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FEATURED ARTICLE

Subjective cognitive decline and stage 2 of Alzheimer disease in patients from memory centers

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Abstract

Introduction: It is uncertain whether subjective cognitive decline (SCD) in individuals who seek medical help serves the identification of the initial symptomatic stage 2 of the Alzheimer's disease (AD) continuum.

Methods: Cross-sectional and longitudinal data from the multicenter, memory clinic–based DELCODE study.

Results: The SCD group showed slightly worse cognition as well as more subtle functional and behavioral symptoms than the control group (CO). SCD–A+ cases (39.3% of all SCD) showed greater hippocampal atrophy, lower cognitive and functional performance, and more behavioral symptoms than CO–A+. Amyloid concentration in the CSF had a greater effect on longitudinal cognitive decline in SCD than in the CO group.

Discussion: Our data suggests that SCD serves the identification of stage 2 of the AD continuum and that stage 2, operationalized as SCD-A+, is associated with subtle, but extended impact of AD pathology in terms of neurodegeneration, symptoms and clinical progression.

KEYWORDS
amyloid beta 42, Alzheimer's disease, apolipoprotein E, cerebrospinal fluid, longitudinal, magnetic resonance imaging, mild cognitive impairment, positron emission tomography, subjective cognitive decline, tau

1 | INTRODUCTION

A substantial proportion of individuals at higher age who consult memory services report decline in cognitive functioning, while achieving unimpaired performance on diagnostic cognitive tests.[1,2] This condition has been termed subjective cognitive decline (SCD).[3] As a group individuals with SCD are at increased risk of objective cognitive decline and dementia and it has been shown that SCD is associated with various degrees of amyloid positivity depending on the specific characteristics of the samples studied.[4–6] Considering the future need for very early treatment of Alzheimer's disease (AD) when aiming to prevent dementia it is critical explore whether SCD reported by individuals who seek medical help can serve as a clinical marker for identifying individuals at a very early disease stage.[7]

The research framework by the National Institute on Aging–Alzheimer's Association (NIA-AA) defines AD by the presence of AD pathology indicated by biomarkers of amyloid and tau aggregation.[8] In this framework, the clinical symptomatology of AD is classified by a numeric scheme with six stages spanning from the fully asymptomatic preclinical stage 1 to the severe dementia stage 6. This stage of initial subtle symptoms is labeled stage 2 and occurs before the extensively studied pre-dementia mild cognitive impairment (MCI) stage (stage 3).[9,10] Symptomatic features proposed for stage 2 of AD are SCD, subtle objective cognitive decline, not yet meeting MCI criteria, and mild changes in mood or behavior.[6]

Here we present data from the multicenter memory clinic–based DZNE (German Center for Neurodegenerative Diseases) Longitudinal Cognitive Impairment and Dementia Study (DELCODE), which is unique as it specifically focuses on individuals with SCD who seek medical help[11] and also comprises a cognitively unimpaired control group without SCD complaints (controls [CO]). We explored whether the SCD group differs from the CO group regarding symptomatic characteristics and AD biomarkers. We further tested whether individuals with SCD, who are in the pathological AD continuum (amyloid positive, SCD–A+) differ from amyloid-positive CO (CO–A+) on these variables. Finally, we tested the difference of the effect of amyloid pathology on cognitive decline in SCD and CO individuals over up to 5 years.

2 | METHODS

The protocol of the DELCODE study has been published previously.[11] In brief, DELCODE is conducted at 10 university-based DZNE partner memory centers in Germany. The ethical committees of all participating sites approved the protocol. All participants provided informed consent prior to study entry.

2.1 | Participants

All individuals in DELCODE were 60 years of age or older and were enrolled in the study between April 2014 and August 2018. Participants were included as SCD (n = 445) if they presented to a memory clinic with a complaint of cognitive decline (SCD index criterion) and fulfilled the SCD research criteria, which are (1) self-experienced persistent decline in cognitive capacity compared to a previously normal status and unrelated to an acute event and (2) normal age-, sex-, and education-adjusted performance on standardized cognitive tests, which are used to classify MCI.[3] Normal cognition was operationalized by a performance of better than −1.5 standard deviations (SD) of the age-, sex-, and education-adjusted normal range on all subtests of the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) neuropsychological test battery.[12] The non-SCD CO group (n = 236) was recruited by advertisement, which explicitly addressed individuals who felt no relevant cognitive problems of concern (index criterion for the CO group). Unimpaired cognitive performance in the CO group was defined according to the same definition as the SCD group. Additionally, participants with amnestic MCI (n = 190) and mild dementia of the Alzheimer's type (DAT; Mini-Mental State Examination [MMSE] ≥18 points; n = 126) were recruited within DELCODE through the memory clinics based on clinical diagnoses, which were guided by the current research criteria for MCI and DAT (NIA-AA).[10,13] For additional inclusion and exclusion criteria we refer to the initial description of the protocol.[11] After baseline, annual follow-ups were performed with the identical protocol as the one of baseline. Figure S1 in supporting information depicts the analysis flowchart.

2.2 | Clinical assessment and cognitive testing

We report the results of core variables of DELCODE. At baseline and at all follow-ups these include the Clinical Dementia Rating (CDR), the 15-item Geriatric Depression Scale (GDS), the short version of the Geriatric Anxiety Inventory (GAI-SF), the Neuropsychiatric Inventory (NPI-Q), and the Functional Activities Questionnaire (FAQ). For the assessment of subjectively experienced changes in cognition by the participants, we conducted the structured subjective cognitive decline interview (SCD-I).[14] The SCD-I was not used for group classification. The cognitive test data reported here include the MMSE and the Free and Cued Selective Reminding Test Immediate Recall (FCSRT-IR). We additionally calculated the proposed Preclinical Alzheimer's Cognitive Composite (PACC5; supporting information)[15] and the factor scores of memory, language abilities, executive function, working memory, and visuospatial abilities derived from a confirmatory factor analysis of the individual test score data across all applied tests of the DELCODE neuropsychological test battery (supporting information).[11,16]

2.3 | Biomarkers

Cerebrospinal fluid (CSF) was obtained from n = 481 participants of the groups reported here (sampling rate: 48%). Amyloid beta (Aß)42, Aß40, and total tau (t-tau) were determined centrally in one lab (supporting information). Cut-offs were calculated from the DELCODE dataset by Gaussian mixture modeling using the R package flexmix (version 2.3-15).[17] The following cut-offs were determined: Aß42: < = 638.7 pg/ml, Aß42/Aß40: < = 0.08, t-tau:>510.9 pg/ml, phosphorylated tau (p-tau): > = 73.65 pg/ml, and Aß42/p-tau:<9.68. Apolipoprotein E (APOE) genotypes were determined (supporting information). For all analyses, the cut-off of the Aß42/Aß40 ratio was used to define amyloid positivity. A comparison of all demographic, clinical, and additional data between those participants with and without CSF biomarkers is provided in the supporting information (Table S1).

RESEARCH IN CONTEXT

1. **Systematic Review**: The literature on subjective cognitive decline (SCD) in relation to Alzheimer's disease (AD) as well as on stage 2 of the AD continuum is rapidly expanding. We searched PubMed, meeting abstracts, and presentations and focused the citations on comparable cross sectional and longitudinal case-control and cohort studies.
2. **Interpretation**: We found that close to 40% of individuals who consult memory clinics with SCD are in the AD continuum at stage 2 as indicated by positive amyloid biomarkers (SCD–A+). This group showed extended subtle symptoms and accelerated longitudinal cognitive decline.
3. **Future Directions**: The concept of using SCD in memory clinics as an indicator of stage 2 of the AD continuum with potentially high relevance for early treatment requires further validation. In addition, refined identification of and new markers for those SCD–A+ cases with rapid decline need to be developed for future clinical trials.

HIGHLIGHTS

- Of memory clinic patients with subjective cognitive decline (SCD), 39.3% were amyloid positive.
- SCD was associated with other signs of stage 2 in the Alzheimer's disease continuum.
- Amyloid had greater impact on cognitive decline in SCD than in unimpaired controls.
- Amyloid-positive SCD patients are a promising target group for early interventions.

TABLE 1 Baseline characteristics of all groups

Characteristic	Controls (*N* = 236)		SCD (*N* = 445)		MCI (*N* = 190)		DAT (*N* = 126)		Contrast controls versus SCD		
									Chi²/*t*-value	df	*P*-value (fdr)
Age. mean (SD). mean (SD) year	68.94	5.39	70.95	6.03	72.57	5.56	74.81	6.29	−4.27	678	<**0.001**
Sex female *n* (%)	134 (56.8%)		207 (46.5%)		85 (44.7%)		74 (58.7%)		6.497	1	**0.011**
Education mean (SD) year	14.71	2.74	14.84	2.97	14.03	3.12	12.90	3.11	−0.57	678	0.570
APOE ε4 positive n/N (%)	49/232 (21.1%)		142/434 (32.7%)		90/185 (48.6%)		77/123 (62.6%)		9.94	1	**0.004**
MMSE total score mean (SD)	29.47	0.83	29.22	1.02	27.65	2.00	23.05	3.14	−2.18	677	0.055
CDR Global Score mean (SD)	0.00	0.00	0.21	0.25	0.48	0.14	0.77	0.29	not tested. no variance in HC group		
CDR Sum of Boxes mean (SD)	0.03	0.13	0.36	0.57	1.51	1.20	4.58	2.08	10.56	664	<**0.001**
PACC5 mean (SD)	0.18	0.54	−0.12	0.673	−1.57	1.05	−3.83	1.21	4.06	677	<**0.001**
FCSRT Free recall score mean (SD)	32.71	5.83	29.98	6.66	19.93	7.97	8.25	6.83	3.87	675	<**0.001**
Memory and learning mean (SD)	0.61	0.45	0.37	0.55	−0.77	0.68	−1.94	0.53	2.81	675	<**0.001**
Language abilities mean (SD)	0.55	0.46	0.35	0.58	−0.66	0.63	−1.81	0.66	2.44	675	**0.012**
Executive functions mean (SD)	0.50	0.55	0.29	0.67	−0.55	0.77	−1.74	0.83	0.81	675	**0.030**
Working memory mean (SD)	0.38	0.57	0.26	0.68	−0.43	0.76	−1.46	0.79	0.501	675	0.519
Visuospatial abilities mean (SD)	0.33	0.52	0.24	0.59	−0.47	0.66	−1.38	0.78	0.67	675	0.592
FAQ Total Score mean (SD)	0.07	0.32	0.61	1.20	3.27	4.07	12.34	7.43	7.13	653	<**0.001**
SCD-I Score number of domains mean (SD)	0.88	0.99	2.75	1.15	2.53	1.28	2.34	1.40	22.303	677	<**0.001**
Geriatric Depression Scale Score mean (SD)	0.67	1.31	1.97	2.01	2.17	1.95	2.46	2.11	12.01	661	<**0.001**
Geriatric Anxiety Inventory SF Score, mean (SD)	0.67	0.82	1.20	1.23	1.03	1.10	1.14	1.31	5.79	676	<**0.001**
NPI-Q Total Score, mean (SD)	0.46	0.91	1.84	2.86	3.34	3.42	3.94	3.98	7.65	643	<**0.001**
Imaging Biomarkers (*N* = 943)	**Controls (*N* = 224)**		**SCD patients (*N* = 378)**		**MCI (*N* = 157)**		**DAT (*N* = 108)**		**Chi²/*t*-value**	**df**	***p*-value (fdr)**
FBB_SUVR (only in *n* = 65 SCD)			1.44	0.23							
FBB_SUVR (>1.39), *n* (%)			25 (38.5%)								
Total HC vol.(mm^3), mean (SD)	6224.33	628.29	6151.66	705.11	5561.11	829.00	4843.65	786.00	1.42	597	0.239
WML number of lesions, mean (SD)	8.90	5.49	11.73	8.73	14.69	9.29	18.92	15.80	2.86	592	**0.011**
CSF biomarkers (*N* = 527)	**Controls (*N* = 92)**		**SCD (*N* = 211)**		**MCI (*N* = 112)**		**AD (*N* = 66)**		**Chi²/*t*-value**	**df**	***p*-value (fdr)**
Aß42 pgml, mean (SD)	834.50	301.93	769.85	335.15	586.31	306.00	425.83	229.00	−1.424	299	0.239
Aß42 < = 638.7 pgml. *n*(%)	25 (27.2%)		86 (40.8%)		81 (72.3%)		61 (92.4%)		3.46	1	0.109
tTau pgml, mean (SD)	373.04	166.61	370.84	185.29	541.77	299.00	798.10	376.00	−1.277	299	0.278
tTau >510.9 pgml, *n* (%)	16 (17.4%)		37 (17.5%)		48 (42.9%)		48 (72.7%)		0.83	1	0.631

(Continues)

TABLE 1 (Continued)

CSF biomarkers (N = 527)	Controls (N = 92)		SCD (N = 211)		MCI (N = 112)		AD (N = 66)		Chi^2/t-value	df	p-value (fdr)
pTau181 pgml, mean (SD)	50.90	19.71	54.06	24.04	70.57	41.90	95.88	43.60	−0.058	299	0.954
pTau181 > = 73.65 gml, n (%)	7 (7.6%)		33 (15.6%)		42 (37.5%)		45 (68.2%)		1.78	1	0.278
Aß42/Aß40 ratio, mean (SD)	0.10	0.02	0.09	0.03	0.07	0.03	0.05	0.02	−0.423	299	0.699
Aß42/Aß40 ratio < = 0.0806, n (%)	25 (27.2%)		83 (39.3%)		71 (63.4%)		61 (92.4%)		1.41	1	0.303
Aß42/pTau181 ratio, mean (SD)	17.70	5.68	16.30	7.49	10.83	7.34	5.39	4.57	−0.581	299	0.631
Aß42/pTau181 ratio < = 9.6825, n (%)	8 (8.7%)		57 (27.0%)**		60 (53.6%)		61 (92.4%)		3.05	1	**0.015**

Notes: *P*-Values: *P*-values unadjusted for multiple testing; *P*-values(fdr): *P*-values corrected for multiple testing using the Bejamini-Hochberg procedure to control the false discovery rate. *t*-values: *t*-values derived from linear regression models for the coefficient comparing control to SCD participants. χ^2: Chi^2-values derived from logistic regression model comparing the control to SCD group. All analyses are adjusted for covariates (age, sex, years of education, in addition: total intracranial volume for brain volume measures).

Abbreviations: Aß, amyloid beta; CDR, Clinical Dementia Rating; CO, unimpaired non-SCD controls; DAT, dementia of the Alzheimer type; FAQ, Functional Activities Questionnaire; FBB_SUVR, florbetaben standardized uptake value ratios; FCSRT, Free And Cued Selective Reminding Test; HC, hippocampus; MCI, mild cognitive impairment; MMSE, Mini-Mental-State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; PACC–5, Preclinical Alzheimer's Cognitive Composite; PET, positron emission tomography; pTau181, phosphorylated tau 181; SCD, subjective cognitive decline; SCD-I, subjective cognitive decline interview; SD, standard deviation; SF, short form; tTau, total tau; WML, white matter lesions.

2.4 | Magnetic resonance imaging

Magnetic resonance imaging (MRI) was performed at nine imaging sites on Siemens 3T-MR-Scanners. The full MRI protocol has been described previously.[11] Quality assurance led to the exclusion of 14 participants. Here, we report volumetric data obtained automatically with FreeSurfer from whole-brain T1-weighted (1 mm isotropic) and partial-volume T2-weighted images optimized for the medial temporal lobe (0.5 × 0.5 × 1.5 mm).[18,19] In addition, automatic hippocampal subfield segmentation was carried out using additionally acquired high-resolution T2-weighted images.[20] Whole hippocampal volumes were derived from the hippocampal subfield segmentation. Moreover, we segmented white matter hyperintensities (WMH) on whole-brain fluid-attenuated inversion recovery images (supporting information).

2.5 | Amyloid positron emission tomography

The Florbetaben (FBB; NeuraceqTM; Piramal Imaging) substudy was only performed in participants with SCD ($n = 65$). Data were collected at six sites and analyzed using standardized uptake value ratios (SUVR) in PMOD (PMOD Technologies LLC) with the cerebellar cortex as reference region. An SUVR cut-off of 1.39 was applied to define positron emission tomography (PET)-based amyloid positivity.[21] Note, however, that the definition of amyloid positivity for all further analyses is based to the Aß42/Aß40 CSF ratio cut-off.

2.6 | Statistical analyses

The statistical analyses (IBM SPSS Statistics for Windows, version 22.0 and R version 3.4.4) addressed three topics: (1) the comparison of the SCD and the CO group at baseline, (2) the comparison of SCD amyloid positive (SCD–A+) and control amyloid positive (CO–A+) at baseline, and (3) the longitudinal comparisons of SCD versus CO changes on the PACC5 in relation to CSF Aß42. The Benjamini-Hochberg procedure was used to correct for multiple testing.[22] The handling of missing data, the comparisons of MCI and DAT with the CO group and of MCI–A+ and DAT–A+ with CO–A+ are reported in the supporting information.

2.6.1 | Cross-sectional analyses

The rate of missing data of the cross-sectional clinical and demographic variables was 1.2%. Missing data were evenly distributed across the variables and the diagnostic groups. Further details on missing data are reported in the supporting information. The descriptive baseline data for all clinical groups are listed in Table 1. Due to the differences in age and sex between the two groups, all analyses were adjusted for these variables and in addition for years of education. To test the first question, we calculated contrasts of the SCD data compared to the CO group based on individual linear or logistic regression models. Brain

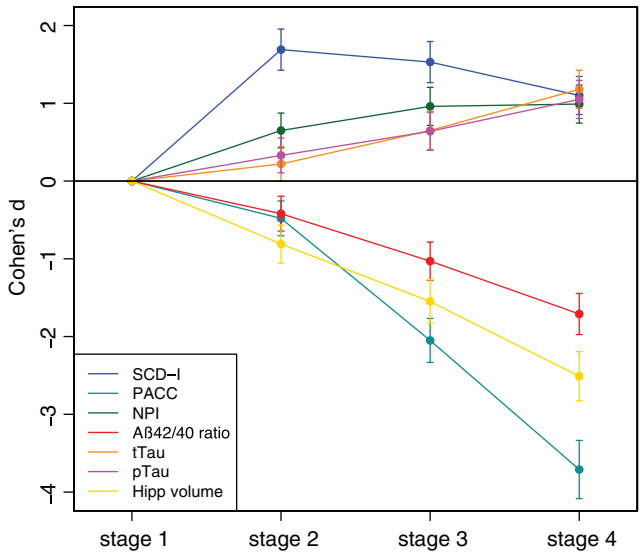

FIGURE 1 Depicted are the effect sizes at baseline (Cohen's *d*) of cognitive and clinical variables as well as biomarkers in stage 2 (SCD–A+), stage 3 (MCI–A+), and stage 4 (DAT–A+) of the AD continuum compared to stage 1 (CO–A+; reference group). According to the definition of the AD continuum, all cases are amyloid positive. Aß, amyloid beta; AD, Alzheimer's disease; CO, control; DAT, dementia of Alzheimer's type; Hipp volume, hippocampal volume; MCI, mild cognitive impairment; NPI, Neuropsychiatric Inventory; PACC, Preclinical Alzheimer's Cognitive Composite; pTau, phosphorylated tau; SCD, subjective cognitive decline; SCD-I, subjective cognitive decline interview; tTau, total tau

volume markers were additionally adjusted for the total intracranial volume (TIV). To test the second question, we compared the CO–A+ to the SCD–A+ groups in the same way (Table 2). Descriptive statistics for MCI and DAT as well as MCI–A+ and DAT–A+ are displayed in addition. We applied Yeo-Johnson power transformations to continuous outcomes showing non-Gaussian residual distributions as implemented in the R package car.[23] For the graphic display of the course of the different variables across the AD continuum stage 1 (CO–A+), stage 2 (SCD–A+), stage 3 (MCI–A+), and stage 4 (DAT–A+) we calculated Cohen's *d* as the effect size estimate compared to stage 1 (Figure 1).

2.6.2 | Analyses of cognitive trajectories (PACC5)

Longitudinal analyses were based on up to 5 years of follow-up. We modeled cognitive trajectories of the PACC5 using a univariate latent process linear mixed model without estimation of multiple latent classes as implemented in the R package LCMM.[24,25] The most appropriate link function (i.e., linear or beta link function, or I-splines with three to seven knots places at quantiles or equidistant across the outcome range) and polynomial of time (i.e., linear or quadratic effect of time as fixed effect and random slope) were chosen according to the Bayesian information criterion (BIC) from models including only a random intercept and random and fixed effects of time. We included all participants as all of them were intended to be followed longitudinally. Attrition from study and missing follow-ups were handled using maximum likelihood estimation in the linear mixed model with a latent process procedure, which yields unbiased estimates under the missing at random assumption.

We compared the cognitive trajectories across the diagnostic groups and within the diagnostic groups according to amyloid status (interaction of amyloid status × time in fixed effects). Finally, we tested the fixed effects three-way interaction of group × amyloid status × time and group × quantitative CSF Aß42/40 ratio × time across the CO and SCD groups. Due to the differences in age and sex distribution between the groups all analyses were controlled for fixed effects of these variables and of education as well as their interaction with time. We modeled a random intercept and a correlated random slope of time. Longitudinal models of MCI and DAT as well as of MCI–A+ and DAT–A+ are displayed in the Figure S2 in supporting information.

3 | RESULTS

3.1 | Baseline data

Table 1 displays the characteristics of the different groups at baseline. Statistical comparisons were only calculated between the SCD and the CO group. The CO group was younger than the SCD group and contained a higher number of female participants. Years of education did not differ between the groups. The SCD group showed worse performance than the CO group on the CDR sum of boxes (CDR-SOB) ($P < 0.001$), the PACC5 ($P < 0.001$), the FCSRT ($P < 0.001$), as well as on the factor scores of memory ($P < 0.001$), of language abilities ($P < 0.012$), and of executive function ($P = 0.03$). There was also a significant difference between both groups in the FAQ ($P < 0.001$), the SCD-I ($P < 0.001$), the GDS ($P < 0.001$), the GAI ($P < 0.001$), and the NPI score ($P < 0.001$). The frequency of the *APOE* ε4 genotype was higher in SCD compared to the CO group ($P = 0.004$). Within the SCD group 39.3% within the CO group 27.2% were amyloid positive according the Aß42/Aß40 ratio in the CSF ($P = 0.303$, not significant [n.s.]). The FBB SUVR positivity rate was 38.5% in the SCD group. The p-tau positivity rate was 15.6% in the SCD group and 7.6% in the CO group ($P = 0.278$, n.s.) The proportion of abnormal Aß42/p-tau ratios (CO: 8.7% vs. SCD: 27%) differed between both groups ($P = 0.015$). The number of white matter lesions was higher in SCD compared to the CO group ($P = 0.011$).

Table 2 shows the data of the amyloid positive cases only. The SCD–A+ group was older and scored higher on the CDR-SOB ($P = 0.017$), the FAQ ($P = 0.017$), the SCD-I ($P < 0.001$), the GDS ($P < 0.001$), and the NPI-Q ($P = 0.030$) than the CO–A+ group. The SCD–A+ group also showed smaller hippocampal volumes than the CO–A+ group ($P = 0.026$). Figure 1 depicts the evolution of the clinical and cognitive scores as wells as biomarkers from the AD continuum stage 1 (CO–A+) to stage 4 (DAT–A+).

TABLE 2 Comparison of the Alzheimer's disease continuum stage 1–4

Characteristic	CO-A+ (stage 1) (*N* = 25)		SCD-A+ (stage 2) (*N* = 83)		MCI -A+ (stage 3) (*N* = 71)		DAT -A+ (stage 4) (*N* = 61)		CO-A+ (stage 1) versus SCD–A+ (stage 2)		
									Chi^{2}/*t*-value	df	*P*-Value(fdr)
Age, mean (SD), year	69.6	5.3	72.8	5.1	72.8	5.4	75.1	6.5	−2.8	106	**0,006**
Sex, female *n* (%)	8 (32%)		29 (34.9%)		37 (52.1%)		39 (63.9%)		0.1	1	0.786
Education, mean (SD), year	14.9	3.0	14.8	2.9	13.4	3.0	13.0	3.0	0.11	106	0.910
APOE ε4 positive *n*/*N* (%)	13 (52%)		51 (62.2%)		45 (63.4%)		40 (65.6%)		0.8	1	0.586
MMSE total score, mean (SD)	29.4	0.7	29.1	1.0	27.2	1.9	23.0	3.0	−0.1	104	0.934
CDR Global Score, mean (SD)	0.00	0.00	0.27	0.25	0.50	0.12	0.78	0.30	Variance = 0 in Stage 1, not tested		
CDR Sum of Boxes, mean (SD)	0.10	0.20	0.51	0.74	1.64	1.19	4.48	2.19	3.0	102	**0,017**
PACC5	−0.053	0.5	−0.34	0.6	−1.9	1.0	−3.8	1.2	1.1	104	0.556
FCSRT Free Recall	30.1	6.2	27.3	6.8	18.8	7.6	8.8	6.7	1.3	103	0,482
Memory and learning	0.43	0.42	0.21	0.50	−0.97	0.70	−1.96	0.54	0.8	104	0,598
Language abilities	0.34	0.45	0.18	0.54	−0.82	0.67	−1.80	0.66	0.1	104	0.934
Executive functions	0.38	0.52	0.09	0.64	−0.78	0.81	−1.71	0.78	0.8	104	0,598
Working memory	0.32	0.53	0.12	0.67	−0.58	0.79	−1.46	0.77	0.2	104	0.933
Visuospatial abilities	0.20	0.50	0.21	0.52	−0.61	0.64	−1.37	0.76	−1.2	104	0.482
FAQ Total Score, mean (SD)	0.00	0.00	0.81	1.43	3.79	3.84	11.49	7.23	3.1	102	**0,017**
SCD-I Score number of domains	0.92	0.91	2.88	1.22	2.72	1.26	2.26	1.33	7.0	104	**0.000**
Geriatric Depression Scale score, mean (SD)	0.88	1.67	2.28	2.26	2.43	2.40	2.22	2.08	4.3	101	**0.000**
Geriatric Anxiety Inventory SF score, mean (SD)	0.60	0.71	1.08	1.21	1.18	1.26	1.33	1.39	1.7	104	0.164
NPI-Q total score	0.46	1.02	2.08	2.76	3.44	3.55	3.85	4.00	2.7	97	**0.030**
Imaging biomarkers	**(*N* = 23)**		**(*N* = 62)**		**(*N* = 56)**		**(*N* = 52)**		**Chi2/*t*-value**	**df**	***p*-value(fdr)**
Total HC vol. (mm^3), mean (SD)	6475.16	712.53	5947.55	626.11	5332.79	743.73	4714.40	696.09	2.8	80	**0.026**
WML number of lesions, mean (SD)	10.70	5.41	13.08	7.75	15.36	11.96	20.15	18.71	0.3	79	0.858
CSF biomarkers	**(*N* = 25)**		**(*N* = 83)**		**(*N* = 71)**		**(*N* = 61)**		**Chi2/*t*-value**	**df**	***p*-value(fdr)**
Aß42, pgml, mean (SD)	547.8	143.0	500.6	165.0	435.0	146.8	384.6	127.7	-	-	-
Aß42 < = 638.7 pgml, *n*(%)	18 (72%)		68 (81.9%)		66 (93.0%)		59 (96.7%)		-	-	-
tTau, pgml, mean (SD)	448.607	209.640	494.330	210.399	637.599	311.665	835.661	366.042	0.426	104	0.839

(Continues)

TABLE 2 (Continued)

CSF biomarkers	(N = 25)		(N = 83)		(N = 71)		(N = 61)		Chi2/t-value	df	p-value(fdr)
tTau > 510.9 pgml, *n* (%)	8 (32%)		31 (37.3%)		42 (59.2%)		48 (78.7%)		0.4	1	0.734
pTau181, pgml, mean (SD)	59.1	27.4	68.4	28.0	85.4	44.5	100.0	42.7	0.987	104	0.593
pTau181 > = 73.65 gml, *n* (%)	5 (20%)		26 (31.3%)		38 (53.5%)		45 (73.8%)		0.8	1	0.598
Aß42/Aß40 ratio, mean (SD)	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	-	-	-
Aß42/Aß40 ratio < = 0.0806, *n* (%)	classification variable										
Aß42/pTau181 ratio, mean (SD)	10.9	4.3	8.3	3.7	6.0	3.2	4.2	1.6	-	-	-
Aß42/pTau181 < = 9.68, *n* (%)	8 (32%)		57 (68.7%)		60 (84.5%)		61 (100%)		-	-	-

Notes: *P*-values: *P*-values unadjusted for multiple testing; *P*-values(fdr): *P*-values corrected for multiple testing using the Bejamini-Hochberg procedure to control the false discovery rate. *t*-values: *t*-values derived from linear regression models for the coefficient comparing control to SCD participants. χ^2: Chi^2-values derived from logistic regression model comparing the control to SCD group. All analyses are adjusted for covariates (age, sex, years of education, in addition: total intracranial volume for brain volume measures).
Abbreviations: Aß, amyloid beta; CDR, Clinical Dementia Rating; FAQ, Functional Activities Questionnaire; FBB_SUVR, florbetaben standardized uptake value ratios; FCSRT, Free and Cued Selective Reminding Test; HC, hippocampus; NPI-Q, Neuropsychiatric Inventory Questionnaire; MMSE, Mini-Mental State Examination; PACC5, Preclinical Alzheimer's Cognitive Composite; PET, positron emission tomography; pTau181, phosphorylated tau 181; SCD-I, subjective cognitive decline interview; SD, standard deviation; SF, short form; tTau, total tau; WML, white matter lesions.

3.2 | Longitudinal data

At the time of data extraction for the present analyses out of 997 participants, 228 (22.9%; SCD: $n = 128$) provided 1 year, 188 (18.9%; SCD: $n = 92$) 2 years, 192 (19.3%; SCD: $n = 78$) 3 years, 186 (18.7%; SCD: $n = 60$) 4 years, and 68 participants (6.8%; SCD: $n = 39$) 5 years follow-up. The mean follow-up time in each group is shown in the study flowchart (Figure S1). Compared to the CO group, the SCD group showed greater decline in the PACC5 as indicated by a significant group x time interaction of $P < 0.001$. Exploratory analyses showed similar results for the comparison of CO with MCI and CO with DAT (Table S2 in supporting information). There was no significant time × amyloid status interaction within the CO group. In contrast, the interaction of time × amyloid status in the SCD group was significant (estimate [est] standard error [SE] = −0.23 (0.08); $P = 0.0046$, $P_{fdr} = 0.009$; Table S3 in supporting information). The group (SCD, CO) × amyloid status × time interaction was not significant (est [SE] = −0.18 [0.13]; $P = 0.159$, $P_{fdr} = 0.186$; Table S3). The three-way interaction with quantitative values of the Aß42/Aß40 ratio was significant (est [SE] = 5.64 [2.36]; $P = 0.017$, $P_{fdr} = 0.024$; Table S4 in supporting information). This indicates that the impact of baseline levels of CSF amyloid pathology on speed of cognitive decline is significantly greater in the SCD than in the CO group. Figure 2 depicts the respective PACC5 slopes of the SCD and the CO group.

4 | DISCUSSION

In this multicenter study, we observed slightly worse cognitive performance, discrete functional, and slightly more behavioral symptoms in individuals with SCD who consult a memory center, compared to the cognitively unimpaired CO subjects. Longitudinally, the SCD group showed greater cognitive decline compared to the CO group. These cross-sectional and longitudinal findings are in agreement with initial DELCODE subset analyses and other studies in medical help–seeking individuals with SCD.[4,5,11,26,27]

We observed a rate of 39.3% amyloid positivity case based on the CSF Aß42/Aß40 cut-off and of 38.5% based on amyloid-PET-SUVR in the SCD group, while the CO group showed an amyloid positivity rate of 27.2%, which is similar to rates reported in other studies for cognitively unimpaired individuals.[28,29] The rate of p-tau positivity was 15.6% in the SCD group and 7.6% in the CO group. Both groups differed in the Aß42/p-tau positivity rate (CO: 8.7%, SCD: 27%), which has been shown to achieve a positive predictive value (PPV) for AD of 0.9.[30] Overall, we interpret these results as an enrichment for the AD continuum in the SCD group, even though significant only in the Aß42/p-tau ratio and not in the amyloid positivity or p-tau positivity rate itself, which is most likely due to statistical power. Taking this into account, this result is in line with the previously proposed assumption that memory center consultation in SCD indicates an increased likelihood of being in the AD continuum.[31] Importantly, some studies, including the French INSIGHT-preAD study, reported an amyloid positivity rate in SCD close to identical to non-SCD control

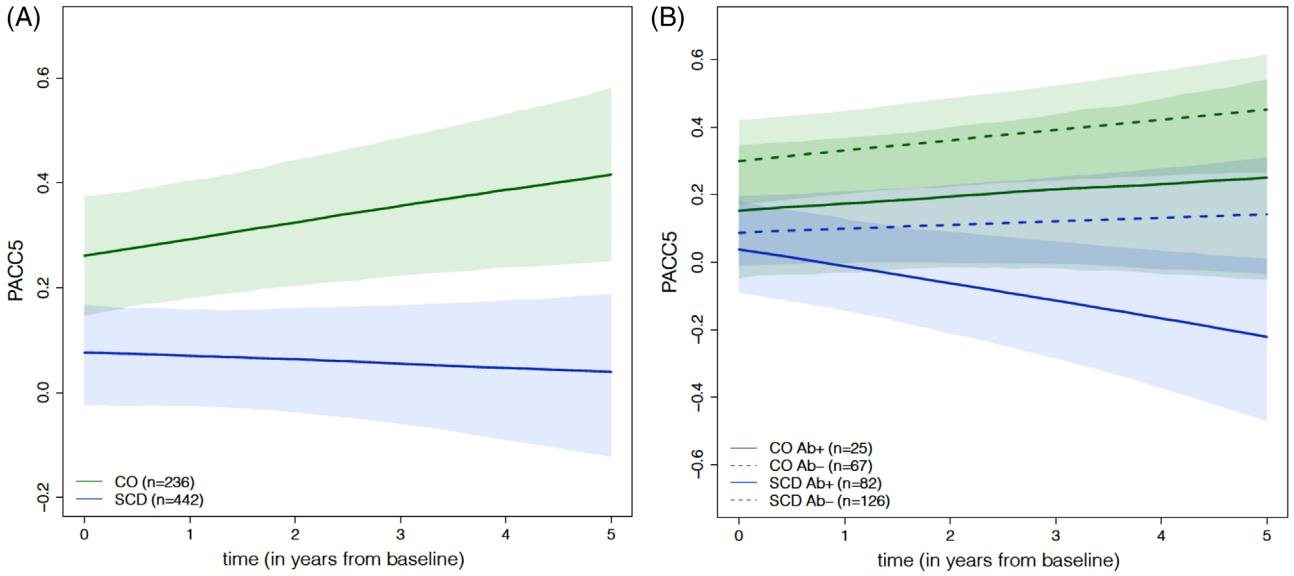

FIGURE 2 Trajectories of the PACC5 over 5 years of the CO and SCD group (A), and the CO and SCD group stratified by amyloid status (B). Plots are derived from different mixed models with a latent process (see Tables S1 and S 2 in supporting information for respective model parameters used to derive the plots). The slope of the SCD group differs from the CO group (P_{fdr} <0.001). Within the CO group A+ and A− individuals do not differ in slope, while within the SCD group, the slope between A+ and A− is significantly different (P_{fdr} = 0.009). The interaction of group x time x Aß42/Aß40 is significant between CO and SCD (P_{fdr} = 0.024) indicating a difference between the two groups in the effect of amyloid on the slopes. CO, control; PACC, Preclinical Alzheimer's Cognitive Composite; SCD, subjective cognitive decline

groups.[28,32] These studies, however, often recruited SCD participants partially or fully through advertisement rather than through memory services, which results in different SCD samples, and they often use subjective memory complaints at the time point of investigation rather than the report of SCD over the past to operationalize SCD.[4,26,32]

We used the amyloid positive cases (A+) to model the AD continuum stages 1–4 according to the NIA-AA criteria.[6] Compared to stage 1 (COA+), we observed higher subjective complaints, lower performance on CDR-SOB, and more mild behavioral symptoms in the stage 2 group (SCD–A+). In addition, we observed smaller hippocampal volumes. We consider our findings supportive of the proposed stage 2 of the AD continuum in terms of a more progressed disease stage compared to stage 1 with greater impact of pathology on brain integrity. This impact is expressed by reduced hippocampal volume and the presence of all proposed clinical signs of stage 2, namely SCD, subtle cognitive dysfunction, and mild behavioral symptoms. Interestingly, all clinical signs occurred in parallel with changes in biomarkers between stage 1 and stage 2 as shown in Figure 1 suggesting close temporal association between biomarker changes and very subtle early symptomatic changes. Importantly, we observed a significant three-way interaction of group (SCD, CO), amyloid concentration as expressed by the Aß42/Aß40 ratio in the CSF, and time with regard to longitudinal cognition. This effect was caused by a greater acceleration of cognitive decline by amyloid in the SCD group compared to the effect of amyloid on cognition in the CO group. Our results are in agreement with the analysis of the Berkeley Aging Cohort Study, a smaller single-center cohort of volunteers.[33] A recent analysis of the population-based volunteer Mayo Clinic Study of Aging on the symptomatic criteria of stage 2 found 4% to 13% of participants at stage 2 worsening at short term follow-up to a more progressed stage and also found that at short term 24% to 41% reverse back to stage 1, when applying operationalized cut-point–based criteria.[34] This study and the DELCODE dataset cannot be directly compared due to the different recruitment setting, the different instruments for symptom assessment of subjective and objective cognition as well as behavioral symptoms and the respective cut-offs applied. The limited comparability highlights the sensitivity of findings in this research area on specific characteristics of the individual studies.[12]

With the strong research focus on the disease-modifying drugs in AD and the recent accelerated licensing of the anti-amyloid-antibody aducanumab by the US Food and Drug Administration the best starting point for the initiation of treatment is still to be defined.[35] SCD–A+ in individuals who seek medical help are often at the initial stage of decompensation of brain reserve and at the beginning of cognitive decline. In the clinical setting, we think that this stage may be a highly promising starting point of treatment in the future, because normal brain functioning is still largely preserved as opposed to later stages with irreversible loss of function, such as MCI (stage 3).[6] Also, individuals who are in the AD continuum and who seek medical help at this stage may be particularly motivated to engage in early treatment aimed at preventing dementia.

The main strengths of our study are: (1) the specific focus on patients with SCD, who approach the health-care system with a cognitive complaint in a multicenter recruitment, which best reflects potential clinical trial cohorts and also mirrors the future patient population for early intervention; (2) the inclusion of a cognitively unimpaired non-SCD control group with biomarkers, which allows the modeling of AD

continuum stages 1 and 2 separately; and (3) the long follow-up time frame, which at present covers up to 5 years and will be extended. The main limitations of the study are: (1) the rate of CSF biomarker sampling of 48%, even though the CSF subsample did not differ in any key variable from the full sample; (2) the ongoing nature of the study with the inclusion of a fraction of participants with only 1 year of follow-up; and (3) the lack of representativeness for the general population at large due to memory center recruitment. Regarding the latter, we are aware that the fact that an individual with SCD consults a memory clinic depends on many factors, such as availability, cultural context, and socioeconomic circumstances and individual conditions.

In summary, the data of the DELCODE study comprehensively characterizes SCD in memory center patients and supports the concept of stage 2 of AD continuum as a transitional stage between the fully asymptomatic stage 1 and stage 3 (MCI) with the symptomatic triad of SCD, subtle cognitive dysfunction and mild behavioral symptoms as well as greater speed of decline. We propose that that stage 2 of the AD continuum indicated by SCD, specifically in those who seek medical help, and confirmed by amyloid pathology, is a promising target for early intervention trials today and for early disease identification and treatment in the future.

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CONFLICTS OF INTEREST

None of the authors declares a conflict of interest related to the content of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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