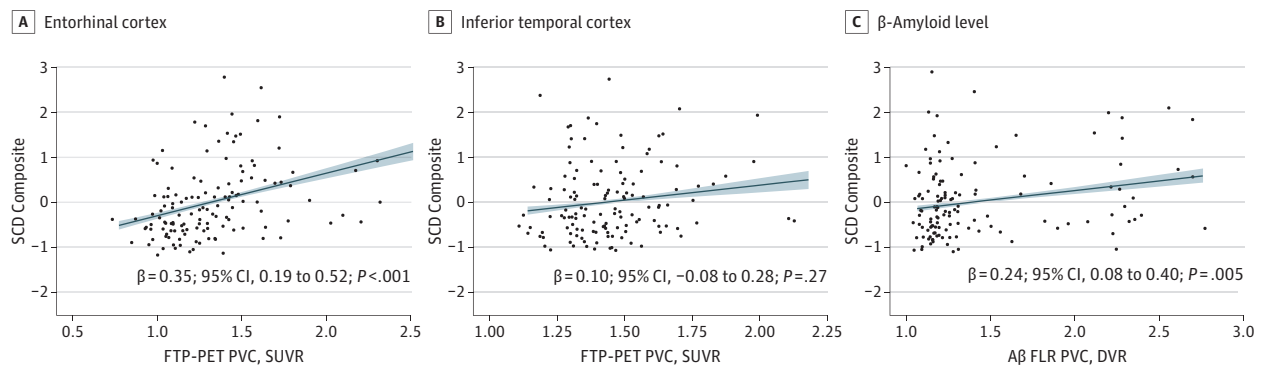
^b Nonparametric local linear kernel-based estimation using independently identically distributed draw bootstrapping (time from NP not included in model).

^c Relative importance using the metric of Lindemann et al.³⁴

The fit of each increasingly complex model was tested against the fit of the prior model by using analysis of variance. A more complex model was rejected in favor of a simpler model if the analysis of variance revealed $P > .05$. Pearson correlations between all covariates and the variables of interest were included to denote the associations between covariates and the dependent variable.

Two post hoc exploratory, whole-brain, voxel-wise general linear models were also conducted to identify evidence of positive associations between (1) voxel-wise FTP-PET SUVR and SCD after covarying age and (2) voxel-wise Aβ FLR DVR and SCD after covarying age. Owing to the exploratory nature of these analyses, parsimonious models were run that accounted only for age. The rationale behind these analyses was

Figure 1. Partial Regression Plots



Plots depict the associations between a composite measure of subjective cognitive decline (SCD; described by Amariglio et al²⁴; greater numbers indicate greater development of SCD) and flortaucipir F 18 positron emission tomography (FTP-PET; previously known as AV 1451, T807) standardized uptake value ratio (SUVR) in the entorhinal and inferior temporal cortices and

between SCD and β -amyloid (A β) frontal, lateral, and retrosplenial tracer (FLR) uptake summary distribution ratio (DVR). Diagonal lines indicate lines of best fit for the correlational analysis; shading, 95% CI; and data points, study participants. PVC indicates partial volume correction.

to determine the spatial specificity of positive associations between SCD and tau and between SCD and A β .

Results

We included 133 patients, of whom 75 (56.3%) were women and 58 (43.6%) were men, with a mean (SD) age of 76 (6.9) years (range, 55-90 years). Increasing SCD was associated with greater age ($r_{131} = 0.23$; $P = .007$) and greater adjusted GDS score ($\rho_{131} = 0.28$; $P = .001$). No effect of sex ($t_{123.4} = -1.01$; $P = .31$) or years of education ($\rho_{131} = 0.01$; $P = .89$) was found on SCD. The mean score on the SCD composite was 0.015 (range, -1.15 to 2.81, with a slight positive skew), with a score above the mean indicating greater cognitive concern.

Greater entorhinal cortical tau deposition was found to be associated with significantly greater SCD beyond the covariates ($\beta = 0.35$; 95% CI, 0.19-.52; $P < .001$) (Figure 1A). The adjusted GDS score was also found to be associated with significantly greater SCD. Including entorhinal cortical tau in model 2a elicited a significantly better-fitting model than that including only covariates (model 1 vs model 2a: change in $F = 17.6$; $P < .001$). No association was found between SCD and inferior temporal cortex tau ($\beta = 0.10$; 95% CI, -0.08 to 0.28; $P = .27$) (model 2b) (Figure 1B), and model fit was not better after the inclusion of inferior temporal cortex tau as a factor (model 1 vs 2b: change in $F = 1.2$; $P = .27$). Table 2 depicts model estimates for all regression models. Greater A β FLR was found to be associated with significantly greater SCD ($\beta = 0.24$; 95% CI, 0.08-.40; $P = .005$; model 3).

A post hoc calculation of relative importance that used the metric of Lindeman et al³⁴ was run for each factor in the linear regression entorhinal cortex tau model (model 2a in Table 2). The entorhinal cortical tau was found to account for most of overall explained variance in the model (47%), followed by the adjusted GDS score (36%) and other covariates (16%). A post hoc linear regression was run to determine whether entorhinal

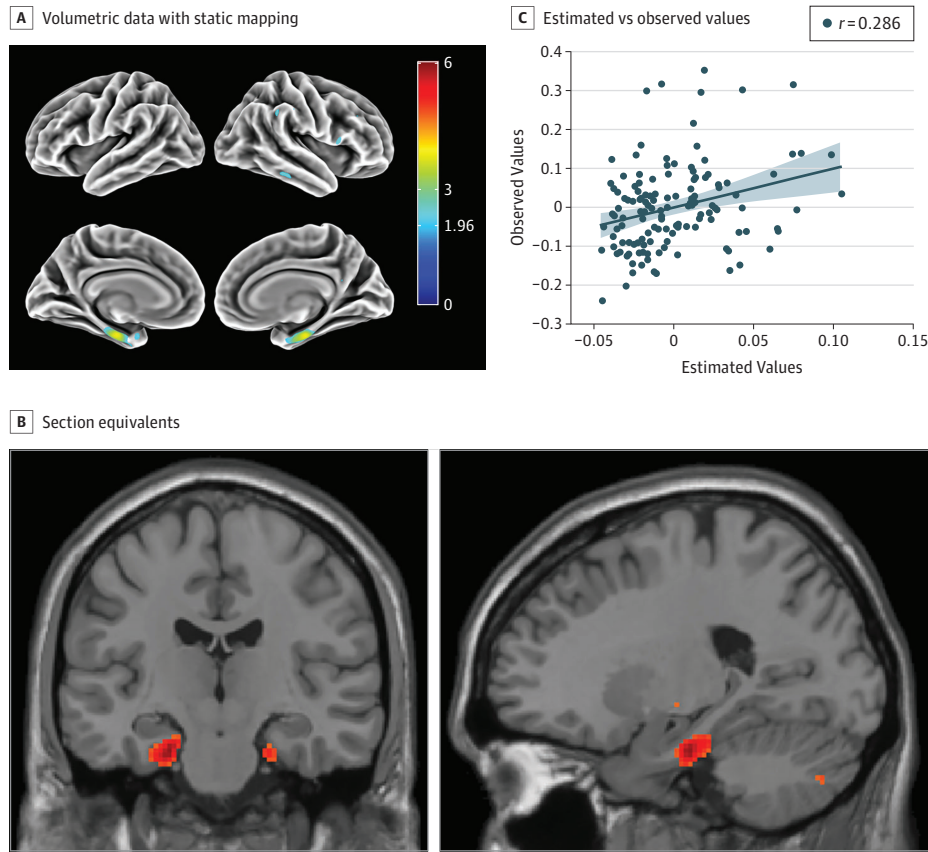
cortical tau maintained an association with SCD after including the effects of inferior temporal cortical tau and covariates because entorhinal cortical and inferior temporal cortical tau are associated ($r_{131} = 0.65$; $P < .001$). In this model, entorhinal cortical tau was found to be significantly associated with SCD ($\beta = 0.45$; 95% CI, 0.24-.65; $P < .001$) (Table 2).

In model 4a, no interactive effect between A β FLR and entorhinal cortical tau was found on SCD (Table 2). Furthermore, including A β FLR in the model did not create a significantly better-fitting model (model 2 vs 4a: change in $F = 1.4$; $P = .24$). Simply assessing the main effects of A β FLR and entorhinal cortical tau (without any interactive term) resulted in a significant effect of entorhinal cortical tau on SCD ($\beta = 0.30$; 95% CI, 0.11-.49; $P = .002$) and no significant effect of A β FLR ($\beta = 0.09$; 95% CI, -0.09 to 0.28; $P = .32$). In the inferior temporal cortical tau model (model 4b), no interactive effect of inferior temporal cortical tau and A β FLR was found on SCD ($\beta = 0.05$; 95% CI, -0.15 to 0.26; $P = .61$).

To examine any effects of multicollinearity, we present correlations between covariates and SCD in the eTable in the Supplement; we found moderate significant correlations between age and inferior temporal cortical tau ($r_{131} = 0.37$; $P < .001$), age and entorhinal cortical tau ($r_{131} = 0.31$; $P < .001$), and age and A β ($r_{131} = 0.18$; $P = .03$); however, these correlations did not explain more than 13% of the variance in the model and thus were not considered to impact collinearity assumptions.³⁵

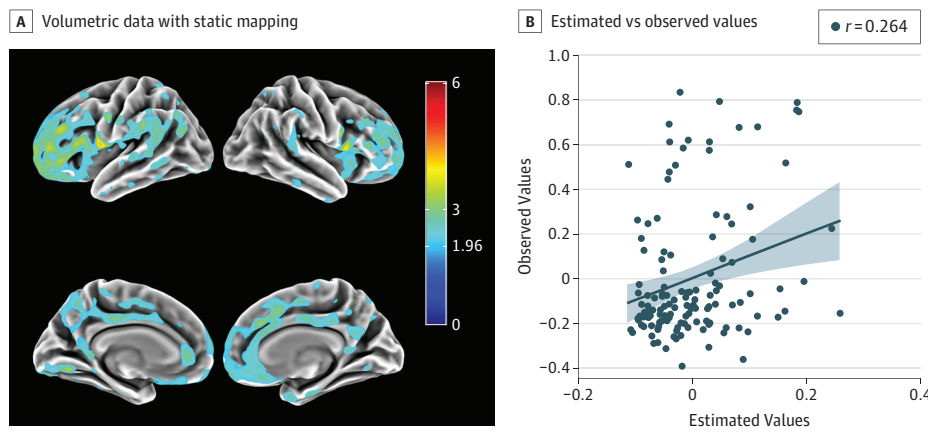
A post hoc exploratory whole-brain voxel-wise general linear model was conducted to identify evidence of positive associations between voxel-wise FTP-PET SUVR and SCD after taking into account the main effects of age. Whole-brain analysis supported the notion that greater SCD was moderately associated with greater FTP-PET SUVR in the entorhinal cortical region (peak effect: $r = 0.30$) after accounting for age (Figure 2). The association was most apparent in the left hemisphere and was not found convincingly in any other regions. By contrast, SCD was found to be associated with PiB-PET DVR in a widespread neocortical

Figure 2. Association of Subjective Cognitive Decline (SCD) With Flortaucipir F 18 Positron Emission Tomography (FTP-PET) Findings



Whole-brain voxelwise analysis with FTP-PET (previously known as AV 1451, T807) standardized uptake value ratio (SUVR) was performed after accounting for age. A, Surface rendering of volumetric data with static mapping from Montreal Neurological Institute (MNI) space to fsaverage from FreeSurfer software. B, Brain section equivalents are shown to better visualize the medial temporal lobe (chosen from apex t value in the region of interest; ie, MNI coordinates $-22 - 18 - 26$). Color bar indicates t values. C, Plot of the estimated and observed values from the apex of the entorhinal cortex region of interest from the general linear model of FTP-PET SUVR approximated as SCD + age. Diagonal lines indicate lines of best fit for the correlational analysis; shading, 95% CI; and data points, study participants.

Figure 3. Association of Subjective Cognitive Decline (SCD) With Pittsburgh compound B Carbon 11-Labeled Positron Emission Tomography (PiB-PET) Findings



Whole-brain voxelwise analysis with summary distribution volume ratio (DVR) was performed after accounting for age. A, Surface rendering of volumetric data with static mapping from Montreal Neurological Institute space to fsaverage from FreeSurfer software. B, Plot of the estimated and observed values from the apex of the inferior lateral frontal region from the general linear model of PiB-PET DVR approximated as SCD + age. Diagonal lines indicate lines of best fit for the correlational analysis; shading, 95% CI; and data points, study participants.

distribution prominently in the medial and lateral frontal regions and the cingulate after accounting for age (Figure 3); no association was found in medial temporal regions. After accounting for entorhinal cortex FTP-PET, most associations became attenuated, with only a few very-low-magnitude effect clusters remaining in lateral frontal regions.

Discussion

Subjective cognitive decline in clinically healthy older adults manifests in the context of increasing entorhinal cortical tauopathy. These findings existed regardless of whether we adjusted for subclinical levels of depressive symptoms, which

have been found in previous literature to be associated with SCD.³⁶ An exploratory whole-brain analysis demonstrated an entorhinal-specific FTP-PET association with SCD, supporting this notion of regional specificity. Although SCD was also found to be elevated with a higher A β burden, supporting previous study findings,^{15,37} this effect was weaker; an interactive effect between tau and A β on SCD was not apparent. Whole-brain analyses of A β with SCD revealed more diffuse associations across frontal and parietal regions, consistent with previous work,⁵ but no evidence of associations in medial temporal regions. Only individuals in the more developed stages of tau deposition (ie, late in the entorhinal cortex and earlier in the inferior temporal cortex) may drive the link between A β and SCD; however, this question will remain unclear until tau-stage-based measures can be quantified. Considering that FTP-PET and ¹¹C-PiB uptake are associated in the HABS,¹¹ this lack of interaction may also be interpreted as indicative of multiple pathologic pathways that motivate the endorsement of SCD symptoms. A similar mechanism has been reported in previous work,³⁸ in which endorsement of SCD symptoms was elevated in the context of additive, rather than interactive, evidence of A β and neurodegeneration. Taken together, we posit that our findings support SCD as an early behavioral manifestation of entorhinal cortical tauopathy.

Our findings support a potential temporal sequence of events, with SCD marking one of the earliest behavioral changes among increasing pathologic change in clinically healthy older adults.³⁹ Entorhinal tauopathy in the presence of minimal A β load is argued to be the earliest component of the AD pathologic continuum,⁴⁰ and as such, endorsement of SCD symptoms may represent the earliest signs of preclinical AD in some cases. With consideration of evidence that inferior temporal cortical tau is representative of later stages in the tau topographic cascade,^{11,12,16,41,42} a lack of an association with SCD provides additional evidence for its appearance in the earliest stages of the preclinical trajectory. Inferior temporal cortical FTP-PET findings have been associated with increasing clinical impairment,⁴² as measured by clinical screening tools such as the Clinical Dementia Rating Scale sum of boxes, the Mini-Mental State Examination, and Logical Memory test,¹¹ and are associated with episodic memory dysfunction.^{12,42} Therefore, a lack of an association between SCD and inferior temporal cortical tau may represent a subtle change of insight with the progression of AD-related tauopathy. We did not examine measures to interrogate this hypothesis; thus, future studies should examine associations between SCD and inferior temporal cortical tau in light of an informant's report.

Entorhinal cortical tau deposition is common with advancing age^{15,16,41,43} and is the earliest cortical involvement in the succession of tauopathy stages that, along with A β pathologic changes, define AD.^{15,40,41} Our present findings do not enable us to estimate whether an individual with an elevated entorhinal cortical tau PET signal will inevitably develop AD. Thus, the association that we found between the entorhinal cortex and SCD does not permit definitive conclusions about whether those individuals with a strong association will progress to AD. We are currently conducting serial evaluations to clarify this point. Our study does, however, raise the possibil-

ity that SCD signifies age-related neural insult and subsequent cognitive decline that is independent of fully expressed AD pathologic changes.^{44,45} In the present study, A β did not provide more than 1% added variance (R^2 value) in models 4a and 4b, and did not affect entorhinal cortex-FTP-PET regression coefficients, findings that may support this possibility. Our findings were unable to fully characterize the A β contribution, however, possibly owing to PET limitations with measuring lower ranges of A β burden.⁴⁶ Thus, we cannot definitively determine whether entorhinal cortical tauopathy and its SCD phenotypic feature are biologically distinct from early AD pathologic changes.

Another alternative explanation of our findings is that SCD is, in part, a manifestation of heterogenic strains of tau; some studies suggest a prionlike propagation of tau, with neurodegenerative disease associated with different sets of strains.⁴⁷ In addition, the appearance of neurofibrillary tangles is a byproduct of a range of causes^{48,49} that are maladaptive for optimal synaptic function.^{48,50} Regardless of whether SCD is AD specific, endorsement of SCD symptoms reveals some level of underlying neuropathologic change.

Limitations

This study has a few limitations. The FTP-PET tracers were introduced into the HABS midway through the progression of the study; we chose the closest SCD measure from the time of the FTP-PET scan and covaried the delay between SCD and tau PET collections to account for cross-sectional idiosyncrasies. Unintentional biases may have related to the cross-sectional investigation of SCD after baseline; that is, individuals may have recalibrated their SCD according to their experience and judgment of their performance on cognitive testing that did not exist at the baseline of the HABS. Future studies will require longitudinal analyses that relate change in tau deposition to change in SCD. In addition, we used a composite of SCD that is honed on items related primarily to subjective concerns of memory decline; SCD from other cognitive domains may also be sensitive to PET markers of tauopathy in other regions. Finally, participants in the HABS cohort generally exhibited lower levels of SCD on our composite measure, which restricted our ability to measure very severe SCD and may have contributed to our null findings with inferior temporal cortical FTP-PET.

Conclusions

Our findings support the notion that SCD is an early indicator of tauopathy in clinically healthy older adults. This study is the first, to our knowledge, to show associations between SCD and region-specific tauopathy, with the implication that SCD robustly manifests with increasing tau deposition specific to the entorhinal cortical region regardless of A β burden. Future work will need to isolate the temporal pattern of associations between AD biomarkers and the appearance of SCD; however, we argue that our findings support the notion of SCD as an early behavioral marker of pathologic change. Further work should examine longitudinal change-on-change

associations between these biologic and subjective markers. In sum, we argue that these data, and the work of others,^{51,52} support an association between SCD and AD biomarkers; however, an alternative argument that SCD is motivated by AD-unrelated tauopathy cannot be discounted and will also

need to be examined. Our findings suggest multiple and potentially nonoverlapping pathologic drivers of endorsement of SCD symptoms. This complexity must be taken into consideration when assessing the genesis of SCD in clinically healthy older adults.

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