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Objective subtle cognitive difficulties predict future amyloid accumulation and neurodegeneration

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Abstract

Objective
To determine the temporal sequence of objectively defined subtle cognitive difficulties (Obj-SCD) in relation to amyloidosis and neurodegeneration, the current study examined the trajectories of amyloid PET and medial temporal neurodegeneration in participants with Obj-SCD relative to cognitively normal (CN) and mild cognitive impairment (MCI) groups.

Method
A total of 747 Alzheimer's Disease Neuroimaging Initiative participants (305 CN, 153 Obj-SCD, 289 MCI) underwent neuropsychological testing and serial amyloid PET and structural MRI examinations. Linear mixed effects models examined 4-year rate of change in cortical ^{18}F-florbetapir PET, entorhinal cortex thickness, and hippocampal volume in those classified as Obj-SCD and MCI relative to CN.

Result
Amyloid accumulation was faster in the Obj-SCD group than in the CN group; the MCI and CN groups did not significantly differ from each other. The Obj-SCD and MCI groups both demonstrated faster entorhinal cortical thinning relative to the CN group; only the MCI group exhibited faster hippocampal atrophy than CN participants.

Conclusion
Relative to CN participants, Obj-SCD was associated with faster amyloid accumulation and selective vulnerability of entorhinal cortical thinning, whereas MCI was associated with faster entorhinal and hippocampal atrophy. Findings suggest that Obj-SCD, operationally defined using sensitive neuropsychological measures, can be identified prior to or during the preclinical stage of amyloid deposition. Further, consistent with the Braak neurofibrillary staging scheme, Obj-SCD status may track with early entorhinal pathologic changes, whereas MCI may track with more widespread medial temporal change. Thus, Obj-SCD may be a sensitive and non-invasive predictor of encroaching amyloidosis and neurodegeneration, prior to frank cognitive impairment associated with MCI.

Glossary

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The National Institute on Aging–Alzheimer's Association (NIA-AA) research criteria for preclinical Alzheimer disease (AD) proposed that subtle cognitive decline appears after amyloidosis and neurodegeneration, but prior to mild cognitive impairment (MCI).[1] Although some investigators recommend using subjective report of cognitive decline to define subtle cognitive decline,[2,3] other work has identified objectively defined subtle cognitive difficulties (Obj-SCD) using neuropsychological assessment.[4–8] One method that uses neuropsychological assessment incorporates both total scores and sensitive process scores that are consistent with an overall memory profile of early AD.[5]

Neuropsychological process scores are the quantification of errors or an individual's approach to completing a task such as a neuropsychological test, irrespective of whether the overall total score was within the normal range.[9] For example, one may recall an average number of correct words on a list-learning test, yet simultaneously produce extra-list intrusion errors. Process score analyses of memory tests have demonstrated that flattened learning slope, increased susceptibility to interference, and more intrusion errors may be sensitive to early AD-related changes.[10–18] Our recent work that operationally defined Obj-SCD via integration of these process scores showed associations with CSF AD markers and predicted faster progression to MCI/dementia when compared to cognitively normal (CN) participants.[5]

Given these findings, we aimed to determine whether Obj-SCD appears after amyloidosis and neurodegeneration or, instead, predicts future amyloid accumulation and medial temporal lobe (MTL) neurodegeneration. If, according to the NIA-AA criteria[1] and amyloid cascade model,[2,17] amyloid does invariably accumulate (stage 1) prior to neurodegeneration (stage 2) and detectable cognitive changes (stage 3), we expect that Obj-SCD, at best, would be associated with future MTL degeneration, but not increasing amyloid pathology.

Methods

Data used in the preparation of this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI)

database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review boards at each of the participating institutions, and written informed consent was obtained from all participants or authorized representatives at each site.

Participants

Specific enrollment criteria for ADNI have been described previously in detail elsewhere.[19] Briefly, participants from ADNI were between 55 and 90 years old, had at least 6 years of education or work history equivalent, had a Geriatric Depression Scale score <6, had a Hachinski Ischemia Scale score <5, had adequate vision and hearing in order to perform neuropsychological tests, were in generally good health and without significant head trauma or neurologic disease, were stable on permitted medications, had a reliable study partner, and were fluent in either English or Spanish. Participants included 747 older adults without dementia from ADNI who had baseline florbetapir amyloid PET imaging with processed data. Available PET and MRI data were included at baseline and 12-, 24-, 36-, and 48-month follow-up visits.

Cognitive groups

Cognitive status of CN or MCI was determined using Jak/Bondi actuarial neuropsychological criteria, which define MCI by performance >1 SD below the demographically adjusted (age, education, sex) mean on (1) 2 neuropsychological measures within the same cognitive domain or (2) at least 1 measure across all 3 sampled cognitive domains or (3) a score of 6 or higher on the Functional Activities Questionnaire.[20,21]

Consistent with previous work, 6 neuropsychological test scores were used in the Jak/Bondi diagnostic criteria for MCI.[21,22] There were 2 measures in 3 different cognitive domains (memory, language, attention/executive function). The memory domain included the Rey Auditory Verbal Learning Test delayed free recall correct responses and AVLT recognition (hits minus false-positives). The language domain included the 30-item Boston Naming Test total correct and Animal Fluency total score. The attention/executive function domain included Trail-Making Test parts A and B times to completion.

Participants without dementia who did not meet Jak/Bondi criteria for MCI were considered for either the CN or Obj-SCD groups. Consistent with our previous work, Obj-SCD status was determined by the following criteria: (1) 1 impaired total test score (>1 SD below demographically

adjusted mean) in 2 different cognitive domains (memory, language, attention/executive) or (2) 2 impaired neuropsychological process scores (>1 SD below demographically adjusted mean) from the AVLT (learning slope, retroactive interference, intrusion errors) or (3) 1 impaired total test score and 1 impaired process score.[5] Total test scores were the 6 neuropsychological variables described above for determining MCI classification. Three process scores derived from the AVLT were also used in the classification of Obj-SCD. The AVLT is a word-list learning and memory test of 15 semantically unrelated words and includes 5 learning trials (list A, trials 1–5), an interference list trial (list B), a short delay free recall trial (list A, trial 6), a long delay free recall trial (list A, trial 7), and delayed recognition. Process scores used in the Obj-SCD criteria included learning slope ([list A trial 5–list A trial 1]/5), retroactive interference (list A trial 6/list A trial 5), and total intrusion errors (total number of extra-list intrusion errors across all recall trials). These scores were previously shown to differ between CN individuals who remained stable and those who progressed to MCI within 5 years in ADNI.[16] For both the neuropsychological total scores and process scores, the demographically adjusted (age, sex, education) z scores for the neuropsychological measures were based on regression coefficients derived from a sample of CN participants in ADNI who did not progress to MCI for the duration of their study participation (i.e., robust controls; n = 385).[22,23]

Florbetapir PET

PET imaging using the ^{18}F-florbetapir AV-45 tracer was used to quantify amyloid burden. The details of data acquisition and processing of ADNI florbetapir PET data are available on the ADNI website (loni.usc.edu). Briefly, florbetapir scans collected at baseline and follow-up visits were coregistered, averaged, reoriented into a standard $160 \times 160 \times 96$ voxel image grid with 1.5 mm cubic voxels, and smoothed to a uniform isotropic resolution of 8 mm full width at half maximum. Structural MRIs (see below for method details) were skull-stripped, segmented, and parcellated using Free-Surfer (version 5.1). This structural image was coregistered to the first florbetapir image for each participant. A summary standardized uptake value ratio (SUVR) was then calculated by dividing the mean florbetapir uptake across 4 main cortical regions (i.e., frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices) by whole cerebellar (white and gray matter) florbetapir uptake. Greater retention of florbetapir is thought to reflect a greater cortical amyloid load. A recommended threshold of 1.11 for cross-sectional descriptive florbetapir analyses, using cerebellum as the reference region, was used to determine amyloid positivity.[24–27]

T1-weighted anatomical MRI

The details of ADNI MRI data acquisition and processing can be found on the ADNI website (loni.usc.edu). Briefly, structural scans collected at baseline and follow-up visits were motion corrected, skull-stripped, segmented, and parcellated using FreeSurfer (version 5.1).[28,29] FreeSurfer-derived

entorhinal cortical thickness and hippocampal volume were a priori dependent variables given their implication in early stages of AD (e.g., Braak stages I/II). Normalized hippocampal volume, which was used in the analysis, was created by dividing absolute hippocampal volume by FreeSurfer-derived estimated total intracranial volume and then multiplying the resulting value by 100.

Statistical analyses

Analysis of variance, Kruskal-Wallis tests, or χ^2 tests examined baseline differences in demographic and clinical characteristics by group (CN, Obj-SCD, MCI). Pairwise comparisons were Bonferroni-corrected for 3 groups. Proportions of participants who progressed to MCI and dementia at each visit by group are also described.

Multivariable linear mixed effects (LME) modeling was used to examine the 48-month trajectories of change in amyloid burden (as measured by florbetapir PET SUVR), entorhinal cortex thickness, and hippocampal volume as a function of cognitive group status (CN, Obj-SCD, or MCI). All models adjusted for age, education, sex, *APOE* ε4 allele frequency, and the baseline summary amyloid PET SUVR. The longitudinal amyloid model was run both with and without the inclusion of baseline amyloid PET as a covariate; the pattern of the cognitive group × time interaction did not differ between models, so the model with baseline amyloid PET as a covariate is reported to be consistent with the covariates in the models of neurodegeneration. Time was mean-centered and treated as a continuous variable. Random intercept and slope were included. CN status was used as the reference group for the primary analyses; secondary analysis of the models was then run with MCI as the reference group to ascertain each comparison. Full information maximum likelihood was used to allow all available data to be included,[30,31] in order to reduce biases relative to other methods (e.g., list-wise deletion).

Differences in demographic (age, education, sex) and clinical characteristics (e.g., *APOE* ε4 status, ischemic risk measured by the modified Hachinski Ischemia Scale, depressive symptoms measured by the Geriatric Depression Scale) between participants who were missing (n = 424) or nonmissing (n = 323) at the 48-month follow-up visit were examined. Analyses revealed that only age differed between the missing (mean age 72.88 years, SD 6.89) and nonmissing groups (mean age 71.33 years, SD 7.06) (t[745] = 3.01; p = 0.003).

Data availability

ADNI data were obtained from adni.loni.usc.edu and are available to investigators in the scientific community who have been approved by the ADNI Data Sharing and Publications Committee and who agree to the terms of the ADNI Data Use Agreement for purposes of replicating procedures and results. Anonymized ADNI participant identification numbers used in this article are available by request from any qualified investigator.

Results

Participant characteristics

Table 1 shows the baseline demographic and clinical characteristics of participants by cognitive status (CN: n = 305, Obj-

Table 1 Baseline demographic and clinical characteristics by cognitive group status

	Total sample (n = 747)		CN (n = 305)		Obj-SCD (n = 153)		MCI (n = 289)		F, H, or χ^2	p Value
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD		
Age	72.21	7.00	71.34	6.64	73.10	7.15	72.66	7.21	F = 4.24[a]	0.015
Education	16.36	2.61	16.57	2.60	16.40	2.44	16.12	2.69	F = 2.23	0.108
Female, %	48.4%	—	54.1%	—	46.4%	—	43.6%	—	χ^2 = 6.88[b]	0.032
MMSE	28.43	1.61	29.00	1.15	28.58	1.44	27.75	1.83	H = 81.82[a,b,c]	<0.001
***APOE* ε4+, %**	41.0%	—	31.5%	—	39.9%	—	51.7%	—	χ^2=25.24[b,c]	<0.001
PET amyloid SUVR	1.18	0.21	1.12	0.17	1.16	0.20	1.24	0.24	F = 26.56[b,c]	<0.001
PET amyloid positive, %	46.6%	—	35.4%	—	43.8%	—	59.9%	—	χ^2 = 36.33[b,c]	<0.001
Entorhinal cortical thickness	3.44	0.41	3.56	0.31	3.51	0.34	3.29	0.48	F = 38.48[b,c]	<0.001
Hippocampal volume	0.48	0.08	0.51	0.06	0.49	0.07	0.46	0.08	F = 38.08[a,b,c]	<0.001

Abbreviations: CN = cognitively normal; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; Obj-SCD = objectively defined subtle cognitive difficulties; SUVR = standardized uptake value ratio.
F statistic reported for one-way analyses of variance, H statistic reported for Kruskal-Wallis tests, χ^2 statistic reported for χ^2 tests.
[a] Significant difference between CN and Obj-SCD.
[b] Significant difference between CN and MCI.
[c] Significant difference between Obj-SCD and MCI.

Table 2 Proportions of participants who progressed by cognitive group at follow-up visits

	12-Month visit	24-Month visit	36-Month visit	48-Month visit
CN	N = 246	N = 256	N = 117	N = 142
Progressed to MCI	11.0% (n = 27)	12.9% (n = 33)	13.7% (n = 16)	16.9% (n = 24)
Progressed to dementia	0.8% (n = 2)	1.2% (n = 3)	2.6% (n = 3)	4.2% (n = 6)
Obj-SCD	N = 125	N = 127	N = 70	N = 63
Progressed to MCI	34.4% (n = 43)	37.0% (n = 47)	41.4% (n = 29)	46.0% (n = 29)
Progressed to dementia	0.8% (n = 1)	4.7% (n = 6)	10.0% (n = 7)	4.8% (n = 3)
MCI	N = 262	N = 222	N = 156	N = 113
Reverted to CN	21.0% (n = 55)	19.8% (n = 44)	17.9% (n = 28)	18.6% (n = 21)
Stable MCI	65.6% (n = 172)	55.0% (n = 122)	48.1% (n = 75)	50.4% (n = 57)
Progressed to dementia	13.4% (n = 35)	25.2% (n = 56)	34.0% (n = 53)	31.0% (n = 35)

Abbreviations: CN = cognitively normal; MCI = mild cognitive impairment; Obj-SCD = objectively defined subtle cognitive difficulties.
At baseline, CN n = 305, Obj-SCD n = 153, MCI n = 289. MCI status based on Jak/Bondi actuarial neuropsychological criteria; dementia status based on diagnosis from Alzheimer's Disease Neuroimaging Initiative.

SCD: n = 153, MCI: n = 289). There were group differences such that the Obj-SCD group was older, had lower Mini-Mental State Examination (MMSE) scale scores, and had smaller hippocampal volumes than CN participants. Participants with Obj-SCD had slightly higher levels of amyloid at baseline than did CN participants; however, this was not a statistically significant difference. Relative to participants with MCI, participants with Obj-SCD had higher MMSE scores, lower proportion of *APOE* ε4 carriers, lower levels of amyloid, smaller proportion of amyloid-positive participants, greater entorhinal cortical thickness, and larger hippocampal volumes. Compared to CN participants, participants with MCI were less likely to be female and had lower MMSE scores, a higher proportion of *APOE* ε4 carriers, higher levels of amyloid, greater proportion of amyloid-positive participants, lower entorhinal cortical thickness, and smaller hippocampal volumes. The proportions of participants from each group who progressed to MCI and dementia at each follow-up visit are shown in table 2. The Obj-SCD group had nearly 3 times the proportion of those who are later classified as MCI (46.0%) at 48 months compared to CN participants (16.9%).
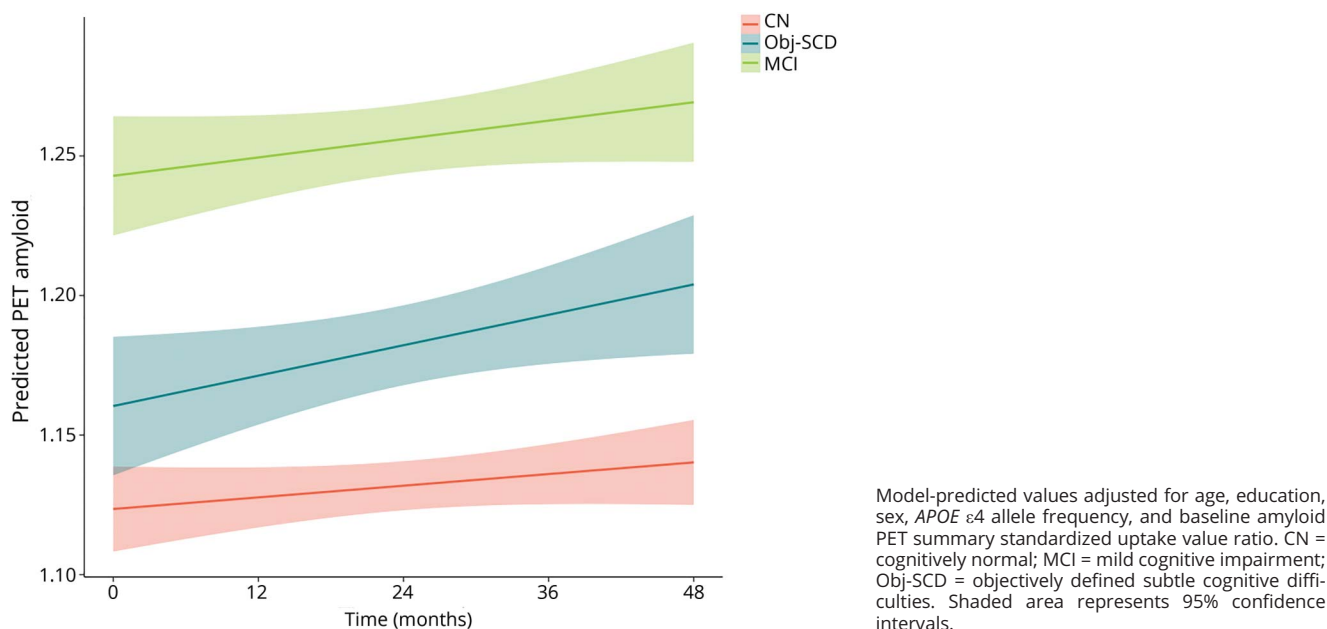
Figure 1 Trajectories of amyloid PET by cognitive group

Model-predicted values adjusted for age, education, sex, *APOE* ε4 allele frequency, and baseline amyloid PET summary standardized uptake value ratio. CN = cognitively normal; MCI = mild cognitive impairment; Obj-SCD = objectively defined subtle cognitive difficulties. Shaded area represents 95% confidence intervals.

Table 3 Estimates for change in amyloid PET, entorhinal cortical thickness, and hippocampal volume by cognitive group status

	Amyloid PET				Entorhinal cortical thickness				Hippocampal volume			
	Estimate	SE	p Value	r	Estimate	SE	p Value	r	Estimate	SE	p Value	r
Intercept	−0.1225	0.0207	0.555	−0.020	4.9421	0.1916	<0.001[a]	0.686	0.8946	0.0322	<0.001[a]	0.713
Age	0.0002	0.0002	0.423	0.028	−0.0166	0.0021	<0.001[a]	−0.273	−0.0041	0.0004	<0.001[a]	−0.382
Education	0.0042	0.0061	0.483	0.024	0.0032	0.0055	0.570	0.021	−0.0026	0.0009	0.005[a]	−0.102
Female	0.0014	0.0032	0.458	0.016	−0.0297	0.0291	0.308	−0.037	0.0191	0.0049	<0.001[a]	0.141
APOE ε4 alleles, n												
0 (ref)	—	—	—	—	—	—	—	—	—	—	—	—
1	0.0062	0.0036	0.085	0.059	−0.0133	0.0331	0.687	−0.015	0.0033	0.0056	0.554	0.022
2	0.0181	0.0065	0.006[a]	0.095	−0.0506	0.0591	0.392	−0.031	−0.0168	0.0010	0.092	−0.062
Baseline PET amyloid SUVR	0.9985	0.0084	<0.001[a]	0.970	−0.2482	0.0765	0.001[a]	−0.118	−0.0672	0.0129	<0.001[a]	−0.188
Time	0.0003	0.0001	0.003[a]	0.092	−0.0021	0.0005	<0.001[a]	−0.187	−0.0005	0.0001	<0.001[a]	−0.369
Cognitive group												
CN (ref)	—	—	—	—	—	—	—	—	—	—	—	—
Obj-SCD	0.0097	0.0043	0.025[a]	0.077	−0.0554	0.0387	0.153	−0.051	−0.0091	0.0065	0.159	−0.054
MCI	−0.0006	0.0037	0.879	−0.005	−0.3111	0.0334	<0.001[a]	−0.316	−0.0441	0.0056	<0.001[a]	−0.273
Cognitive group × time												
CN × time (ref)	—	—	—	—	—	—	—	—	—	—	—	—
Obj-SCD × time	0.0006	0.0002	0.010[a]	0.077	−0.0023	0.0008	0.003[a]	−0.126	−0.0002	0.0001	0.074	−0.082
MCI × time	0.0002	0.0002	0.258	0.034	−0.0044	0.0007	<0.001[a]	−0.261	−0.0004	0.0001	<0.001[a]	−0.174

Abbreviations: CN = cognitively normal; MCI = mild cognitive impairment; Obj-SCD = objectively defined subtle cognitive difficulties; ref = reference group; SUVR = standardized uptake value ratio.
Effect size (*r* values) interpretation: small = 0.10, medium = 0.30, large = 0.50.
[a] Statistically significant < *p* < 0.05.

Florbetapir PET trajectories

LME models, adjusting for baseline age, education, sex, *APOE* ε4 frequency, and baseline amyloid PET SUVR, examined whether cognitive group predicted increased rate of amyloid accumulation over 48 months. Figure 1 depicts the trajectories of amyloid PET by group and table 3 shows the model estimates. There was a significant interaction between cognitive group and time such that, relative to CN participants, participants with Obj-SCD had a faster increase in amyloid PET SUVR ($t[1109.08] = 2.58$, $p = 0.010$, $r = 0.077$). Participants with MCI did not differ from CN participants ($t[1133.51] = 1.13$, $p = 0.258$, $r = 0.034$) or participants with Obj-SCD ($t[1173.95] = 1.59$, $p = 0.113$, $r = 0.046$) in the rate of amyloid accumulation over 48 months.

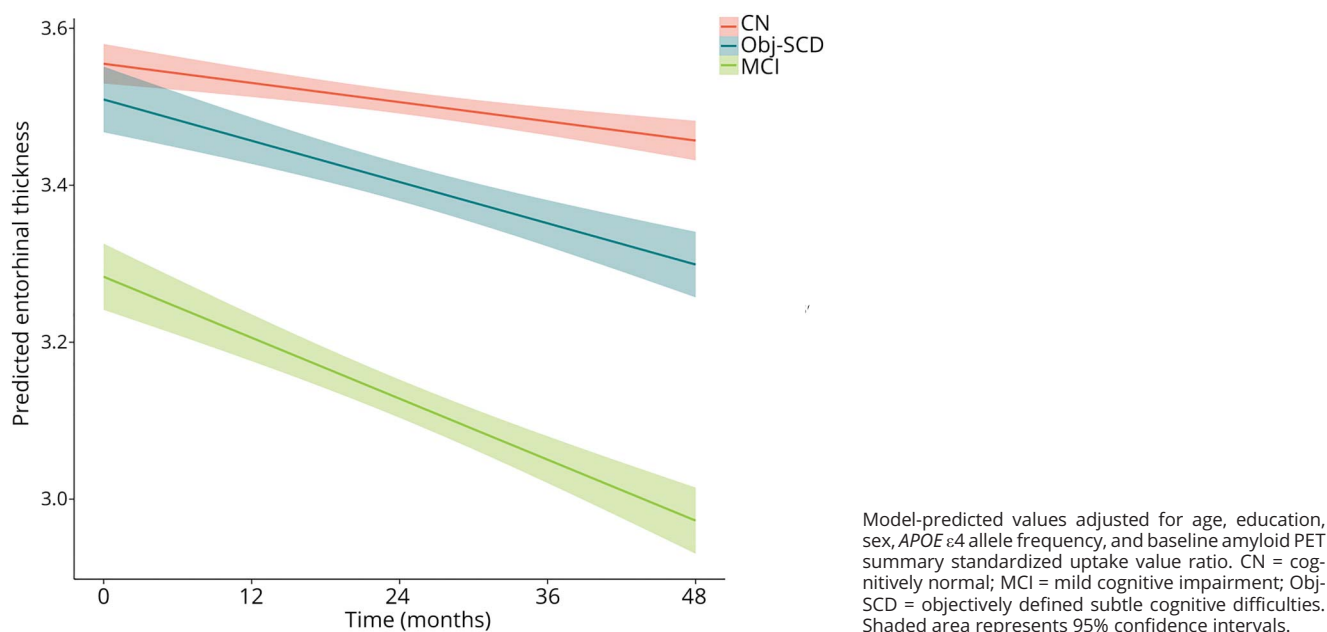## Entorhinal cortex thickness trajectories

Next, LME models, adjusting for age, education, sex, and baseline amyloid PET SUVR, examined whether cognitive group predicted entorhinal cortex thinning and hippocampal volume loss over 48 months. Figure 2 shows the trajectories of entorhinal cortex thinning by cognitive group and table 3 shows the model estimates. There was a significant interaction between cognitive group and time such that, relative to CN participants, Obj-SCD ($t[540.45] = −2.95$, $p = 0.003$, $r = −0.126$) and MCI ($t[590.28] = −6.57$, $p < 0.001$, $r = −0.261$) groups had faster entorhinal cortex thinning over 48 months. Relative to participants with MCI, those with Obj-SCD had a slower rate of entorhinal cortex thinning ($t[571.96] = 2.56$, $p = 0.011$, $r = 0.107$).

Hippocampal volume trajectories

Figure 3 shows the trajectories of hippocampal volume loss by cognitive group and table 3 shows the model estimates. There was a significant interaction between cognitive group and time such that, relative to CN participants, participants with MCI ($t[525.68] = −4.06$, $p < 0.001$, $r = 0.174$) had a faster rate of hippocampal volume loss over 48 months. The rate of volume loss for participants with Obj-SCD did not statistically differ from

Figure 2 Trajectories of entorhinal cortex thinning by cognitive group

Model-predicted values adjusted for age, education, sex, *APOE* ε4 allele frequency, and baseline amyloid PET summary standardized uptake value ratio. CN = cognitively normal; MCI = mild cognitive impairment; Obj-SCD = objectively defined subtle cognitive difficulties. Shaded area represents 95% confidence intervals.

that of CN participants ($t[478.21] = -1.79$, $p = 0.074$, $r = -0.082$) or participants with MCI ($t[511.81] = 1.62$, $p = 0.105$, $r = 0.071$).

Discussion

The amyloid cascade model and NIA-AA research criteria for preclinical AD both depict amyloid deposition and early neurodegenerative changes as occurring prior to the onset of cognitive symptoms.[1,3,32] This study examined associations of Obj-SCD with amyloid PET and MTL atrophy trajectories. Results show that participants with Obj-SCD and CN participants did not statistically differ from one another at baseline on levels of amyloid deposition, though, qualitatively, participants with Obj-SCD had slightly higher amyloid levels. Thus, this nonsignificant difference in baseline amyloid alone does not rule out the possibility that there are small effects of amyloid contributing to subtle cognitive inefficiencies. However, the nonsignificant baseline finding, in combination with the result that Obj-SCD was associated with a faster rate of amyloid accumulation even after adjusting for baseline amyloid levels, provides more support that Obj-SCD was identified prior to or coincident with the early phase of amyloid accumulation, rather than after amyloid deposition presumably levels off. Prior work has also demonstrated that subtle impairments on sensitive neuropsychological measures can in fact precede or emerge in tandem with amyloid positivity in participants who later progress to MCI and AD.[4,16,33] However, this is the first study, to our knowledge, to investigate the relationship between Obj-SCD, defined using sensitive neuropsychological measures, and the trajectory of amyloid PET changes. In addition to participants with Obj-SCD showing faster rates of amyloid accumulation, our results also demonstrated that

relative to the CN group, the Obj-SCD group had faster thinning of the entorhinal cortex and nearly 3 times the proportion who are later classified as MCI over 48 months, whereas the MCI group showed faster thinning of the entorhinal cortex and hippocampal atrophy over 48 months.

Related to neurodegeneration, the finding that the Obj-SCD group had faster entorhinal cortical thinning, but only trend-level changes in hippocampal volume relative to the CN group, may suggest that Obj-SCD captures individuals very early in the neurodegenerative process. Indeed, this pattern of atrophy, first of the entorhinal cortex and then the hippocampus, parallels the very early Braak staging of tau pathology (i.e., Braak stage I to II).[34–36] These findings are also consistent with recent work by Bangen et al.,[37] who found that intraindividual variability of neuropsychological performance, thought to be a sensitive marker of early cognitive difficulties,[38] was related to longitudinal entorhinal and hippocampal atrophy in participants with MCI, but only entorhinal cortex thinning in CN participants.

Given evidence that tau pathology is more strongly related to cognition than amyloid pathology,[39–42] examination of the cross-sectional and longitudinal relationships between Obj-SCD and tau is needed to determine if early tau deposition, first in the entorhinal cortex (i.e., Braak stage I) and then in the hippocampus (i.e., Braak stage II), may be causing the subtle cognitive difficulties we observed in this Obj-SCD group. Specifically, it is plausible that early tau accumulation may be related to Obj-SCD status since this would closely track with the spatial temporal relationship between Obj-SCD and selective entorhinal cortex thinning that we observed. We

Model-predicted values adjusted for age, education, sex, *APOE ε4* allele frequency, and baseline amyloid PET summary standardized uptake value ratio. CN = cognitively normal; MCI = mild cognitive impairment; Obj-SCD = objectively defined subtle cognitive difficulties. Shaded area represents 95% confidence intervals.
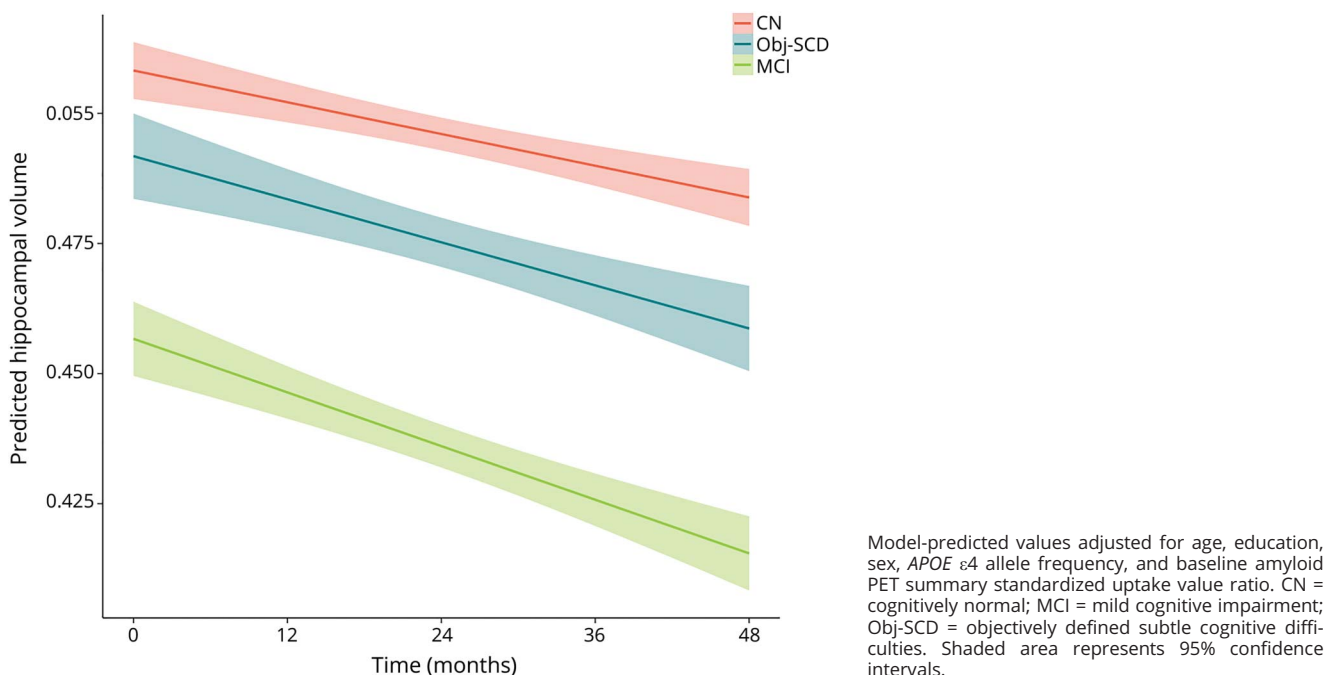
hypothesize that Obj-SCD is capturing those individuals with early tau pathology, leading to the MTL atrophy[43] that was observed in these analyses. There are also known associations between white matter hyperintensity volume and cognitive decline,[44,45] which may be mediated by MTL thickness/volume.[46] Indeed, one recent study demonstrated that, although AD was the most frequent (65%) pathology in an autopsy study of 1,079 individuals, it rarely occurred in isolation (9%) and, remarkably, more than 230 different neuropathologic combinations were observed.[47] Therefore, future work, particularly as more longitudinal tau PET imaging becomes available within ADNI, will examine the associations of Obj-SCD status, tau, white matter, and other pathologies.

The findings of Obj-SCD being a predictor of entorhinal cortex thinning were largely in line with our hypotheses. However, given evidence that those with Obj-SCD progress to MCI/AD faster than CN participants,[5] the fact that Obj-SCD predicts future cortical amyloid accumulation and was not significantly related to cross-sectional PET amyloid is in stark contrast with the biomarker only model of AD.[3] Our findings add to previous work within ADNI showing that amyloid is not always the first marker to emerge in preclinical AD. In fact, previous work by Edmonds et al.[4] showed that neurodegeneration was the most common marker to emerge first among those who are known to progress to MCI/AD. Further, simply the number of abnormal markers (amyloid, neurodegeneration, cognition), regardless of the temporal sequence in which they appear, was shown to be just as predictive of future progression to MCI/AD as the traditional NIA-AA criteria[1] that invariably require amyloid to emerge

first. Accumulating evidence of inconsistency in the temporal sequence of AD pathogenesis, in combination with a string of clinical trials that have successfully cleared amyloid but did not affect the clinical trajectory of the cognitive symptoms,[48,49] continues to call into question the accuracy and utility of the persistent focus on amyloid in AD.

ADNI data were used in this study, which allowed for a large, well-characterized sample with longitudinal neuropsychological testing and neuroimaging. However, this sample is limited in that it is highly educated, mostly white, and generally very healthy. Therefore, these findings need to be replicated in more generalizable community-based samples with increased diversity. This study includes a 48-month follow-up period, which may be a relatively short period of time to detect changes in brain structure, so future work should continue to investigate the temporal sequence of amyloid, neurodegeneration, and subtle cognitive changes as more participants have longer follow-up durations. In addition, as described above, there were no significant differences in baseline amyloid levels between the CN and Obj-SCD groups and adjusting for baseline amyloid in the longitudinal did not weaken the relationship between Obj-SCD and future amyloid accumulation; however, we cannot rule out the possibility that amyloid had already begun to accumulate at a faster rate in the participants with Obj-SCD. Thus, future work should investigate the transition from CN to Obj-SCD and determine the associated longitudinal changes in amyloid, tau, neurodegeneration, and white matter.

The Obj-SCD classification and neuropsychological process scores have demonstrated value for classifying individuals at

risk and predicting future cognitive impairment.[5,16] These past findings in combination with the current associations with pathologic changes suggest that Obj-SCD classification may be a particularly useful tool for research to recruit participants at risk for future disease progression. Compared to PET or lumbar puncture, Obj-SCD is a relatively inexpensive and noninvasive method for identifying those at greater risk for progression, and has the potential to be a marker of risk for AD in those who may not have access to or are medically unable to complete more invasive biomarker testing.

We applied a previously described operational definition of Obj-SCD that considers both neuropsychological total scores and sensitive neuropsychological process/error scores and balances the sensitivity of the >1 SD cutoff for impairment on a particular measure with the reliability of the requisite of at least 2 impaired scores to be present. This operational definition of Obj-SCD that incorporates neuropsychological process scores has previously predicted progression to MCI and AD.[5] The current findings suggest that Obj-SCD is also a sensitive and noninvasive predictor of future amyloid accumulation and early neurodegenerative changes, prior to frank cognitive impairment consistent with MCI.

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Disclosure

Publication history

Appendix Authors

Name	Location	Role	Contribution
Kelsey R. Thomas, PhD	University of California, San Diego; VA San Diego Healthcare System	Author	Designed and conceptualized study, obtained and analyzed the data, drafted the manuscript for intellectual content.
Katherine J. Bangen, PhD	VA San Diego Healthcare System; University of California, San Diego	Author	Obtained, processed, and interpreted the data, revised the manuscript for intellectual content.
Alexandra J. Weigand, BA	University of California, San Diego; VA San Diego Healthcare System; San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology	Author	Obtained and interpreted the data, revised the manuscript for intellectual content.
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Mark W. Bondi, PhD	University of California, San Diego; VA San Diego Healthcare System	Author	Conceptualized the study, obtained and interpreted the data, revised the manuscript for intellectual content.

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