Minor neuropsychological deficits in patients with subjective cognitive decline

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Search Terms: [26] Alzheimer's disease; [38] Assessment of cognitive disorders/dementia; [201] Memory; [205] Neuropsychological assessment; [additional] Subjective Cognitive Decline.

Submission Type: **Article**

Title Character count: **80**

Word count of Abstract: **225**

Word count of paper: **4267**

Number of references: **42**

Number of Tables: **3**

Number of Figures: **1**

Supplementary data: **1 appendix and 1 figure**

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1   **Abstract**

2   **Objective:** To determine the nature and extent of minor neuropsychological

3   deficits in patients with subjective cognitive decline (SCD) and their

4   association with cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease

5   (AD).

6   **Method:** We analyzed data from n=449 cognitively normal participants

7   (n=209 healthy controls, n=240 SCD patients) from an interim data release of

8   the *German Center for Neurodegenerative Diseases Longitudinal Cognitive*

9   *Impairment and Dementia Study* (DELCODE). An extensive

10 neuropsychological test battery was applied at baseline for which we

11 established a latent, five cognitive domain factor structure comprising learning

12 & memory, executive functions, language abilities, working memory and

13 visuospatial functions. We compared groups regarding global and domain-

14 specific performance and correlated performance with different CSF markers

15 of AD pathology.

16 **Results:** We observed worse performance (Cohen's d≈0.25-0.5, adjusted for

17 age-, sex differences with ANCOVA) in global performance, memory,

18 executive functions and language abilities for the SCD group compared to

19 healthy controls. In addition, worse performance in these domains was

20 moderately (r≈0.3) associated with lower CSF-Aβ42/40 and CSF-

21 Aβ42/ptau181 in the whole sample and specifically in the SCD subgroup.

22 **Conclusions:** Within the spectrum of clinically unimpaired (i.e., "pre- mild

23 cognitive impairment") cognitive performance, SCD is associated with minor

24 deficits in memory, executive function and language abilities. The association

1   of these subtle cognitive deficits with AD CSF biomarkers speaks to their

2   validity and potential use for the early detection of underlying preclinical AD.

3

1 **Introduction**

2 Individuals with subjective cognitive decline (SCD) subjectively experience a

3 decline in cognitive functioning while still performing within the age-, sex- and

4 education-adjusted normal limits on standard cognitive tests [1,2]. Due to their

5 preserved cognition, help-seeking behavior and increased risk for future

6 Alzheimer's disease (AD) dementia [3], individuals with SCD, especially within

7 the memory clinic setting [4], are highly relevant for the concept of early

8 intervention. Recent research has largely focused on identifying the

9 quantitative and qualitative aspects of SCD specifically related to underlying

10 AD pathology [5]. In contrast, a deeper characterization of neuropsychological

11 performance in this group has been somewhat neglected. Objective

12 neuropsychological information in SCD is primarily used to demark it from the

13 mild cognitive impairment (MCI) stage. This may have implicitly suggested

14 that variance in neuropsychological performance may not have further

15 relevance for the prediction of underlying AD pathology and the risk of clinical

16 progression in "cognitively unimpaired" SCD patients. Thus, it currently

17 remains unclear (1) whether memory clinic patients with SCD still exhibit

18 minor cognitive deficits compared to cognitively normal individuals *without*

19 *SCD*, (2) whether these patients manifest deficiencies in specific domains of

20 cognition, and (3) whether these deficiencies are associated with the self-

21 /informant reported extent of SCD as well as biomarkers of AD pathology. In

22 the present study, we therefore compared neuropsychological performance in

23 five different cognitive domains between memory clinic patients with SCD and

24 healthy controls and associated it with the extent of self-/informant rated SCD

25 and CSF biomarkers of AD pathology.

1   **Methods**

2   *Standard Protocol Approvals, Registrations, and Patient Consent*

3   The study protocol was approved by local institutional review boards and

4   ethical committees of all participating sites of the *German Center for*

5   *Neurodegenerative Diseases (DZNE) Longitudinal Cognitive Impairment and*

6   *Dementia Study* (DELCODE). All participants in the study provided written

7   informed consent.

8   *DELCODE study*

9   DELCODE is an observational longitudinal multicenter study carried out by

10   ten university-based memory clinics collaborating with local sites of the DZNE

11   [6]. All patients of DELCODE are referrals, including self-referrals, to the

12   participating memory centers, while two nonpatient groups were recruited by

13   standardized public advertisement (see below). All participants were required

14   to be age ≥60 years. Further requirements were fluent German language

15   skills, capacity to provide informed consent, and presence of a study partner.

16   Recruitment started in 2015 and, at time of data extraction for the present

17   study (Oct 2018), was still ongoing.

18   DELCODE has a focus on cognitively normal memory clinic patients with SCD

19   and includes a comparison group of healthy controls (HC) without subjective

20   or objective impairment. The study also recruited cognitively normal first-

21   degree relatives of patients with AD dementia (hereafter named "AD

22   relatives") as an exploratory at risk group. However, we did not include them

23   in the present report due to a yet to small sample size. In addition, the study

24   also included amnestic MCI and mild AD dementia patients. A detailed

1 description of the complete study protocol, including all general

2 inclusion/exclusion criteria as well as diagnostic criteria of all groups, has

3 been published recently [6]. Here, we included n=209 HC and n=242 SCD

4 patients selected from an interim data release. In addition, this data release

5 sample included n=115 amnestic MCI patients, n=77 mild AD dementia

6 patients and n=44 AD relatives. We used the latter three groups only in the

7 model estimation to derive the cognitive domain scores (see below and

8 appendix e-1).

9 *Definition of cognitively normal participant groups*

10 In line with current research criteria [1,2], the SCD patient group was defined by

11 the presence of subjectively self-reported decline in cognitive functioning with

12 concerns as expressed to the physician of the respective memory center and

13 a test performance of better than -1.5 standard deviations (SD) below the

14 age, sex, and education-adjusted normal performance on all subtests of the

15 *Consortium to Establish a Registry for Alzheimer's Disease* (CERAD)

16 neuropsychological battery. We applied the CERAD battery as part of the

17 clinical routine at each site. This provided the neuropsychological information

18 for the entry diagnosis in DELCODE (i.e., this assessment was not part of the

19 DELCODE baseline visit itself).

20 We recruited the HC group by local newspaper advertisement explicitly asking

21 for individuals who felt healthy and without relevant cognitive problems. We

22 screened all individuals who responded to the advertisement by telephone

23 with regard to the presence of SCD. The report of very subtle cognitive

24 decline experienced as normal for the age of the individual and not causing

25 concerns was not an exclusion criterion for the HC group.

1 The HC group had to achieve unimpaired cognitive performance according to

2 the same definition as the SCD group. Neuropsychological information to

3 verify adherence to this criterion for these participants stems from the

4 DELCODE baseline assessment because, unlike the SCD patient group,

5 these participants did not undergo the routine diagnostic work-up in the

6 memory clinic.

7 *Assessments*

8 Standardized assessment and diagnostic procedures of DELCODE have

9 been described previously [6]. Here, we focus on a description of the

10 assessments relevant to the present study, i.e., assessment and processing

11 of neuropsychological data and CSF biomarker data.

12 *Neuropsychological assessment and derivation of cognitive domain scores via*

13 *confirmatory factor analysis*

14 As part of the clinical assessment, we applied the DELCODE

15 neuropsychological assessment battery (hereafter called "DELCODE-NP") at

16 baseline. We selected the tests to serve the aims of (1) comparability with

17 similar ongoing studies addressing prodromal and preclinical AD (e.g., ADNI,

18 WRAP) [7,8], (2) measuring different cognitive domains (see below) and (3)

19 including tests used in cognitive composite scores (e.g., the "Preclinical

20 Alzheimer cognitive composite" (PACC) [9]) for tracking cognitive decline.

21 The DELCODE-NP includes the Mini Mental State Examination (MMSE) [10],

22 ADAS-Cog 13 [11], the Free and Cued Selective Reminding Test (FCSRT) [12],

23 which includes a serial subtraction task, Wechsler Memory Scale revised

24 version (WMS-R) Logical Memory (Story A) and Digit Span [13], two semantic

1 fluency tasks (animals and groceries [14]), the Boston Naming Test (15 item

2 short version analogue to the CERAD battery [15], supplemented by 5

3 infrequent items from the long version [14]), the oral form of the Symbol-Digit-

4 Modalities Test (including a subsequent free recall of symbols and symbol-

5 digit pairings[16]), Trail Making Test A and B [17], Clock Drawing and Clock

6 Copying [18], and a recall task of previously copied figures (as in the CERAD

7 test battery [15]). In addition to these established tests, two newly developed

8 computerized tests were implemented: the Face Name Associative

9 Recognition Test [19] and a Flanker task to assess executive control of attention

10 [20].

11 Of note, comparability between the DELCODE-NP and the CERAD test

12 battery is ensured by the fact that every CERAD test is included in the

13 DELCODE-NP, either by addition to the battery as a single test or (in the case

14 of word list learning and recall, object naming, and figure copying) by using

15 the equivalent of the ADAS-Cog 13 with minor adjustments of items and/or

16 scoring according to the CERAD version. Raw behavioral data were recorded

17 to allow scoring analogous to both the CERAD and ADAS-Cog 13

18 procedures. For the present study, we scored the tests according to CERAD

19 procedures [11] to ensure applicability of the CERAD-based criteria for cognitive

20 normality (see above) in the HC group. We also developed parallel versions of

21 the word list learning task to counteract potential practice effects due to item

22 familiarity in the SCD patient group, as for these participants the baseline

23 assessment was the second time they were exposed to those tests of the

24 DELCODE-NP that were also part of the CERAD-based neuropsychological

25 examination during the screening visit. Importantly, all participant groups were

1   tested with exactly the same test battery, including the same version of the

2   word list, at the baseline visit.

3   We then used confirmatory factor analysis (CFA) to derive five cognitive

4   domain scores: Learning & memory (MEM), language ability (LANG),

5   executive functions and mental processing speed (EXEC), working memory

6   (WM) and visuo-spatial abilities (VIS). In addition, we derived a global

7   cognitive performance score as the average of the five domain scores.

8   Further details of the CFA procedures are given in appendix e-1 and figure-

9   e1. Two participants from the SCD group had to be excluded from the model

10   estimation due to missing data on all neuropsychological variables (reducing

11   the SCD sample of the present study to n=240).

12   *Interview-based assessment of the extent of subjective cognitive decline*

13   We assessed subjective reports of cognitive decline in different domains with

14   a structured clinical interview ("Subjective Cognitive Decline Interview; SCD-I;

15   [21]). The SCD-I allows assessment of SCD in five different cognitive domains

16   (memory, language, planning, attention, others). All interviews were

17   administered by trained study physicians and lasted approximately five

18   minutes. For each cognitive domain, the physician asked the patient if he/she

19   had noticed any worsening in function (e.g., "do you feel like your memory has

20   worsened?"). If the participant answered this question with yes, the physician

21   added more in-depth questions about the domain to assess the

22   presence/absence of SCD-plus features [2], i.e., specific questions proposed to

23   increase the likelihood of underlying AD pathology if confirmed. These are,

24   e.g., questions about the presence of associated worries ("Does this worry

25   you?") or the onset ("How long ago did you start to notice the decline?"). In

1   addition, the semistructured interview was administered to a study-partner

2   (relative) of the participant to obtain information on confirmation of the

3   participant's perceived decline in each cognitive domain. The quantification of

4   response data allows derivation of different sum scores, including the total

5   number of cognitive domains (memory, language, planning, attention, others)

6   in which the participant endorses a worsening in function (maximum score =

7   5). The same score can be derived for the informant report. We used these

8   two scores for our analyses.

9   *CSF biomarker assessment*

10   Procedures of CSF acquisition, processing and analysis in DELCODE have

11   been previously described [6]. In the present study, we focused on the CSF-

12    $A\beta42/A\beta40$ ratio as the arguably best CSF marker for amyloid pathology [22]. In

13   addition, we used the CSF-pTau181 level as a marker for aggregated tau

14   neurofibrillary tangles and the total CSF-Tau level as a marker for

15   neurodegeneration, according to the most recent NIA-AA guidelines' "AT(N)

16   system" [23]. We decided to use continuous biomarker values (rather than

17   categorical variables based on cutoffs) to explore the strength of the

18   association of cognitive performance with biomarkers within the complete

19   spectrum of preclinical AD pathological change, without loss of information

20   due to dichotomization. The latter would be required in a study of diagnostic

21   utility, which is not the focus of this study. In line with this, we used the ratio of

22    $CSF-A\beta42/p-Tau181$ as a continuous, highly AD-specific biomarker [24].

23   *Statistical analysis*

1   The following statistical analyses were conducted with IBM SPSS Statistics

2   for Windows, Version 22.0. Armonk, NY. As this is an exploratory rather than

3   a confirmatory analysis, we reported unadjusted p-values. We reported

4   descriptive statistics of the combined sample as well as differences between

5   the HC and SCD group based on ANOVA for continuous and Chi-square tests

6   for categorical variables. We further compared the two groups with regard to

7   their performance in the CFA-derived factor scores as the main dependent

8   variables of interest. We rescaled the factor score values using a z-

9   transformation with mean and standard deviation taken from the HC group.

10 For this group comparison, we employed a series of ANCOVAs with age and

11 sex as covariates (we refrained from controlling for education, as descriptive

12 statistics revealed no group differences for this potential covariate).

13 In addition, we associated the domain scores with CSF biomarker values in

14 the complete sample, as well as in the two subsamples (Pearson

15 correlations). This analysis was conducted in a reduced sample of n=180

16 participants (n=76 HC, n=104 SCD). Individuals with available CSF were

17 slightly younger (M=69.5, SD=5.34) than those without CSF data (M=70.3,

18 SD=5.78). However, this difference was not significant, nor did they differ in

19 terms of sex or education years. CSF availability (36.4% in HC, 43% in SCD)

20 did not significantly differ between the groups.

21 Finally, as we observed a significantly higher proportion of APOE4 carriers in

22 the SCD compared to the HC group (see table 1), we reran the analyses of

23 group differences in cognitive performance with APOE status as an additional

24 covariate. The same was done for the analyses of association of CSF

25 markers with cognitive performance (multiple regressions with APOE status

1   and the respective biomarker as predictors). APOE genotype information was

2   available in 86% of the HC and SCD cases. Availability of APOE information

3   did not differ between groups and no differences in age, sex or education was

4   found between those with vs. without genetic data.

5   *Data availability*

6   Anonymized data generated and analyzed in the current study will be made

7   available upon request from any qualified investigator for purposes of

8   replicating procedures and results.

9   **Results**

10   Descriptive statistics of demographical, clinical, APOE4 and

11   neuropsychological data for the two subgroups are shown in table 1.

12   *Group differences in global and domain-specific cognitive performance*

13   *(figure 1)*

14   Age- and sex-adjusted comparisons of cognitive domain scores (ANCOVA)

15   revealed significantly lower performance of similar magnitudes in MEM,

16   EXEC, LANG and the global performance scores (Cohen's d= 0.2-0.5,

17   p<0.05) in the SCD compared to HC group. No significant group differences

18   were found for WM and VIS. Addition of APOE status as a covariate did not

19   alter these results and no main effects of APOE status were observed.

20   *Association of cognitive performance with self-experienced and informant-*

21   *rated cognitive decline (table 2)*

22   In the complete sample, we observed significant associations between worse

23   objective cognitive performance and more domains with self-experienced and

1 informant-rated cognitive decline. These associations were stronger for the

2 informant report. The association between the number of domains with

3 subjectively experienced decline and objective cognitive performance was

4 less pronounced and not significant within the two subgroups. However, for

5 the SCD group, we observed consistent associations of stronger (i.e., more

6 domains) informant-reported cognitive decline and worse cognitive

7 performance.

8 *Association of cognitive performance with AD biomarkers (table 3)*

9 In the complete sample, we observed significant associations of small to

10 moderate effect size for MEM, LANG and EXEC with biomarkers of amyloid

11 pathology, neurodegeneration (total Tau), and the CSF-Aβ42/p-Tau181 ratio.

12 Correlations to pTau181 alone were weaker and reached significance only for

13 MEM and EXEC. WM and VIS were not associated with any of the AD

14 biomarkers. Subgroup analysis showed that consistent associations between

15 cognitive performance and biomarkers of amyloid as well as Tau pathology

16 were present in the SCD but not in the HC group. Again, these were strongest

17 for MEM, followed by EXEC and LANG with a smaller association with WM.

18 Addition of APOE4 as a covariate did not change this pattern of results and no

19 main effects of APOE status were observed.

20 **Discussion**

21 The present study adds important novel evidence to a growing body of

22 literature characterizing memory clinic patients with SCD as an at risk group

23 for preclinical AD. Several studies have already demonstrated that individuals

24 with SCD, particularly when seeking help at a memory clinic, are of increased

1 risk of clinical progression [4] and show increased risk of having abnormal

2 biomarkers consistent with preclinical AD (e.g. [25–27]). However,

3 neuropsychological performance in memory clinic SCD patients compared to

4 healthy controls has not been extensively studied so far, possibly due to the

5 assumption that SCD by default implies "cognitive normality". The few studies

6 reporting on differences in cognitive scores between memory clinic SCD

7 patients and healthy controls either had to rely on rather small samples

8 (e.g.[26]) or only reported on differences in a single memory test [27].To our

9 knowledge, the present study is the first to demonstrate a profile of subtle

10 neuropsychological deficits and their relation to CSF biomarkers in a

11 considerably large sample of memory clinic SCD patients in comparison to

12 healthy control subjects. Certain strength of this study is that we measured

13 cognitive performance with an extensive neuropsychological battery allowing

14 us to employ state-of-the-art CFA methods to derive domain-specific cognitive

15 performance scores of high psychometric quality. We confirmed a 5-factor

16 structure with very good model fit and comparability to similar cohorts, such

17 as the ADNI and WRAP study cohorts, which is important in terms of

18 replication and integrative data analysis [28]. The factors in DELCODE show a

19 somewhat higher intercorrelation compared to the WRAP cohort (see figure e-

20 1). However, the same is true for the ADNI cohort, which, similar to

21 DELCODE, has a higher mean age (and variance) and based their CFA

22 model on a mixed population of cognitively normal and impaired (MCI, mild

23 AD dementia) individuals. Both aspects can influence the factor structure of

24 neuropsychological test batteries [29]. However, each factor still yielded

25 approximately 50% unique variance, which justifies the modeling of domain-

26 specific scores of cognitive performance. This may enhance the potential to

1   detect differential deficits across a wide range of at-risk individuals. Such

2   domain-specific deficits (or decline) may then be differentially associated with

3   genetic and other risk factors or biomarkers of neurodegenerative disease [30].

4   There are several important findings from the recent study. First, we indeed

5   observed a significantly reduced overall cognitive performance (about -0.3

6   SD) in SCD vs. HC. To put this in perspective, the MCI and AD-dementia

7   group of DELCODE have global performance scores of -2.37 and -5.24,

8   respectively, when expressed as z-scores with the DELCODE HC group

9   performance as reference. Thus, the performance deficits in SCD are indeed

10   subtle and well within the range of cognitive normality. We found that deficits

11   were strongest in the memory domain, for which a performance deficit of

12   similar magnitude (Cohen's d≈0.5, based on ADAS-Cog delayed recall) was

13   recently reported in a memory clinic SCD sample from the BioFINDER study

14   [27]. We further observed significant deficits in executive functions and

15   language abilities. These findings are in line with previous findings on the

16   earliest AD-related cognitive decline and subtle impairment in the stage of

17   cognitive normality [31–36].

18   We observed a higher proportion of APOE4 carriers compared to HC

19   suggesting that the SCD patient group is enriched for genetic risk (and, thus,

20   very likely also for familial history) of AD. However, results from our

21   supplementary analyses with additional covariate control for APOE status

22   suggested that the subtle deficits in SCD vs. HC and their association to CSF

23   biomarker pathology could not be directly attributed to an APOE4 effect.

24   Nevertheless, familial history of AD may be a driving factor for developing

25   worries and, consequently, help-seeking behavior in elderly individuals who

1 experience subjective cognitive decline. It is, thus, of high interest to further

2 investigate the association of familial history as a clinical feature with

3 cognition and biomarker abnormalities in our SCD group. Likewise it is of

4 interest whether presence of SCD (or specific features thereof) in cognitively

5 normal elderly with a family history of AD may be associated with AD

6 biomarkers, as has recently been shown in a study using data from the

7 PREVENT-AD cohort, albeit relying on a SCD group classification based on a

8 single SCD question[37]. We will conduct further analyses to address the

9 aforementioned questions once data on familial history of AD in the SCD and

10 HC group, as well as a sufficient sample size of the AD relatives group will be

11 available with the complete DELCODE baseline data set.

12 Second, despite being subtle, the consistent relation to AD biomarkers

13 supports the validity of these earliest deficits as being related to AD pathology

14 in the SCD group. Here, we observed consistent associations with CSF AD

15 biomarkers of amyloid and Tau pathology in exactly those cognitive domains

16 that showed a deficit in comparison to HC (MEM, LANG, EXEC). In contrast,

17 covariance between worse cognitive performance and AD biomarkers was all

18 but absent in HC. With regard to the early identification of preclinical AD,

19 refined assessment of objective cognitive deficits in combination with

20 assessment of subjective experience of cognitive decline may, thus, prove to

21 be the most valuable approach, i.e., exceeding a strategy relying on only one

22 of these clinical phenotypes.

23 This distinctive pattern of results has highly relevant implications for the

24 conceptualization of future clinical trials for disease modifying interventions in

25 the pre-MCI stages of AD and, more specifically, for consideration of SCD

1   patients as a target population for these interventions. The general implication

2   of our results is that cognitive function, if measured by a combination of

3   sensitive neuropsychological tests, can be considered a suitable and

4   adequate outcome measure to test "disease modification" in preclinical AD

5   stages, supporting its recent FDA approval as a key outcome measure

6   irrespective of functional measures [38]. In addition, the stronger correlation

7   between Aβ42/pTau181 and MEM, LANG, EXEC supports a specific

8   weighting of cognitive outcome measures towards these domains rather than

9   using a global cognitive performance score. Of note, this is already realized in

10   some composite scores developed to track cognitive decline in preclinical AD,

11   such as the PACC [9]. With regard to SCD in particular, our results support this

12   clinical stage as the transitional "sweet spot" between HC and MCI, where AD

13   pathology (of both amyloid *and* Tau) initially translates into *detectable*

14   cognitive dysfunction. This is particularly striking in consideration of the

15   relatively similar amounts of AD pathology in both HC and SCD at the group

16   level (table 1). This finding is also consistent with previous nonclinical studies

17   showing that more severe subjective cognitive decline in healthy elderly

18   patients with the presence of amyloid pathology was associated with steeper

19   objective cognitive decline [39] and a higher risk of clinical progression [40].

20   Furthermore, a very recent study by Timmers et al. based on data from the

21   Amsterdam SCIENCE project [34] – a memory clinic SCD patient study with

22   high comparability to DELCODE – reported cognitive decline in the presence

23   of higher PET amyloid load in tests of memory, attention/executive function

24   and language. Combined with these longitudinal results, the results from our

25   study that contrasted SCD patients with a healthy control group are

26   particularly promising with regard to clinical trials: they suggest that at the

1   SCD stage, potential disease-modifying effects will translate into the relatively

2   strongest, and thus most likely detectable, effects on a cognitive outcome,

3   especially if optimally tailored with regard to domain specificity. Although more

4   longitudinal data are needed to further confirm this assumption, our results, in

5   line with that of Timmers et al. [34], provide important empirical support for the

6   inclusion of SCD as an indicator of "stage 2" in the latest NIA-AA research

7   framework's numerical clinical staging system of individuals in the Alzheimer's

8   continuum [23].

9   Last, we found only weak and inconsistent associations between the cognitive

10   domain scores and self-reported levels of cognitive complaint. This finding is

11   in line with previous studies based on questionnaires for self- vs. informant

12   rated everyday cognitive function (such as the ECog [41]). It emphasizes the

13   common observation that SCD, reflecting the notion of a subtle decline from a

14   *previous* level of cognitive function, is predictive of future AD dementia and

15   AD biomarkers irrespective of an association with a single, concomitant

16   measurement of objective cognitive performance [5]. On the other hand, we

17   here found informant reports of cognitive decline consistently associated with

18   worse objective cognitive performance. Specifically, in the SCD group, the

19   latter was in turn associated with AD pathology. This supports "informant

20   corroboration of SCD" as one of the "SCD-plus" features, which, pending

21   further empirical evidence, were proposed specifically to increase the

22   likelihood of underlying AD pathology [1,2]. In line with this, Miebach and

23   colleagues [21] indeed reported an association of informant confirmation of self-

24   reported cognitive decline with AD biomarker pathology in the DELCODE

25   cognitively normal participants. Given the aforementioned findings, examining

26   the relative contribution of subtle *objective* deficits, *self- and informant*

1   reported decline in the prediction of preclinical AD is of high interest. While

2   this is beyond the scope of the present study, we will address these questions

3   in future analyses.

4   This study is not without limitations. As mentioned, longitudinal data will be

5   needed to more thoroughly test some of the aforementioned assumptions

6   concerning the benefits of the SCD concept and domain-specific cognitive

7   outcomes in clinical trial conceptualization. However, as DELCODE is a

8   relatively new study, we had to rely on cross-sectional baseline data for the

9   present analysis. Once follow-up data from DELCODE are available, we will

10   also analyze the sensitivity of our derived cognitive domain scores to detect

11   AD-related cognitive decline, comparing them with other composites (like the

12   PACC). It will then also be of interest to test whether changes in biomarkers

13   are associated differentially with decline in different cognitive domains. As

14   already mentioned above, the yet relatively small number of AD relatives

15   (n=44 of which n=22 had available CSF) led us to postpone inclusion of

16   comparative analyses with the SCD group in the present study. We will

17   address the issue of parental history of AD in future analyses. Finally, it

18   should be emphasized that the SCD group in DELCODE is recruited from

19   help-seeking individuals attending a memory clinic for diagnostic work-up.

20   While this is first and foremost a clear strength rather than a limitation of the

21   present study, it still implies that results should not be generalized to

22   individuals with SCD in nonclinical, i.e., general population-based settings.

23   There is growing evidence supporting the greater relevance of SCD with

24   regard to AD risk in the clinical, help-seeking setting rather than in the general

25   elderly population [4,26], and harmonization of SCD research criteria will need to

26   take this into account [2,42].

1   In summary, we conclude that SCD patients presenting to a memory clinic

2   have, on average, minor neuropsychological deficits. These earliest deficits

3   seem to be domain specific, detectable with sensitive assessment and

4   appropriate psychometric techniques, and associated with biomarkers of AD

5   pathology. Thus, cognitive performance in patients with SCD will likely be a

6   sensitive outcome measure in studies of risk factors and in interventional

7   trials, and may also predict clinical progression. Albeit their measurement in

8   individual patients remains a challenge, minor cognitive deficits should also be

9   considered in the ongoing efforts to refine the conceptualization of SCD in the

10   context of preclinical AD research.

Appendix 1 - Author's contribution to the manuscript

Name	Location	Role	Contribution
Steffen Wolfsgruber, PhD	German Center for Neurodegenerative Diseases (DZNE) Bonn, Germany	Author	Conceptualization and design of the study; Statistical Analysis; Interpretation of data; Drafting and/or revision of manuscript for important intellectual content
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References

1.   Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer's & dementia the journal of the Alzheimer's Association; 2014;10(6):844–852.

2.   Molinuevo JL, Rabin LA, Amariglio R, et al. Implementation of subjective cognitive decline criteria in research studies. Alzheimer's & dementia the journal of the Alzheimer's Association; 2017;13(3):296–311.

3.   Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta‐analysis. Acta Psychiatrica Scandinavica; 2014;130(6):439–451.

4.   Slot, Rosalinde E R, Sikkes, Sietske A M, Berkhof J, et al. Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. Alzheimer's & dementia the journal of the Alzheimer's Association; 2019;15(3):465–476.

5.   Rabin LA, Smart CM, Amariglio RE. Subjective Cognitive Decline in Preclinical Alzheimer's Disease. Annual review of clinical psychology; 2017;13:369–396.

6.   Jessen F, Spottke A, Boecker H, et al. Design and first baseline data of the DZNE multicenter observational study on predementia Alzheimer's disease (DELCODE). Alzheimer's research & therapy; 2018;10(1):15.

7.   Dowling NM, Hermann B, La Rue A, Sager MA. Latent structure and factorial invariance of a neuropsychological test battery for the study of preclinical Alzheimer's disease. Neuropsychology; 2010;24(6):742–756.

8.   Park LQ, Gross AL, McLaren DG, et al. Confirmatory factor analysis of the ADNI Neuropsychological Battery. Brain imaging and behavior; 2012;6(4):528–539.

9.   Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. JAMA neurology; 2014;71(8):961–970.

10.   Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research; 1975;12(3):189–198.

11.   Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer disease and associated disorders; 1997;11 Suppl 2:S13-21.

12.   Grober E, Ocepek-Welikson K, Teresi JA. The free and cued selective reminding test: evidence of psychometric adequacy. Psychology Science Quarterly; 2009;51(3):266–282.

13.   Petermann F, Lepach AC. Wechsler Memory Scale–Fourth Edition (WMS-IV). Manual zur Durchführung und Auswertung. Deutsche Übersetzung und Adaptation der WMS-IV von David Wechsler: Pearson Assessment, Frankfurt/Main; 2012.

14.   Lezak MD. Neuropsychological assessment: Oxford University Press, USA; 2004.

15.   Thalmann B, Monsch AU, Schneitter M, et al. The cerad neuropsychological assessment battery (Cerad-NAB)—A minimal data set as a common tool for German-speaking Europe. Neurobiology of Aging; 2000;21:30.

16.   Smith A. Symbol digit modalities test (SDMT) manual (revised) Western Psychological Services. Los Angeles; 1982.

17.   Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Perceptual and motor skills; 1958;8(3):271–276.

18.   Rouleau I, Salmon DP, Butters N, Kennedy C, McGuire K. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. Brain and cognition; 1992;18(1):70–87.

19.   Polcher A, Frommann I, Koppara A, Wolfsgruber S, Jessen F, Wagner M. Face-Name Associative Recognition Deficits in Subjective Cognitive Decline and Mild Cognitive Impairment. Journal of Alzheimer's disease JAD; 2017;56(3):1185–1196.

20.   Van Dam, Nicholas T, Sano M, Mitsis EM, et al. Functional neural correlates of attentional deficits in amnestic mild cognitive impairment. PloS one; 2013;8(1):e54035.

21.   Miebach L, Wolfsgruber S, Polcher A, et al. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. Alzheimer's research & therapy; 2019;11(1):66.

22.   Lewczuk P, Kornhuber J, Toledo JB, et al. Validation of the Erlangen Score Algorithm for the Prediction of the Development of Dementia due to Alzheimer's Disease in Pre-Dementia Subjects. Journal of Alzheimer's disease JAD; 2016;49(3):887.

23.   Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & dementia the journal of the Alzheimer's Association; 2018;14(4):535–562.

24.   Bjerke M, Engelborghs S. Cerebrospinal Fluid Biomarkers for Early and Differential Alzheimer's Disease Diagnosis. Journal of Alzheimer's disease JAD; 2018;62(3):1199–1209.

25.   SNITZ BE, Lopez OL, McDade E, et al. Amyloid-β Imaging in Older Adults Presenting to a Memory Clinic with Subjective Cognitive Decline: A Pilot Study. Journal of Alzheimer's disease JAD; 2015;48 Suppl 1:S151-9.

26.   Perrotin A, La Joie R, de La Sayette, Vincent, et al. Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. Alzheimer's & dementia the journal of the Alzheimer's Association; 2017;13(5):550–560.

27.   Mattsson N, Insel PS, Palmqvist S, et al. Increased amyloidogenic APP processing in APOE ε4-negative individuals with cerebral β-amyloidosis. Nature communications; 2016;7:10918.

28.   Curran PJ, Hussong AM. Integrative data analysis: the simultaneous analysis of multiple data sets. Psychological methods; 2009;14(2):81–100.

29.   Delis DC, Jacobson M, Bondi MW, Hamilton JM, Salmon DP. The myth of testing construct validity using factor analysis or correlations with normal or mixed clinical populations: lessons from memory assessment. Journal of the International Neuropsychological Society JINS; 2003;9(6):936–946.

30.   Crane PK, Trittschuh E, Mukherjee S, et al. Incidence of cognitively defined late-onset Alzheimer's dementia subgroups from a prospective cohort study. Alzheimer's & Dementia; 2017;13(12):1307–1316.

31.   Bäckman L, Jones S, Berger A, Laukka EJ, Small BJ. Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. Neuropsychology; 2005;19(4):520.

32.   Baker JE, Lim YY, Pietrzak RH, et al. Cognitive impairment and decline in cognitively normal older adults with high amyloid-β: a meta-analysis. Alzheimer's & dementia: Diagnosis, assessment & disease monitoring; 2017;6:108–121.

33.   Schneider AL, Senjem ML, Wu A, et al. Neural correlates of domain-specific cognitive decline. Neurology; 2019;92(10):e1051-e1063.

34.   Timmers T, Ossenkoppele R, Verfaillie SCJ, et al. Amyloid PET and cognitive decline in cognitively normal individuals: the SCIENCe project. Neurobiology of Aging; 2019;79:50–58.

35.   van Harten AC, Smits LL, Teunissen CE, et al. Preclinical AD predicts decline in memory and executive functions in subjective complaints. Neurology; 2013;81(16):1409.

36.   Verfaillie SCJ, Witteman J, Slot RER, et al. High amyloid burden is associated with fewer specific words during spontaneous speech in individuals with subjective cognitive decline. Neuropsychologia; 2019.

37.   Verfaillie, Sander C J, Pichet Binette A, Vachon-Presseau E, et al. Subjective Cognitive Decline Is Associated With Altered Default Mode Network Connectivity in Individuals With a Family History of Alzheimer's Disease. Biological psychiatry. Cognitive neuroscience and neuroimaging; 2018;3(5):463–472.

38.   U.S. Department of Health and Human Services Food and Drug Administration. Early Alzheimer's Disease: Developing Drugs for Treatment: Guidance for Industry; 2018.

39.   Vogel JW, Doležalová MV, La Joie R, et al. Subjective cognitive decline and β-amyloid burden predict cognitive change in healthy elderly. Neurology; 2017;89(19):2002–2009.

40.   Buckley RF, Maruff P, Ames D, et al. Subjective memory decline predicts greater rates of clinical progression in preclinical Alzheimer's disease. Alzheimer's & Dementia; 2016;12(7):796–804.

41.   Rueda AD, Lau KM, Saito N, et al. Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer's disease. Alzheimer's & dementia the journal of the Alzheimer's Association; 2015;11(9):1080–1089.

42.   Wolfsgruber S, Molinuevo JL, Wagner M, et al. Prevalence of abnormal Alzheimer's disease biomarkers in patients with subjective cognitive decline:

cross-sectional comparison of three European memory clinic samples.

Alzheimer's research & therapy; 2019;11(1):8.

Table 1: Baseline characteristics of the whole study sample and subgroups

Variable	Whole sample	Healthy Controls	SCD
Demographics	**n=449**	**n=209**	**n=240**
Age (years, mean SD)[a]	69.96 (5.62)	68.7 (5.25)	71.1 (5.72)
Sex (female; n, %)[a]	266 (53.7)	120 (57.4)	117 (48.3)
Education (years, mean, SD)	14.8 (2.92)	14.8 (2.76)	14.8 (3.06)
MMSE (mean, SD)[a]	29.3 (0.976)	29.4 (0.85)	29.2 (1.06)
No. of domains with *self-experienced* cognitive decline (mean, SD)[a]	1.87 (1.41)	0.91 (1.03)	2.73 (1.13)
No. of domains with *informant-rated* cognitive decline (mean, SD)[a]	0.98 (1.35)	0.37 (0.74)	1.53 (1.52)
APOE genotype	**n=386**	**n=182**	**n=204**
APOE4 genotype (n, %)[a]	113 (27.2)	36 (19.8)	66 (32.4)
CSF biomarkers	**n=180**	**n=76**	**n=104**
Aß42/Aß40 (mean, SD)	0.091(0.025)	0.096 (0.022)	0.088 (0.027)
Total Tau (mean, SD)	408.4 (192.2)	389.9 (160.1)	408.4 (192.2)
pTau181 (mean, SD)	51.8 (21.8)	51.3 (18.4)	52.2 (24.1)
Aß42/pTau181 (mean, SD)	16.5 (6.4)	17.6 (5.34)	15.7 (7.04)

Note. [a] group differences significantly different at the α≤.05 level, Chi^2-Test for categorical variables and ANOVA for continuous variables.

Table 2: Associations of cognitive domain scores with self- and informant-rated number of domains with experienced cognitive decline.

Whole cognitively normal sample (N=449)	No. of domains with *self-experienced* cognitive decline	No. of domains with *informant-rated* cognitive decline
MEM	-,153[**]	-,304[**,a]
LANG	-,107[*]	-,239[**,a]
EXEC	-,120[**]	-,221[**,a]
WM	-,066	-,120[*]
VIS	-,085	-,106[*]
Global score	-,125[**]	-,235[**,a]
Healthy Controls (N=209)		
MEM	,041	-,132
LANG	,039	-,091
EXEC	,062	-,020
WM	,056	,047
VIS	,084	-,097
Global score	,058	-,038
SCD patients (N=240)		
MEM	,003	-,276[**,a]
LANG	-,044	-,241[**,a]
EXEC	-,088	-,244[**,a]
WM	-,073	-,168[*]
VIS	-,133[*]	-,174[**]
Global score	-,074	-,252[**,a]

Note: Values are Spearman-Rho correlation coefficients. ** p<0.01 (two-tailed); * p<0.05 (two-tailed). [a] significant difference in the correlation coefficient for self-experienced vs. informant-reported decline.

Table 3: Associations of cognitive domain scores with AD biomarkers.

Whole cognitively normal sample (N=180)	CSF-Aß42/40	CSF-Tau	CSFpTau-181	CSF Aß42/ pTau-181
MEM	.316[**]	-.287[**]	-.270[*]	.350[**]
LANG	.250[**]	-.178[*]	-.142	.247[**]
EXEC	.176[*]	-.171[*]	-.159[*]	.216[**]
WM	.089	-.094	-.098	.104
VIS	.049	-.094	-.054	.087
Global score	.214[*]	-.200[**]	-.175	.244[**]
Healthy controls (N=76)				
MEM	.208	-.080	-.117	.283[*]
LANG	.158	-.022	.067	.171
EXEC	.110	-.024	-.017	.118
WM	.028	.136	.130	-.017
VIS	.122	-.081	-.015	.126
Global score	.157	-.013	.008	.171
SCD patients (N=104)				
MEM	.343[**]	-.389[**,a]	-.346[**,a]	.355[**]
LANG	.279[**]	-.262[**,a]	-.230[**,a]	.265[**]
EXEC	.187	-.232[*]	-.220[*,a]	.240[*]
WM	.114	-.195[*,a]	-.195[*,a]	.154
VIS	.002	-.102	-.080	.065
Global score	.224[*]	-.282[**,a]	-.256[**,a]	.259[**]

Note: Values are Pearson correlation coefficients. ** $p<0.01$ (two-tailed); * $p<0.05$ (two-tailed); [a] significant difference in correlation coefficient compared to Healthy controls ($p<0.05$; one-sided test according to the hypothesis that there is a closer association between worse cognitive performance and more pathological CSF-values in SCD compared to HC).

Legend to Figure 1. Age- and sex-adjusted cognitive domain score performance across subgroups.

Note: Figure 1 shows age- and sex-adjusted performance differences between the groups of healthy controls and memory clinic patients with subjective cognitive decline (SCD) based on ANCOVA (see the Methods section for details). Values are expressed as z-scores with the mean and standard deviation taken from the healthy control group. For visualization, the covariate age is set to the sample mean of 69.96 years. This value is higher than the mean age of the healthy control group, and age has a negative effect on performance. Hence, the mean performance of healthy controls in this depiction is also slightly below zero. * significant ($p<0.05$) difference in comparison to healthy control group.