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DISSERTATION

Novel approaches for the differentiation between subjects with preclinical and clinical Alzheimer's disease and healthy subjects validated by cerebrospinal fluid

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List of Abbreviations

AD	Alzheimer's Disease
APOE	Apolipoprotein E
AUC	Area under the curve
BBB	Blood brain barrier
BDNF	Brain-derived neurotrophic factor
BNT	Boston Naming Test
CDT	Clock Drawing Test
CERAD-NP	Neuropsychological testing battery of the Consortium to Establish a Registry for Alzheimer's Disease
CSF	Cerebrospinal fluid
DAT	Dementia of Alzheimer's type
DELCODE	DZNE-Longitudinal Cognitive Impairment and Dementia Study
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
DZNE	German Center for Neurodegenerative Diseases
GDS	Geriatric Depression Scale
GP	General practitioner
HC	Healthy Controls
ICD-10	International Classification of Diseases 10th Edition
IGF-1	Insulin-like growth factor 1
IL-18	Interleukin 18
LP	Lumbar puncture
MCI	Mild cognitive impairment
MCP-1	Monocyte chemoattractant protein 1
MDE	Major depressive episode
MMSE	Mini-Mental Status Examination
MRI	Magnetic resonance imaging
NIA-AA	National Institute on Aging and Alzheimer's Association

PET	Positron emission tomography
ROC	Receiver operating characteristic
SCD	Subjective cognitive decline
SCD-I	Subjective cognitive decline interview
TGF-ß1	Transforming growth factor ß 1
TMT-A/B	Trail Making Test A/B
VEGF	Vascular endothelial growth factor

English Abstract

Introduction: Diagnosing Alzheimer's Disease (AD) is complex, the earlier the disease's stage, the more difficult. Various factors are hindering an effortless diagnosis of the disease. Depressive symptoms can be a confounding variable, and the established diagnostic tools to find neurobiological evidence for a developing AD are high in cost and effort. Therefore, novel approaches providing differential diagnostic information are wanted.

Methods: For Menne *et al*., 2020, sensitivity and specificity of different neuropsychological tests to discriminate between 190 CSF-positive and 307 CSF-negative subjects with varying numbers of depressive symptoms were calculated. For Schipke & Menne *et al*., 2020, a logistic algorithm with 6 serum biomarkers was trained and validated to be used for dichotomous classification (suspicious/not suspicious of AD) on 55 subjects with MCI AD, 25 subjects with MCI non-AD, and 68 healthy controls. For Miebach *et al*., 2019, a semi-structured interview on subjective cognitive decline was conducted with memory clinic patients and controls without objective cognitive decline (healthy controls n=76, AD relatives n=24, subjective cognitive decline n=105). Subsequently, interview questions were associated with CSF biomarkers.

Results: For Menne *et al*., 2020, we found that the neuropsychological test TMT-B is best in discriminating between patients with and without CSF values typical for AD in subjects with elevated numbers of depressive symptoms. For Schipke & Menne *et al*., 2020, it could be shown that the biomarker panel can differentiate between MCI due to AD patients and healthy controls with an accuracy of 86%. For Miebach *et al*., 2019, it was found that reported decline in memory and language abilities is associated with lower Aß-42 levels in CSF.

Discussion: Early and differential diagnostic for AD is crucial for taking preventive action as early as possible. The established diagnostic gold standard, for which neurobiological evidence for AD is essential, is not readily available to the broader public for various reasons. With the findings presented here, we demonstrate alternative approaches to the established diagnostic measures, which are possible to be performed outside of specialized memory clinics. Furthermore, they are lower in cost and effort and less invasive.

German Abstract

Einleitung: Die Diagnose der Alzheimer-Krankheit (AD) ist komplex, je früher das Stadium der Erkrankung, desto schwieriger. Es gibt verschiedene Faktoren, die eine einfache Diagnose der Krankheit erschweren. Depressive Symptome können dabei eine Stör-Variable sein, und die etablierten Diagnosewerkzeuge, um neurobiologische Hinweise für eine beginnende AD zu finden, sind mit hohen Kosten und Aufwand verbunden. Daher sind neuartige Ansätze nötig, die differentialdiagnostische Informationen liefern.

Methoden: Für Menne *et al*., 2020, wurden Sensitivität und Spezifität verschiedener neuropsychologischer Tests zur Unterscheidung zwischen 190 CSF-positiven und 307 CSF-negativen Probanden mit verschiedener Anzahl depressiver Symptome berechnet. Für Schipke & Menne *et al*., 2020, wurde ein logistischer Algorithmus mit 6 Serumbiomarkern trainiert und validiert, um dann für eine dichotome Klassifizierung (hinweisgebend / nicht hinweisgebend auf AD) bei 55 Probanden mit MCI bei AD, 25 Probanden mit non-AD MCI sowie 68 gesunden Kontrollen angewendet zu werden. Für Miebach *et al*., 2019, wurde ein halbstrukturiertes Interview zu subjektiven Gedächtnisbeschwerden mit Patienten und Kontrollen ohne objektivierbare kognitive Einschränkungen aus verschiedenen Memory Clinics durchgeführt (gesunde Kontrollen n=76, AD-Verwandte n=24, subjektive

Gedächtnisbeschwerden n=105). Anschließend wurden die Interviewfragen mit CSF-Biomarkern assoziiert.

Ergebnisse: Für Menne *et al*., 2020, fanden wir, dass bei einer erhöhten Anzahl depressiver Symptome der neuropsychologische Test TMT-B am besten zur Unterscheidung zwischen Patienten mit und ohne AD-typische Liquor-Werte geeignet ist. Für Schipke & Menne *et al*., 2020, konnte gezeigt werden, dass das Biomarker-Panel mit einer Genauigkeit von 86% zwischen MCI aufgrund von AD-Patienten und gesunden Kontrollen unterscheiden kann. Für Miebach *et al*., 2019, wurde festgestellt, dass ein subjektiver Rückgang der Gedächtnis- und Sprachfähigkeiten mit niedrigeren Aß-42-Spiegeln im Liquor verbunden ist.

Diskussion: Früh- und Differentialdiagnostik für AD ist essenziell zur frühestmöglichen Prävention. Der etablierte diagnostische Goldstandard, für den neurobiologische Hinweise auf AD unerlässlich sind, ist aus verschiedenen Gründen für die breite Öffentlichkeit nicht niedrigschwellig zugänglich. Mit den hier vorgestellten Ergebnissen zeigen wir, dass es alternative Ansätze zu den etablierten diagnostischen Maßnahmen gibt, die außerhalb spezialisierter Gedächtnisambulanzen durchgeführt werden können. Darüber hinaus sind sie kostengünstiger und weniger invasiv.

Preface

Parts of the following dissertation were already published in Menne *et al*., 2020 [1], Schipke & Menne *et al*., 2020 [2], and Miebach *et al*., 2019 [3]. The author F. Menne made adaptions for the present dissertation. The author's contributions to the respective publications are given in detail in section 7.

1. Introduction

Millions of people worldwide are affected by neurodegenerative diseases that can lead to dementia, first and foremost by Alzheimer's Disease (AD) [4]. This poses a heavy burden individually for the patients themselves and their caretakers. It furthermore has large-scale social and economic implications for the whole community in the form of financing needed for diagnostics and treatment of the disease, including palliative care. It was estimated that in 2015, the number of people affected by dementia worldwide was 46.8 million. This number is projected to nearly double every 20 years until it reaches ca. 131 million in 2050. The economic impact of dementia in 2018 would surpass US$ 1 trillion [5].

These numbers show the importance of developing diagnostic and therapeutic measures in the field of AD. The hallmarks of AD, the most common cause for dementia, are extracellular amyloid plaques and intracellular neurofibrillary tangles [6], and it is believed that intracerebral cellular changes, especially the accumulation of amyloid, occur up to 20 years before the onset of clinical symptoms such as loss of memory or decline of orientation or speech [7]. For diagnostic and curative approaches, it is necessary to gain access to these alterations in the brain, which is prevented by different factors. One crucial factor is the blood-brain barrier (BBB). The BBB is a semipermeable border of endothelial cells [8] supposed to protect neurons from pathogens circulating in the blood while simultaneously allowing transport of needed elements such as nutrients, glucose, or water [9]. This highly effective system, preventing the passage of molecules between the brain and blood system, may obscure access to the intracerebral pathological changes and its substrates needed for diagnosing neurodegenerative disorders. Furthermore, it impedes developing a possible AD treatment since many therapeutic compounds are prevented from passing the BBB [10]. Nevertheless, there is evidence that the BBB becomes more permeable in AD, for a review, see Sweeney, Sagare & Zlokovic [11]. This might be one reason why AD is measurable in bodily specimens other than cerebrospinal fluid (CSF), which is becoming increasingly important.

There are several reasons why there is a need for an easily accessible, minimally invasive, economic, and reliable diagnostic test capable of validly detecting the presence of AD earlier than is currently the case. According to a 2019 World Alzheimer Report survey, 95% of about 70,000 respondents thought it likely to develop dementia in their lifetime, and 82% would take a genetic test to learn about their risk [12]. Being aware of having an elevated risk for developing dementia due to AD and subsequently making lifestyle changes can delay cognitive worsening in subjects at risk for dementia [13]. Besides, evidence shows the positive and lasting effects of primary and secondary prevention in AD [14], such

as physical and cognitive activity. For preventive action, a timely diagnosis for finding out a personal risk is vital for implementing these preventive measures as early as possible. By doing so, there could be several millions of fewer patients and their caregivers burdened by the disease [15]. Furthermore, accurate diagnostic measures are in demand by pharmaceutical companies for different reasons. So far, no causal therapy against AD is available, but the search for adequate curative treatment is continuing. Due to the not yet fully understood etiology and the reasons for AD heterogeneity, a more comprehensive range of biomarkers is needed to determine the individual risk and nature of a patient's disease. It is not only for attaining an easy and economical diagnostic tool to identify participants at risk to include them in clinical trials, but also to gain more insight into the disease's causes to develop a causal treatment eventually. In the future, there might even be personalized therapy against AD and other dementia causes, much like it has become standard in certain tumor diseases such as breast [16] or lung [17] cancer.

1.1. Today's gold standard for diagnosing Alzheimer's Disease

Today, the diagnosis of AD is still complex. Depending on the stage of the disease, a multitude of information is needed. Due to extensive advances in the past 20 years, diagnosing AD, especially gathering replicable neurobiological evidence for underlying AD-related neurodegeneration, has become more clinically established. Today, there are various methods available to obtain evidence for an underlying AD pathology in cognitively impaired patients; the more biomarkers and further clinical information are combined, the more accurate the diagnosis [18].

1.1.1. Anamnesis

The first thing clinicians usually do when faced with patients complaining about cognitive decline is taking their anamnesis. Ideally, they ask specific questions about the nature of the perceived mental worsening. While finding a diagnosis in later stages of the diseases is less demanding with evident loss of memory or orientation, it is more challenging in earlier stages, especially when the decline is not (yet) objectifiable. It has been shown that subjective cognitive decline (SCD), defined as the subjective experience of worsening cognitive performance among cognitively unimpaired older individuals, can represent an at-risk AD stage [19,20]. A group of researchers proposed a set of "SCD-plus criteria". Subjects fulfilling these criteria have an even higher likelihood of being in a stage of preclinical AD [19]: *(a) Subjective decline in memory rather than other domains, (b) onset of SCD within the last five years, (c) age of onset ≥ 60 years, (d) particular concerns associated with SCD, (e) the feeling of worse performance than others of the same age group, (f) confirmation of perceived cognitive decline by an informant, and (g) the presence of the Apolipoprotein (APOE) ε4 genotype.* These criteria focused on memory decline, and there is research suggesting to involve other cognitive domains, e.g., complaints about worsening executive function, which is associated with amyloid-beta deposition in cognitively normal individuals [21]. An amyloid-Positron emission tomography (PET) study found that cognitively

normal subjects who perceived their general memory ability to be worse than peers of the same age have a higher amyloid-beta deposition [22].

1.1.2. The role of depressive symptoms in diagnosing AD

There are factors such as depressive symptoms that might interfere with the process of finding a clear-cut clinical diagnosis. However, in diagnostic processes ruling out other etiologies for cognitive decline is essential. Especially in old age patients, cognitive impairment may not only be attributable to neurodegenerative disorders like AD [23] but may also occur during a major depressive episode (MDE) [24]. The interrelation between depression and AD is an ongoing debate in the existing literature. There is evidence that a history of depression in one's lifetime may increase the risk of developing AD later in life [25]. On the other hand, depression in old age might represent a prodromal stage of AD [23,26,27]. In geriatricians' everyday work, depression and cognitive decline often co-occur [28]. This may impede determining whether cognitive impairment is "only" a symptom of a clinically manifest MDE or if there additionally is an underlying neurodegenerative disease developing. Another issue that needs addressing is the severity of affective symptoms: depression is not only black and white, what classification systems consider as depressed or not depressed, but there are stages in between. These factors need to be considered when interpreting clinical symptoms and neuropsychological test results.

1.1.3. Neuropsychology

A critical puzzle piece in diagnosing cognitive impairment and subsequent ideal treatment is a neuropsychological assessment to determine different cognitive decline stages [29,30]. This staging and the attained anamnesis define the clinical diagnosis ranging from SCD via mild cognitive impairment (MCI, i.e., symptoms are objectifiable but not severe enough to interfere with daily living) to the different dementia stages. Similar to detecting cognitive decline during a structured clinical anamnesis, specific neuropsychological impairment patterns can provide hints pointing towards an underlying etiology. A close look at neuropsychological test results might thus help differentiate between early AD and late-onset depression. Two neuropsychological domains are of particular interest in this regard: memory and executive functions. For episodic memory, subjects with early AD and those with MDE exhibit below-average test results in immediate and delayed recall tests. However, MDE subjects retain the learned information, measured with recognition tasks, better than early AD patients [31]. Additionally, there is evidence of impairment in executive function measured by the Trail Making Test Part B (TMT-B) in AD patients with comorbid MDE compared to AD patients without depression [32]. Another study in patients with MDE found that long-term memory impairment was associated with developing AD to a greater extent than executive functioning [33]. Numerous studies highlight specific tests' ability to differentiate between AD, depression, and normal aging [34–36]. Furthermore, there is evidence that the validity of neuropsychological test results can differ depending on the test subjects' affective state [37,38]. These factors need consideration in the interpretation of neuropsychological test results.

1.1.4. Cerebrospinal fluid

Evidence for AD-typical pathophysiological changes in the brain plays a crucial role in recent perceptions of a diagnostic strategy: The updated 2018 research framework for the definition of AD is based on biomarkers [39] and gives a biological definition of the disease. According to this framework, AD is defined by evidence for abnormal phosphorylated tau (T+) and beta-amyloid 1-42 (A+) levels in the brain. These criteria show sensitivity and specificity up to 83% for diagnosing AD in older adults with dementia [40]. However, lumbar punctures (LP) for obtaining CSF, in which the biomarker levels can be measured, might be perceived as highly invasive by some patients. Furthermore, processing and analyzing CSF is highly demanding, and sample processing alterations can lead to varying results [41]. Lastly, lumbar punctures might be contraindicated in some patients taking anticoagulants or suffering from conditions such as scoliosis.

1.1.5. Neuroimaging

An important source of information in AD diagnosis is brain magnetic resonance imaging (MRI) scans [42]. They are especially needed to examine brain atrophy patterns and rule out other causes for cognitive decline, such as vascular damages [43] or brain tumors [44]. PET for detecting an abnormal presence of both amyloid β and tau, another common diagnostic tool aiding in the diagnosis of AD [45,46], is an alternative to lumbar punctures. However, it is high in effort and cost, and patients must face a dose of radiation.

1.2. Challenges in this gold standard

This gold standard allows the most accurate diagnosis possible antemortem. Depending on how much information can be gathered, high in cost, effort, and time and not readily available to the general public. However, it needs to be stated that to date, there is no diagnostic measure that can detect AD in a living patient with 100% accuracy. The actual verification of amyloid plaques and neurofibrillary tangles can only be given in tissue utilizing brain histopathology, as first described by Alois Alzheimer [47]. Furthermore, there remains a big gap between the desirable research-based diagnostic measures and the factual community-based diagnostics, that outpatients can access at their general practitioners (GP). GPs, in most cases, are the first contact to medical professionals of community-dwelling older adults regarding health complaints. However, GPs usually do not perform LPs, and there is no data on how many neurologists or psychiatrists carry out LPs in their practice and have the technical equipment and staff expertise to conduct CSF analyses reliably and validly. It can thus be assumed that most LPs investigating neurodegenerative processes are done in hospitals with specialized memory clinics, which, depending on the place of residence, are not easily available. Furthermore, depending on the number of diagnostic tools used, they can be a heavy burden on the patient, their caregivers, and not least on the social system covering the cost, if applicable. Thus, there is an urgent need for novel approaches for finding evidence for developing AD as early as possible.

1.3. Novel approaches

The discovery of APOE ε4, a genetic marker that can be measured in blood, which is associated with an increased risk for AD [48], was an important milestone in diagnosing the disease. Today, one of the most pursued approaches is the utilization of blood or blood components in novel biomarkers for AD. Currently, most research activities into blood-borne biomarkers for AD focus on the biomarkers that were established as the gold standard for the diagnosis of AD in CSF: amyloid-beta- and tau-species. By now, there is some evidence accrued that plasma p-tau181 [49–51] and plasma p-tau217 [52] have high diagnostic and differential diagnostic value. For amyloid-beta, there is even more literature showing high correlations to CSF amyloid-beta and diagnostic value in blood and blood plasma [53–58]. New approaches in blood outside of the biomarkers usually of interest, i.e., amyloid and tau, might reflect neurodegenerative processes like AD. For example, there is evidence that systemic infection and inflammation are associated with neurodegenerative disorders [59,60], making it a potential target for novel diagnostic developments. Different studies aiming to find evidence for these processes were able to show the good diagnostic value of different panels of blood serum markers [61–63]. However, previous work mostly focused on patients in more advanced stages of AD [61,63]. In particular, it was shown before that the combination of six biomarkers quantified in blood serum could indicate AD at the dementia stage [63]. These markers have been selected based on their general association with the immune system in neurological diseases, specifically with AD: Brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), transforming growth factor-beta type 1 (TGF-ß1), monocyte chemoattractant protein 1 (MCP-1), and interleukin-18 (IL-18). These factors are involved in neuroprotective and neurodegenerative processes. BDNF is generally known to regulate age-associated pathways as well as neuronal plasticity [64], TGF-β1 is involved in neurogenesis [65], and IGF-1 is a neuroprotective factor whose role in AD is still controversial [66]. VEGF, a factor related to vascular processes, has neuroprotective effects, and lowered levels in AD have previously been described [67]. IL-18, in combination with IL-1beta, may contribute to neuroinflammatory processes in AD via the inflammasome pathway [68]. Monocyte chemoattractant protein-1 is a chemokine that mediates inflammation in AD [69].

2. Aims and hypotheses

Timely diagnosis is crucial in AD to implement preventive measures at the earliest time possible. With this work, we aimed for novel diagnostic and differential diagnostic tools that can help to find evidence for or against a developing AD in symptomatic and presymptomatic subjects. In particular, we sought to find useful diagnostic measures outside the gold standard of CSF biomarkers, namely clinical anamnesis (Miebach *et al*., 2019 [3]), neuropsychological testing (Menne *et al*., 2020 [1]) as well as blood serum markers (Schipke & Menne *et al*., 2020 [2]).

We hypothesized that there are clinical features, neuropsychological testing results, and blood serum biomarker constellations associated with changes in amyloid and tau metabolism in CSF as evidence for an underlying AD. Furthermore, we hypothesized that depending on the number of depressive symptoms present, neuropsychological tests differ in their ability to discriminate between patients with and without evidence for a developing AD.

3. Methods

3.1. Cohorts

3.1.1. Cohort of Menne *et al*., 2020

The study "*Value of Neuropsychological Tests to Identify Patients with Depressive Symptoms on the Alzheimer's Disease Continuum*" [1] was conducted on a sample of patients of the memory clinic within the Charité Universitätsmedizin Berlin, Germany. These patients visited the clinic between 2007 and 2018, reporting a cognitive decline. A total of 2101 of these patients were extensively assessed via medical history, neuropsychological testing, cranial imaging, and lumbar puncture to assess CSF biomarkers (Aβ40, Aβ42, and t-Tau). DSM-IV/-V diagnosis for each patient was reached in a clinical conference. Since we focused on early disease stages, we excluded patients with a Mini-Mental Status Examination (MMSE[70]) score of <24, a total of 1414. Furthermore, we excluded patients who did not fulfill our established CSF positive or CSF negative criteria as described below. We obtained an ethical vote from the Ethics Committee of the Charité Universitätsmedizin Berlin, vote number EA4/057/20.

3.1.2. Cohort of Schipke & Menne *et al*., 2020

The sample for the study *"Value of a panel of six serum biomarkers to differentiate between healthy controls and mild cognitive impairment due to Alzheimer's disease"* [2] consisted of memory clinic patients who underwent a diagnostic workup in the memory clinics of the Charité Universitätsmedizin Berlin, Germany and the Technical University of Munich, Germany. The patients' extensive characterization was conducted as described in 3.1.1. For some patients, CSF p-Tau values were also assessed. Criteria for MCI were set according to National Institute on Aging and Alzheimer's Association (NIA-AA [71]). For the diagnosis of MCI due to AD, there additionally needed to be evidence for underlying AD pathophysiology, i.e., amyloid and tau abnormality in CSF. Furthermore, for the diagnosis of MCI due to AD, other reasons for cognitive decline, such as extensive vascular damage or depression, were excluded. We recruited healthy blood donors (n=68) from the Kantonsspital Aarau AG, Switzerland, for the group of controls. From this analysis, we excluded subjects with a history of malignant diseases, severe renal insufficiency, HIV infection, acute infections, autoimmune diseases, neurodegenerative diseases other than AD, acute stroke, and history of stroke with residual symptoms, delirium, substance abuse, and psychotic disorders. Furthermore, participants with regular statin intake were excluded since there is evidence that statins may influence BDNF [72], IGF-1 [73], and VEGF levels [74]. Local ethics committees approved the examination, and we received ethical votes from local ethics committees; Technical University of Munich, School of Medicine (reference no.11/16S) and from Charité, EA4/078/14.

3.1.3. Cohort of Miebach *et al*., 2019

Subjects for the study "*Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study*" [3] participated in the DZNE-Longitudinal Cognitive Impairment

and Dementia Study (DELCODE). DELCODE is an observational longitudinal memory clinic-based multicenter study in Germany to improve characterization of the early, preclinical stage of AD, focusing on SCD patients [75]. Institutional Review Boards approved the study protocol of all participating study centers of the German Center for Neurodegenerative Diseases (DZNE), all subjects provided written informed consent. 205 participants without objective cognitive impairment were included in the study: healthy controls (HC, n=76), first-degree relatives of patients with AD dementia (AD relatives, n=24), and memory clinic patients with unimpaired test performance but with a report of worrisome subjective cognitive decline at the initial screening (SCD patients, n=105). The diagnostic criteria for group definition and the study protocol have been described elsewhere [75].

3.2. Design of the studies

3.2.1. Neuropsychological tests

For Menne *et al*., 2020, and Schipke & Menne *et al*., 2020, patients' cognitive performance was assessed with the neuropsychological testing battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-NP [30]). This testing battery consists of the MMSE [70] as well as tests for phonemic fluency and visual naming (Boston Naming Test [76]), constructional praxis, and constructional praxis delayed recall and verbal memory tasks. Furthermore, tests to measure processing speed and executive function, i.e., the Trail Making Test A (TMT-A) and B (TMT-B) [77], as well as the Clock Drawing Test (CDT [78]). Results on each CERAD-NP-subscale were z-standardized according to gender, age, and years of education. For Miebach *et al*., 2019, an extended testing battery including the CERAD-NP was used, as previously described elsewhere [75].

3.2.2. Assessment of affective symptoms

Depressive symptoms were assessed with the Geriatric Depression Scale (GDS), a yes/no dichotomous scale with scores ranging from 0-30, scores are proportional to depressive symptoms [79]. This self-administered questionnaire was shown to be a valid instrument to help identify late-life depression [80]. A cut-off score of ≥11 is considered a possible indicator of depression, with a sensitivity of 84% and a specificity of 95% for accurately detecting late-life depression [81]. According to our clinical experience, GDS scores of 21 or higher are highly indicative of clinical depression. For these reasons, we decided to divide patients into one of three GDS subgroups, namely patients with a GDS-score ≤10 (low GDS), 11-20 (moderate GDS), and ≥21 (high GDS). For Miebach *et al.*, the 15-item short version of the GDS was used.

3.2.3. Cerebrospinal fluid sampling

CSF was collected and analyzed according to a standardized protocol described in detail elsewhere [82]. In the Berlin memory clinic, we established the following CSF biomarker cut-offs as indicative of AD-typical pathology: Aβ42≤600 pg/ml (sensitivity 0.82, specificity 0.80) or ratio Aβ42/Aβ40 ≤ 0.065 (sensitivity 0.80, specificity 0.75), added by t-Tau≥350pg/ml (sensitivity 0.74, specificity 0.78). Following the NIA-AA research framework [39], we defined CSF positive patients showing both

amyloid-pathology (A+) and neurodegeneration (N+). For the analyses in Menne *et al.*, 2020, we defined patients as having AD-typical pathology (i.e., CSF-positive) when t-Tau≥350 pg/ml and Aβ42≤600 pg/ml. In CSF-negative patients, the cut-offs were t-Tau<350pg/ml and Aβ42>600 pg/ml, corresponding to A- and N-.

For Berlin patients in Schipke & Menne *et al*., 2020, we considered an underlying AD pathology likely based on the following CSF biomarkers: t-tau>300pg/ml, Aβ42<600 pg/ml, and Aβ42/Aβ40<0.065. For Munich patients, following values applied: t-tau>252pg/ml, P(181)-tau>60pg/ml, Aβ42<650 pg/ml and Aβ42/Aβ40<0.050.

For Miebach *et al*., 2019, the sampling and processing of CSF, including cut-off values defined as in line with AD pathology, have been described previously [75]. For this study, we used continuous variables of Aβ42, P(181)-tau and total Tau levels rather than cut-off values to investigate associations of SCD within the complete Alzheimer's continuum in cognitively healthy individuals. Besides, we calculated a CSF amyloid/tau ratio score (Aβ42/(240 + 1.18 × tau), established as a specific marker for AD [83].

3.2.4. Subjective cognitive decline interview and scoring procedures

For the systematic assessment of SCD in the sample of Miebach *et al*., 2019, we developed a semi-structured interview (SCD-I). It assesses self-experienced cognitive impairment in the five domains *memory, language, planning, attention,* and *other cognitive decline* as well as the SCD-plus features [19]. All interviews were administered face to face by trained study physicians and lasted approximately 5 minutes. The interview consists of 3 parts, including an open question and a structured part for the participant and the informant, whereas this study's focus was the structured part. For each domain, the physician asked the patient if they had noticed any worsening function (e.g., "*Do you feel like your memory has become worse?*"). If the participant answered this question with yes, the physician added more in-depth questions about the domain to assess the presence/absence of SCD-plus features, i.e., specific questions about associated worries ("*Does this worry you?*"), onset ("*How long ago did you start to notice the decline?*"). Moreover, the performance in comparison to peers ("*Compared to other people of your age, would you say that your performance is worse?*"). A modified SCD-I was also administered to a study partner (usually a relative or spouse) of all participants, asking for an observed decline in any of the same five domains.

The quantification of response data allows the derivation of the total number of domains with a reported decline and the total number of fulfilled SCD-plus features. This scoring was executed as follows:

Number of fulfilled SCD-plus features: Reported as number of fulfilled SCD-plus features ranging from 0 to 5 (*decline in memory, onset within the last five years, worries associated with a decline in a cognitive domain, feeling of worse performance than others of the same age group, confirmation of perceived cognitive decline by an informant*).

The number of reported SCD domains: Sum of the number of cognitive domains (*memory, language, planning, attention, others*) in which the participant endorses a worsening in function (maximum score = 5).

3.2.5. Blood sampling

Blood samples for Schipke & Menne *et al*., 2020, were collected in neutral 7.5 ml S-Monovette R® without additives (Sarstedt, Nürnbrecht, Germany). The samples were left to clot for 60 min and protected from heat before centrifuging at room temperature for 10 min at 2000×g to segregate the serum. The obtained serum was stored in aliquots at -80°C until analysis. Hemolytic, lipemic or icteric samples were excluded, as such quality deficits can potentially influence assay results

3.2.5.1. Measurement of BDNF, IGF-1, VEGF, TGF-β1, MCP-1 & IL-18

The six biomarkers' protein levels were assessed using ELISAs, described in detail previously [63]. The quantifications were performed according to the manufacturer's instructions with the application of the specific sample dilutions. These sample dilutions were optimized and established for each biomarker by our workgroup. In addition to the assay-specific protein standards, an internal control was measured within each assay run. Assay results were quantified using a microplate reader (ELX808, BioTek Instruments Inc., Winooski, VT, USA). The protein concentrations for BDNF, IGF-1, and TGF-β1 are expressed in ng/ml, and pg/ml for VEGF, MCP-1, and IL-18.

3.3. Statistical Analyses

3.3.1. Menne *et al*., 2020

Data were analyzed using the statistical software "R", version 3.2.4. After dividing patients into CSF positive and CSF negative, a single value classification was performed. We calculated receiver operating characteristic (ROC) curves for all neuropsychological tests by calculating the sensitivity and specificity for each value of the neuropsychological test results. The performance of the classification was assessed using the area under the curve (AUC). For further analyses, we formed the cognitive domains *Recall* (Wordlist Recall, Constructional Praxis Savings, Discriminability) and *Executive Function* (Semantic Fluency, Trail Making Test A and B) and calculated AUC values. To investigate the relation between classification performance and depressive symptoms, we performed a series of single value classifications for patients with increasing GDS scores. For a given GDS score, we selected all patients with a score of ±10 and performed single value classifications.

3.3.2. Schipke & Menne *et al*., 2020

Data analysis and plots were computed using Python (version 2.7.9; Python Software Foundation, OR). We used a logistic regression model on input data for the computation of the algorithm to predict a given participant's group (data from all six variables). The result is a one-dimensional value for each dataset and a general classifier that best separates groups. To train and validate the algorithm, we used data of Charité DAT (dementia of Alzheimer's type) patients with CSF-validated AD pathology as well as data of healthy controls (blood donors). The model was trained and then validated with independent data sets

of controls and AD patients. Sensitivity and specificity to discriminate between groups were calculated, receiver operating characteristic (ROC) plots were obtained from the data used for validation. Subsequently, the now trained and validated algorithm was applied to the six biomarkers' datasets in two cohorts of MCI patients with and without AD-typical changes in CSF to dichotomize blood biomarker results from each participant into the group of "AD" or "control". The accuracy of the prediction into the right class, in this case, "AD", is given as the percentage of cases predicted into the AD class.

3.3.3. Miebach *et al*., 2019

All analyses were performed using SPSS Version 23.0 (IBM) for Windows. Group differences in CSF level were reported as age-adjusted results based on ANCOVA. Linear regression models were used to examine the relationship between different SCD scores and the CSF biomarker outcome variables described above. We performed separate analyses for the number of fulfilled SCD-plus features and the number of reported SCD domains. In step 1, we entered one of the SCD scores as a single predictor. In a second step, we adjusted for age, sex, and education. To gauge the added benefit of SCD questions over and above memory testing, we controlled for objective memory performance by using the word list delayed recall score as a covariate. All cases with missing data in any variables were excluded.

Table 1: Summary of study methods

Study	**Sample**	**Method**
Menne *et al*., 2020	Memory clinic patients: CSF-positive n=190, CSF-negative n=307	Calculation of sensitivity and specificity of each neuropsychological test to discriminate between CSF-positive and CSF-negative subjects
Schipke & Menne *et al*., 2020	Memory clinic patients: AD dementia n=42, MCI AD n=55, MCI non-AD n=25; healthy controls: n=68	Training and validation of logistic algorithm with 6 serum biomarkers to then be used for dichotomous classification (suspicious/not suspicious of AD)
Miebach *et al*., 2019	Memory clinic patients and controls without objective cognitive decline: Healthy controls n=76, AD relatives n=24, Subjective cognitive decline n=105	Semi-structured interview on subjective cognitive decline, subsequent association of interview questions with CSF biomarkers

4. Results

4.1. Results of Menne *et al.*, 2020

307 subjects were defined as CSF negative (A- *and* N-) and 190 as CSF positive (A+ *and* N+). In patients with GDS scores of ≤10, the neuropsychological tests with the highest specificity and sensitivity in differentiating between CSF positive and CSF negative were (in descending order) the MMSE (AUC=0.72), Constructional Praxis Recall (0.71), and Wordlist Total (0.71). In patients with GDS scores of 11-20, the Trail Making Test-B (0.77), Wordlist Discriminability (0.75), and Wordlist Recall (0.75) showed the highest specificity and sensitivity. The neuropsychological tests with the highest specificity and sensitivity to differentiate between CSF groups with GDS scores of 21-30 were the Trail Making Test-B (0.82), CDT (0.79), and Wordlist Recall (0.78) tests. When analyzing the discriminatory power throughout GDS scores (0-30), we find a rise in the AUC values of several neuropsychological tests with increasing GDS scores. In particular, the Trail Making Test B (TMT-B) and especially the Boston Naming Test (BNT) test exhibit a marked rise in AUC values with higher GDS scores. There are significant differences when comparing AUCs of the TMT-B (AUC: 0.64 vs. 0.82, $p<0.02$) and the BNT (AUC: 0.55 vs. 0.75, $p<0.02$) between the two groups with low (≤10) and high (≥21) GDS scores. However, we found no significant differences when comparing the cognitive domains Recall (AUC: 0.71 vs. 0.76, $p=0.52$) and Executive Function (AUC: 0.65 vs. 0.75, $p=0.23$) between high and low GDS score groups.

4.2. Results of Menne & Schipke *et al.*, 2020

We calculated an algorithm including data sets from the sex-matched, age-adjusted control cohort (n=20), together with data sets of 42 DAT patients whose diagnosis was neurobiologically validated based on CSF biomarkers. The model was trained with n=10 data sets of controls and n=21 data sets of DAT patients. The trained algorithm was then validated with n=10 data sets of controls and n=21 data sets of DAT patients. For the validation data set (n=31), the correct group (DAT or control) was predicted with an accuracy of 80.6%. Overall, this yields a sensitivity of 80% and a specificity of 81% for the prediction into the right group. Because of the limited number of data sets from controls, we also calculated an algorithm including data sets from the full control cohort (n=68) together with the data sets of the 42 DAT patients. The model was trained with n=45 data sets of controls and n=28 data sets of DAT patients. The trained algorithm was then validated with n=23 data sets of controls and n=14 data sets of DAT patients. For the validation data set (n=37), the correct group (DAT or control) could be predicted with an accuracy of 83.8%. Overall, this yields a sensitivity of 87% and a specificity of 79% for the prediction into the right group.

Subsequently, we applied the algorithm to MCI patients. When analyzing MCI-AD patients from the two different cohorts separately, in the Berlin cohort (30 MCI-AD patients), n=4 were classified as “control”, and n=26 were classified as AD. In the Munich cohort (25 MCI-AD patients), n=4 were

classified as “control”, and n=21 were classified as AD. Accuracy of prediction into the right class was 87% for the Berlin cohort and 85% for the Munich cohort.

Since a considerable number of MCI patients do not exhibit AD-typical alterations in CSF, we also analyzed the algorithm's performance applied to MCI non-AD (n=25) patients, who were not further stratified according to disease etiology. When applying the previously established algorithm, n=6 were classified as “control”, and n=20 were classified as “AD”.

Since the algorithm classified subjects from the MCI non-AD group as “AD”, we further analyzed the frequency distributions and means of biomarker values for all six markers in the two groups. Mean values are significantly different for MCP-1 (p<0.005), with lower levels in the MCI-AD group. While mean levels are not significantly different for all other markers, there is a trend for lower BDNF and TGF-β1levels in MCI-AD patients. Since absolute values are not the primary criterion for our analysis but rather patterns in biomarker concentrations, we further looked at frequency distributions of both groups' biomarker values. We calculated the relative frequency (percentage) of biomarker values with a given bin center for each marker in both groups and plotted those frequencies side by side. For all markers except VEGF, the frequency distributions appear different between groups.

4.3. Results of Miebach *et al.*, 2019

Out of the 205 individuals divided into the three groups of HC, AD relatives, and SCD, 76.1% reported a cognitive decline in at least one domain, and among those experiencing a decline, 72% also endorsed worries associated with the decline. Most complaints were reported in the memory (n=129; 62.9%) and language domain (n=127; 62%). As expected, due to the inclusion criteria, the three participant groups differed in the endorsement of decline in SCD domains and SCD-plus features. Most (93.3%) SCD patients reported a memory decline, but a sizeable proportion of the other participants also did, although less frequently (HC 26.3%; comparison with SCD, χ^2=87.26; p<0.001; AD relatives 45.8%; comparison with SCD χ^2=33.65; p<0.001). The same pattern was observed for experienced decline in language abilities (SCD=82.9%, HC=36.8%, pairwise comparison χ^2=40.29; p<0.001; AD relatives=50%, pairwise comparison to SCD χ^2=11.82; p<0.001). The number of fulfilled SCD-plus features differed highly significantly between the three groups (F(2,202)=99.807; p<0.001). Participants in the SCD group fulfilled more SCD-plus features (M=3.5) than participants in the HC group (M=0.93, p (bonf. adj.)≤0.001) and in the AD relatives (M=1.63, p (bonf. adj.)≤0.001), which also differed from each other (p (bonf. adj.)≤0.05).

In the combined sample of all three groups, lower age-adjusted CSF-Aß-42 levels were found in those fulfilling the SCD-plus features of a decline in memory (F(1,202)=7.65, p<0.01, $\eta 2_p$=0.036), onset within the last 5 years (F(1,202) 6.07, p<0.05, $\eta 2_p$=0.029), and the confirmation by an informant (F(1,202)=4.19, p<0.05, $\eta 2_p$=0.032). Hierarchical linear regression analysis showed that the number of fulfilled SCD-plus features was a significant predictor of a reduced CSF-Aß-42 level (β= −0.225,

p<0.005) and of a reduced CSF Aß-42/tau-ratio (β= −0.189, p<0.01) independent of age, sex, and education. In contrast, the relationship between the number of fulfilled SCD-plus features and CSF total Tau (β= −0.055, p> .05) and pTau-181 (β = −0.077, p >0.05) was not significant. Using objective memory performance (word list delayed recall) as an additional covariate to control for subtle group deficits in cognition, we found that the SCD-plus score was still a significant predictor, explaining more variance than objective memory performance (as seen by the contribution to R^2 in the prediction model) in CSF-Aß42 and CSF Aß-42/tau ratio. We further observed that participants endorsing a decline in memory or language had significantly lower age-adjusted Aß-42 levels than those who did not report a decline in these domains. A reported decline in the other domains (which occurred less often than a reported decline in memory and language) was not significantly associated with Aß-42. The number of reported domains with experienced decline was also a significant predictor of lower CSF-Aß42 level (β= −0.209, p<0.01) and lower CSF Aß42/tau-ratio (β = −0.146, p<0.05) after including age, sex, education, and the delayed recall score to the model. For CSF-ptau18 and total Tau, only age (total Tau β=0.260, p<0.001; p-tau: β=0.215, p<0.01) and delayed recall score (total tau: β= −0.167, p<0.05; p-tau: β= −0.151, p<0.05) were significant predictors.

Table 2: Summary of study findings

Study	**Main findings**	**Further findings**
Menne *et al*., 2020	TMT-B is best in discriminating between patients with and without CSF values typical for AD in subjects with elevated numbers of depressive symptoms	With rising GDS scores, the discriminative power of most neuropsychological tests increases
Schipke & Menne *et al*., 2020	A panel of 6 serum biomarkers can differentiate between MCI due to AD patients and healthy controls with an accuracy of 86%	The same panel classified 80% of patients with MCI due to other etiologies than AD as suspicious for AD
Miebach *et al*., 2019	A reported decline in memory and language abilities is associated with lower Aß-42 levels in CSF	Quantitative SCD scores are associated with lower Aß42 and lower Aß42/Tau ratio, but not with total Tau or p-Tau181

5. Discussion

5.1. Discussion of Menne *et al.*, 2020

This paper aimed to find neuropsychological tests that hint towards AD-typical CSF changes while considering varying numbers of depressive symptoms. For this, we explored the sensitivity and specificity of different neuropsychological in patients verified for AD-typical CSF biomarkers. Our findings support our hypothesis that depending on the number of depressive symptoms, neuropsychological tests will vary in their ability to differentiate between subjects with and without AD-typical changes in CSF. We found that in subjects with a moderate to a high number of depressive symptoms, assessing executive function with the TMT-B has the highest power to discriminate between CSF-positive and CSF-negative patients. Furthermore, we observed an increasing discriminatory power of several CERAD-NP subtests throughout rising GDS scores.

Specific neuropsychological tests are not only used in specialized memory clinics but at the GP as well, like the MMSE and the CDT [84]. It was shown before that both tests could add to the diagnosis and differential diagnosis of AD and depression [85,86]. However, there are limitations in both test instruments, like lacking sensitivity and specificity in different cohorts [87,88] or the influence of age and education [89], for which in the original versions of the tests, there is no controlling. In our data presented here, upon closer examination of different neuropsychological subtests and their ability to discriminate between CSF-positive and negative subjects in our data, CDT and MMSE are valuable testing instruments in different GDS subgroups, respectively. However, depending on the GDS subgroup, other tests outperform these two. The TMT-B test was best at differentiating between CSF positive and negative patients with moderate to high GDS scores (11-30). The TMT-B assesses, among others, executive function, which is impaired not only in mild AD [90] but also in earlier stages of AD (i.e., MCI due to AD) [91], and there is evidence the TMT-B may help distinguish between cognitively healthy controls, AD and depressed patients [92,93]. Our results are in-line with these previous findings. Hence, we can confirm the value of testing patients' executive function to establish a differential neuropsychological diagnosis.

We furthermore observed a broad rise in the AUC values of a few CERAD-NP subtests in our data. Higher depressive symptoms in CSF positive patients seem to influence test performance more than in CSF negative patients. Since being at risk for AD as defined by CSF-typical biomarker changes typically leads to a significant difference in test performance compared to CSF negative patients [94], a concurrent high number of depressive symptoms might lead to an even more pronounced difference in test performance. This can be seen as a "double hit", resulting in a few neuropsychological tests' higher power to differentiate between the two CSF groups.

We consider the high number of patients with available CSF data a strength of this analysis. To the best of our knowledge, we are not aware of any published data of monocentric databases with a similar

amount of CSF data available. Furthermore, using patients' CSF data and neuropsychological test results rather than their diagnosis reduces the risk of being biased by their clinical diagnosis when interpreting our findings. Moreover, few publications regarding neuropsychological test performance in early AD patients with moderate or high depressive symptoms are available, as mood disorders are often exclusion criteria in studies on neurodegenerative disorders.

The cross-sectional nature of the study may be a limitation. Since no follow-up examinations were conducted, it remains unclear whether the observed CSF abnormalities resulted in neuropsychological and GDS score changes or whether these changes were present before CSF abnormalities. Furthermore, no phosphorylated tau (p-Tau) data was available, which together with Aβ defines AD according to the NIA-AA research framework [39]. Lastly, the unequal GDS subgroups and CSF group sizes limit statistical power; thus, the results presented here must be interpreted with caution.

Our results support previous studies identifying neuropsychological tests that more accurately differentiate between patients with MCI, mild AD, or MDE. Our findings strengthen existing results regarding which neuropsychological tests used in the routine clinical practice are best at differentiating between CSF positive and CSF negative patients while considering varying degrees of depressive symptoms.

5.2. Discussion of Schipke & Menne *et al.*, 2020

In this work, we explored an algorithm's accuracy to identify participants with MCI due to AD from healthy controls and patients with MCI of non-AD origin. We were able to show high diagnostic accuracy of the algorithm to differentiate between patients suffering from MCI due to AD and healthy controls while controlling for center induced effects. Our findings extend previous data that show how neuroinflammatory and neuroprotective blood biomarkers are associated with neurodegenerative disorders like AD, which could be used for diagnostic purposes [61–63]. Previous work often focused on patients in more advanced AD stages [61,63], whereas the data presented here gives evidence that already in the MCI status, there is diagnostic value of our algorithm-based approach.

There are limitations in this study, such as its cross-sectional nature. There are no follow-up examinations of the patients; thus, it remains unclear whether the observed CSF abnormalities in patients resulted in changes in the clinical state. Furthermore, there was no CSF or neuropsychological data of controls available, so there was no proof of amyloid-negativity and participants' cognitive status.

Finally, when applying the algorithm on the MCI non-AD participants, validated by CSF biomarker values, 80% of those subjects were classified into the "AD group". One reason for this might be that for all six examined biomarkers except VEGF, the frequency distributions appear different between groups. Thus, the apparent differences in frequency distributions might indicate differences between these two groups in the six markers' pattern.

Perhaps our panel of six biomarkers does not reflect AD-typical neurodegeneration but cognitive impairment on a clinical level. Also, in this analysis, the group of MCI non-AD patients was not further stratified regarding disease etiology, possibly accounting for a large variance of results in an overall relatively small group. One may also hypothesize that our panel of biomarkers measures a neurodegenerative component that lies beneath the biochemical changes in Amyloid-β and Tau. Further longitudinal research in an incidence study design and an extension of our approach towards other neurodegenerative diseases such as frontotemporal dementia or Lewy-body dementia will be needed to gain evidence for this hypothesis.

5.3. Discussion of Miebach *et al.*, 2019

In the present study, we demonstrate the feasibility and validity of a short semi-structured interview (SCD-I) designed to capture essential aspects of SCD in the context of preclinical AD. We also established the association of SCD-plus items and two quantitative SCD-I scores with CSF biomarkers. All SCD patients reported a decline in one or more cognitive domains within the last years. However, about half of the HC group also endorsed at least some cognitive decline, which is in line with community studies reporting prevalence rates from 25 to 50% of memory complaints increasing with age [95]. This indicates that SCD can be caused by other non-AD etiologies, including personality traits [96], physiological aging, or the research setting [97]. Regarding SCD-plus features, most of the SCD subjects reported a worrisome cognitive decline, which is an expected finding given that a worrisome decline was required for inclusion. Most SCD participants (81%) reported an onset of a decline within the last five years, which is in line with the reported onset in the SCIENCe SCD-cohort, where 83% reported an onset within the last five years [98].

In line with the first interim report from the DELCODE study based on a smaller sample [75], we found that SCD participants had lower age-adjusted CSF-Aß42 levels and lower CSF-Aß42/Tau ratios than HC, while the total Tau level and the p-Tau-181 level did not differ between groups. The SCD-plus sum score and the SCD-I domain score were significantly and specifically associated with amyloid pathology measures, and to the same extent with a derived amyloid/Tau ratio, but not with p-Tau181 or t-tau level alone. The associations with amyloid are in line with previous studies using either CSF amyloid measures [99,100] or amyloid PET [101,102]. Like in the present study, these studies did not find an association of CSF-Tau with quantitative SCD [99,100].

Three of the suggested SCD-plus features were significantly associated with amyloid pathology: experienced decline in memory, the onset of subjective decline within the last five years, and confirmation by an informant. In contrast to our study, two studies of the Amsterdam SCIENCe cohort [98,103] did not find associations with “memory decline” and “onset within five years”. Apart from differences in assessment, this may be due to the younger age of the SCIENCe cohort compared to the DELCODE cohort (64 versus 69 years on average). However, an association of subjective memory decline and informants' cognitive ratings with amyloid pathology has been found before [21,104]. The biomarker associations of the single SCD domains revealed that perceived decline in the memory and

language domain showed the highest associations with AD biomarkers, which is in line with studies suggesting that memory complaints are the best predictor of incident MCI [105] or that memory-related complaints are associated with PIB retention in healthy older adults [21].

The SCD-I discriminated well between the HC and SCD groups in our study, which is somewhat circular for the items of cognitive decline and related concerns, as these SCD-plus criteria were used for group definition at inclusion. However, also the other SCD-plus items assessed at baseline with the SCD-I markedly differ between the groups. Furthermore, most SCD-I items and both SCD-I summary scores were associated with CSF-amyloid, implicating that it captures, to some degree, AD-related cognitive concerns. In sum, this provides a first validation of the SCD-I as a measure for SCD. One limitation of the present SCD-I is that it directly asks for an experienced or observed decline in five neuropsychological domains, using global and commonly used terms like memory, language, or planning. Whether subjects "correctly" identify their specific problems related to one of those domains is unknown. However, subjects can endorse deficits in many domains instead of only one or two, and the domain score, like the SCD-plus score, seems to capture SCD severity, as it is related to AD pathology. Furthermore, it should be noted that individuals included in the present study were recruited in the memory clinic (SCD patients) and the community (HC and relatives). Evidence suggests that the active process of seeking medical help due to self-perceived cognitive decline is a factor with potential prognostic value for the presence of AD pathology [106,107].

5.4. Summary

Cognitive impairment in old age can occur due to numerous reasons, the most common being AD [6]. However, etiologies like vascular damages, other neurodegenerative diseases, or psychiatric disorders can be the root for cognitive decline; often, a combination of two or more is prevalent. Early and differential diagnostic is sought after to implement the appropriate diagnostic and therapeutic measures. Finding the correct diagnosis, especially in old age patients, can be difficult when symptoms of different disorders overlap. Cognitive symptoms like the decline of memory or concentration can be symptoms of prodromal AD [23] but also of a depressive episode [24]. This complicated relation between AD and depression highlights the need for diagnostic and differential diagnostic measures in the field of cognitive decline in old age. These diagnostics are still not easily accessible to the broad public, although there is a wide-spread willingness to be tested for risk factors for dementia [12]. The research criteria-based gold standard for the diagnosis and differential diagnosis of AD is high in cost and effort and usually only available in specialized memory clinics. However, even in these specialized centers, gaining evidence for the AD hallmarks amyloid and tau can be difficult for various reasons, such as technical challenges [41].

Therefore, novel diagnostic approaches are needed to find evidence speaking for or against a developing or manifest AD. We found that detailed questions on a perceived decline in different cognitive domains and the presence or absence of the SCD-plus features were related to AD biomarkers in cognitively

normal participants of the DELCODE study. Combining information on perceived decline in multiple cognitive domains and SCD-plus features is useful for predicting underlying AD pathological change.

Besides, we found that depending on the level of depressive symptoms, traditionally used tests like the MMSE, and the CDT have less power than other tests such as the TMT-B test in discriminating between patients with and without AD-typical CSF pathology. Therefore, for patients with suspected or clinically manifest depression, we recommend focusing on tests that assess executive function rather than the MMSE, CDT, or verbal memory tests for higher diagnostic differentiation. Doing so can help guide clinicians in their decision of whether further diagnostic measures are warranted. However, apart from the timely and costly effort to conduct a neuropsychological testing battery beyond short tests like the MMSE, the testing procedure itself can be stressful for some patients [108] and thus might not represent the actual cognitive status.

Therefore, an approach based on blood-borne markers, as we showed in our findings, may lead the way to a widely available, less expensive, and minimally invasive diagnostic approach in the clinical workup of AD. A blood-based biomarker approach would be well suited as a first step in a diagnostic regimen starting at general practitioners without specialization in the early and differential diagnosis of dementia. Our data may prove useful to improve identifying persons with an increased risk of underlying AD in the community who then can be sent to specialized memory clinics for further diagnostic workup, if possible.

However, even in specialized centers, there might be reasons preventing a comprehensive diagnostic examination since lumbar punctures or PET and genetic data assessment are expensive and a great effort. With this work, we show novel alternative approaches to the established gold standard. They demonstrate an easily accessible and economical way to gain enough evidence to consider or rule out a neurodegenerative process in patients with mild or no objectifiable impairment while at the same time considering depressive symptoms. Future research will be needed to examine which combinations of these described alternatives to CSF, PET, and genetic data may be the most promising approach.

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7. Statutory Declaration

“I, Felix Menne, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “Novel approaches for the differentiation between subjects with preclinical and clinical Alzheimer’s disease and healthy subjects validated by cerebrospinal fluid”/”Neue Ansätze zur Differenzierung zwischen Personen mit präklinischer und klinischer Alzheimer-Erkrankung und gesunden Probanden validiert durch Cerebrospinalflüssigkeit”, independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of your own contribution to the publications

Felix Menne contributed the following to the below-listed publications:

Publication 1: Menne F, Schipke CG, Klostermann A, Fuentes-Casañ M, Freiesleben SD, Bauer C, Peters O (2020) Value of Neuropsychological Tests to Identify Patients with Depressive Symptoms on the Alzheimer’s Disease Continuum. *J. Alzheimer’s Dis*. 78, 819–826.

Contribution:

Felix Menne was responsible for conceptualizing and elaborating the research question and hypotheses and for the project's administration, including the creation of the ethical approval. To a substantial extent, the patients whose data was used for the project were examined by Mr. Menne in the Memory Clinic context throughout their initial consultation, neuropsychological examination, and finding and communicating the diagnosis to patients and caregivers. He also drafted inclusion and exclusion criteria and was responsible for the data selection and checking for completeness and redundancy, and z-transformation of the neuropsychological results. He played a significant

role in drafting the methodology, i.e., the single value classification, creation of the domains "memory" and "executive function" and the relationship between classification performance and increasing GDS scores. He carried out exploratory statistical analyses regarding the study's feasibility and created all tables (1-3, and supplemental table 1) and figure (1) of the paper. Mr. Menne conducted further statistical analyses in close collaboration with C. Bauer. The manuscript was created as the first author by Mr. Menne and submitted for publication to the *Journal of Alzheimer's Disease*.

Publication 2: Schipke CG, Menne F, Rubow S, Sigle J-P, Peters O, Grimmer T (2020) Value of a Panel of 6 Serum Biomarkers to Differentiate between Healthy Controls and Mild Cognitive Impairment Due to Alzheimer Disease. *Alzheimer Dis. Assoc. Disord.* 34, 318–324.

Contribution:

Mr. Menne played a significant role in the project's conceptualization and elaboration of the research question and hypotheses. A substantial part of the Charité cohort patients, whose data were used for the project, was examined by Mr. Menne in the Memory Clinic context throughout their initial consultation, neuropsychological examination, and finding and communicating the diagnosis to patients and caregivers. Furthermore, Mr. Menne carried out exploratory statistical analyzes and, in equal parts with shared first author CG Schipke created all tables (1 and supplemental table 1) and figures (1-4). A significant part of the manuscript was written by Mr. Menne as the shared first author and submitted for publication to the journal *Alzheimer Disease and Associated Disorders*.

Publication 3: Miebach L, Wolfsgruber S, Polcher A, Peters O, Menne F, Luther K, Incesoy E, Priller J, Spruth E, Altenstein S, Buerger K, Catak C, Janowitz D, Perneczky R, Utecht J, Laske C, Buchmann M, Schneider A, Fliessbach K, Kalbhen P, Heneka MT, Brosseron F, Spottke A, Roy N, Teipel SJ, Kilimann I, Wiltfang J, Bartels C, Düzel E, Dobisch L, Metzger C, Meiberth D, Ramirez A, Jessen F, Wagner M (2019) Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. *Alzheimer's Res. Ther.* 11, 66.

Contribution:

Most of the data from the DELCODE study subcohort used for this publication was assessed from patients recruited and examined by the Charité Memory Clinic. Mr. Menne was responsible for the screening, recruitment, and neuropsychological examination for the participants whose data was used for this publication (healthy controls, SCD, AD relatives) and, to a substantial extent, for the subsequent data entry. He was also responsible for the general administration of the project at this participating center of the multicentre DELCODE study, including, in addition to the contributions already listed, personal assistance to study participants before and after the examinations, organization, and implementation of MRI appointments and supervision of study staff to ensure the quality of the collected data. He was substantially involved in reviewing and editing the manuscript submitted for publication.

_____

Signature, date and stamp of first supervising university professor / lecturer

_____

Signature of doctoral candidate

8. Prints of the selected publications

8.1. Value of Neuropsychological Tests to Identify Patients with Depressive Symptoms on the Alzheimer's Disease Continuum

Menne F, Schipke CG, Klostermann A, Fuentes-Casañ M, Freiesleben SD, Bauer C, Peters O (2020) Value of Neuropsychological Tests to Identify Patients with Depressive Symptoms on the Alzheimer's Disease Continuum. J. Alzheimer's Dis. 78, 819–826.

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Value of Neuropsychological Tests to Identify Patients with Depressive Symptoms on the Alzheimer's Disease Continuum

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Abstract.
Background: Depressive symptoms often co-occur with Alzheimer's disease (AD) and can impact neuropsychological test results. In early stages of AD, disentangling cognitive impairments due to depression from those due to neurodegeneration often poses a challenge.
Objective: We aimed to identify neuropsychological tests able to detect AD-typical pathology while taking into account varying degrees of depressive symptoms.
Methods: A battery of neuropsychological tests (CERAD-NP) and the Geriatric Depression Scale (GDS) were assessed, and cerebrospinal fluid (CSF) biomarkers were obtained. After stratifying patients into CSF positive or negative and into low, moderate, or high GDS score groups, sensitivity and specificity and area under the curve (AUC) were calculated for each subtest.
Results: 497 participants were included in the analyses. In patients with low GDS scores ($\leq$10), the highest AUC (0.72) was achieved by Mini-Mental State Examination, followed by Constructional Praxis Recall and Wordlist Total Recall (AUC = 0.714, both). In patients with moderate (11–20) and high ($\geq$21) GDS scores, Trail Making Test-B (TMT-B) revealed the highest AUCs with 0.77 and 0.82, respectively.
Conclusion: Neuropsychological tests showing AD-typical pathology in participants with low GDS scores are in-line with previous results. In patients with higher GDS scores, TMT-B showed the best discrimination. This indicates the need to focus on executive function rather than on memory task results in depressed patients to explore a risk for AD.

Keywords: Alzheimer's disease, cerebrospinal fluid, depression, executive function, memory, neuropsychology

INTRODUCTION

Cognitive impairments in old age may occur as the core symptoms of early dementia due to Alzheimer's disease (AD) [1], or they may accompany an episode of major depression (MDE) [2]. Currently, various hypotheses aiming to clarify the interrelation

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between depression and AD exist. For example, having a history of depression has been found to increase one's risk of developing AD [3]. Depression in old age has also been suggested to represent a prodromal stage of AD rather than a risk factor for AD [1, 4, 5]. In clinical practice with geriatric patients, depressive symptoms and cognitive impairments often co-occur [6]. This makes it difficult to differentiate whether cognitive impairments are caused by depression or whether they manifest as part of a syndrome caused by AD.

There are various methods available to obtain evidence for an underlying AD pathology in cognitively impaired patients, the more biomarkers and further clinical information are available to be combined, the more accurate the diagnosis [7]. Different kinds of biomarkers help to identify the neuropathological substrates and etiology of cognitive impairments. An important source of information in the diagnosis of AD are brain magnetic resonance imaging (MRI) scans [8]. However, MRI scans can be contraindicated due to pacemakers or other electrical implants, anxiety, or economic reasons.

The quantification of total-Tau (*t*-Tau) and amyloid-β 1-42 ($A\beta_{42}$) proteins in the cerebrospinal fluid (CSF) have been established to detect early AD-typical pathology with high sensitivity and specificity [9]. Specialized memory clinics may recommend the quantification of CSF biomarkers in late-life depression to help determine whether an underlying AD pathology exists [10]. However, lumbar punctures for obtaining CSF might be perceived as highly invasive by some patients. Furthermore, processing and analyzing CSF is highly demanding and alterations in sample processing can lead to varying results [11]. Lastly, lumbar punctures might be contraindicated in some patients taking anticoagulants or suffering from conditions like scoliosis.

Neuropsychological assessments together with clinical information is the basis to determine different stages of cognitive decline [12, 13]. Ideally, as much additional diagnostic evidence as possible should be used to accurately diagnose AD [7]. However, for different reasons mentioned earlier, some methods might not be available. Thus, identifying easy to conduct, sensitive, and valid neuropsychological tests can add to a more accurate diagnosis of underlying AD pathology.

Previous studies have aimed to identify neuropsychological tests able to differentiate between early AD and late-onset depression. There is evidence that the meaningfulness of psychological test results can differ depending on the affective state of patients [14, 15], which should be considered when interpreting test results. A frequently cited test helpful in distinguishing cognitive impairments due to depression from those due to AD is the Clock Drawing Test (CDT [16]), although contradictory findings exist regarding the extent to which the CDT is able to fulfill this task [17, 18]. When examining episodic memory function, both patients with early AD and MDE show a below-average performance on immediate and delayed recall tests. However, depressed patients retain the learned information better than early AD patients, as measured by recognition tasks [19]. Moreover, there is evidence that depression in AD patients additionally impairs performance in executive function tasks as measured by the Trail Making Test Part B (TMT-B) compared to AD patients without depression [20].

Many publications address the differences in cognitive domains between depression and AD. However, depression is not black or white, but rather there are varying stages in affective mood between clinically depressed and non-depressed. Taking these considerations into account, we aimed to examine the effect of varying numbers of depressive symptoms when interpreting neuropsychological results. In our approach, we wanted to examine the value of different neuropsychological tests to detect AD-typical pathology in old age CSF classified patients. We hypothesized that depending on the number of depressive symptoms patients present, neuropsychological tests would vary in their ability to differentiate between patients with and without AD-typical changes in CSF.

METHODS

Participants

The sample consisted of memory clinic patients presenting with subjective cognitive impairment between 2007 and 2018. Routine clinical practice comprised of a medical case history assessment, psychopathological examination, comprehensive neuropsychological testing, cranial imaging, and a lumbar puncture to assess CSF biomarkers ($A\beta_{40}$, $A\beta_{42}$, and *t*-Tau). DSM-IV/-V diagnosis for each patient was reached by a consensus panel. The study was conducted in accordance with the Declaration of Helsinki. Ethical vote was obtained from the Ethics Committee of the Charité Universitätsmedizin Berlin, vote number EA4/057/20.

Neuropsychological tests and clinical scales

We assessed cognitive performance with the Consortium to establish a registry for Alzheimer's disease neuropsychological test battery (CERAD-NP). CERAD-NP is a standardized instrument used in routine clinical practice to assess and stage AD-typical cognitive impairments [13].

Specifically, the CERAD-NP consists of the Mini-Mental State Examination (MMSE) [21], phonemic fluency, and visual naming (Boston Naming Test [22]), tests for constructional praxis and constructional praxis delayed recall and verbal memory tasks. Furthermore, tests to measure processing speed and executive function, namely the Trail Making Test A (TMT-A) and the TMT-B [23], as well as the CDT [16] were performed. Results on each CERAD-NP-subscale are z-standardized, taking gender, age, and years of education into account.

Depressive symptoms were assessed with the original 30-item version of the Geriatric Depression Scale (GDS; yes/no dichotomous scale, range 0–30, scores proportional to depressive symptoms) [24]. The GDS is a self-administered questionnaire shown to be a valid instrument to help identify late-life depression [25]. A cut-off score of $\geq$11 can be seen as a possible indicator of depression, as it has been shown to have a sensitivity of 84% and a specificity of 95% for accurately detecting late-life depression [26]. According to our clinical experience, GDS scores of 21 or higher are highly indicative of clinical depression. For these reasons, we decided to divide patients into one of three GDS subgroups, namely patients with a GDS-score $\leq$10 (low GDS), 11–20 (moderate GDS), and $\geq$21 (high GDS).

Cerebrospinal fluid

CSF was collected and analyzed according to a standardized protocol described in detail elsewhere [27]. As it is known that differing and analytical procedures and lot-to-lot variation of analytical kits can strongly influence CSF biomarkers [28], we established the following CSF biomarker cut-offs as indicative of AD-typical pathology in our memory clinic: $A\beta_{42} \leq 600$ pg/ml (sensitivity 0.82, specificity 0.80) or ratio $A\beta_{42}/A\beta_{40} \leq 0.065$ (sensitivity 0.80, specificity 0.75), added by *t*-Tau $\geq$ 350 pg/ml (sensitivity 0.74, specificity 0.78).

Following the NIA-AA research framework [29], we defined CSF positive patients showing both amyloid-pathology (*A*+) and neurodegeneration (*N*+). For the analyses presented here, we defined patients as having AD-typical pathology (i.e., CSF-positive) when *t*-Tau $\geq$350 pg/ml and $A\beta_{42}$ $\leq$ 600 pg/ml. In CSF negative patients, the cut-offs were *t*-Tau < 350 pg/ml and $A\beta_{42} > 600$ pg/ml, corresponding to A- and N-.

Inclusion and exclusion criteria

We included patients that underwent a complete diagnostic assessment in our memory clinic as described above and who had an MMSE score of 24 or higher with the aim to identify patients with mild or no objective cognitive deficits.

We excluded patients that did not fulfill our established CSF positive or CSF negative criteria. No further exclusion criteria (e.g., diagnosis or medication) were defined in order to better reflect a cohort of patients clinicians face in their everyday work.

Statistical analyses

Data were analyzed using the statistical software "R", version 3.2.4. The authors were blind to patients' diagnosis.

After dividing patients into CSF positive and CSF negative, a single value classification was performed. We calculated receiver operating characteristic (ROC) curves for all neuropsychological tests by calculating the sensitivity and specificity for each value of the neuropsychological test results. The performance of the classification was assessed using the area under the curve (AUC). The AUC typically ranges between 0.5 and 1, with an AUC of 1 indicating perfect discrimination and an AUC of 0.5 reflecting a random classification. Confidence intervals and *p*-values to compare ROC curves were calculated according to the Delong algorithm.

For further analyses, we formed the cognitive domains Recall (Wordlist Recall, Constructional Praxis Savings, Discriminability) and Executive Function (Semantic Fluency, Trail Making Test A and B) and calculated AUC values as described above.

To investigate the relation between classification performance and depressive symptoms, we performed a series of single value classifications for patients with increasing GDS scores. For a given GDS score, we selected all patients with a score of $\pm$10 and performed the single value classification as described above.

For the descriptive statistics, Student's *t*-tests or when appropriate non-parametric Wilcoxon

Table 1
Demographics, clinical scale scores and CSF data of CSF-negatives and -positives

	CSF-positive	CSF-negative	*p*
	190	307	
Female sex (%)	53	44	0.15
Years of education	13.4 ± 3.0	13.6 ± 2.9	0.61
Age	68.0 ± 9.0	69.8 ± 9.9	0.61
t-Tau (pg/ml)	549 ± 284	228 ± 65	**<0.001**
$A\beta_{42}$ (pg/ml)	391 ± 115	1054 ± 339	**<0.001**
Ratio *t*-Tau/$A\beta_{42}$	1.52 ± 0.96	0.24 ± 0.10	**<0.001**
MMSE	26.4 ± 1.7	27.7 ± 1.6	**<0.001**
Mean GDS subgroup 0–10 ($n = 214$)	5.8 ± 2.7	6.0 ± 2.9	0.8
Mean GDS subgroup 11–20 ($n = 197$)	14.7 ± 2.8	14.9 ± 2.9	1.0
Mean GDS subgroup 21–30 ($n = 86$)	23.7 ± 2.6	24.1 ± 2.6	1.0

two-sample tests were used to investigate differences between group means on continuous variables.

RESULTS

Patient selection

A total of 2,101 patients underwent a complete diagnostic assessment at our memory clinic between 2007 and 2018. A total of 1,414 patients with an MMSE score of < 24 were excluded from further analyses.

Patient characteristics

Of the remaining 687 patients, 190 had CSF biomarker results that did not fulfill criteria for either being CSF positive (*A + and N+*) or CSF negative (A- *and* N-) and were excluded from further analyses. Of the remaining 497 patients, 307 were defined as being CSF negative and 190 as CSF positive. Table 1 provides information on patients' demographics, MMSE, GDS, and CSF data.

The 190 CSF positive patients performed significantly worse in all CERAD-NP subtests than CSF negative patients. CSF positive patients scored lower than –1.5 SD below the mean in Constructional Praxis Recall (–1.8 ± 1.3), World List Trial 3 (–1.7 ± 1.5), Wordlist Recall (–1.7 ± 1.4), and Wordlist Total (–1.8 ± 1.5) tests. CSF negative patients yielded *z*-scores ≥–1.5 SD in all CERAD-NP subtests, indicating normative cognitive performance. Table 2 shows the complete list of neuropsychological test performance by CSF group.

Table 2
Neuropsychological test performance

	CSF-positive	CSF-negative	*p*
BNT	–0.1 ± 1.3	0.2 ± 1.2	**<0.001**
CDT	2.2 ± 1.0	1.6 ± 0.9	**<0.001**
CP	–0.2 ± 1.3	0.1 ± 1.2	**<0.05**
CPR	–1.8 ± 1.3	–0.4 ± 1.6	**<0.001**
CPS	–1.5 ± 1.3	–0.4 ± 1.2	**<0.001**
MMSE	26.4 ± 1.7	27.7 ± 1.6	**<0.001**
SF	–0.9 ± 1.1	–0.4 ± 1.3	**<0.001**
TMT-A	–0.8 ± 1.3	0 ± 1.4	**<0.001**
TMT-B	–1.2 ± 1.3	0 ± 1.7	**<0.001**
TMT-B/A	–0.6 ± 1.1	–0.1 ± 1.3	**<0.001**
WL_discr	–1.3 ± 1.4	–0.5 ± 1.4	**<0.001**
WL_I	–0.8 ± 1.3	–0.2 ± 1.1	**<0.001**
WL_R	–1.7 ± 1.4	–0.6 ± 1.2	**<0.001**
WL_S	–1.4 ± 2.2	–0.4 ± 1.8	**<0.001**
WL_total	–1.8 ± 1.5	–0.7 ± 1.4	**<0.001**
WL1	–1.2 ± 1.2	–0.5 ± 1.2	**<0.001**
WL2	–1.4 ± 1.3	–0.6 ± 1.3	**<0.001**
WL3	–1.7 ± 1.5	–0.6 ± 1.4	**<0.001**

MMSE and CDT mean raw scores as well as CERAD-NP mean z-standardized scores in the groups of CSF-positives and -negatives (sorted alphabetically). BNT, Boston Naming Test; CDT, Clock Drawing Test. CP: Constructional Praxis; CPR, Constructional Praxis Recall; CPS, Constructional Praxis Savings; MMSE, Mini-Mental Status Examination; SF, Semantic Fluency; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B; TMT-B/A, Ratio of TMT B/A; WL_discr, Wordlist Discrimination; WL_I, Wordlist Intrusions; WL_R, Wordlist Delayed Recall; WL_S, Wordlist Savings; WL_total, Wordlist Total of immediately recalled words; WL_1, Wordlist 1st trial; WL_2, Wordlist 2nd trial; WL_3, Wordlist 3rd trial. All group differences showed significance.

Patient characteristics by GDS subgroup

In patients with low GDS scores (≤10, $n = 214$), 102 were CSF positive (47%). In those with moderate GDS scores (11–20, $n = 197$), 73 were CSF positive (37%), and in those with high GDS scores (≥21, $n = 86$), 15 were CSF positive (17%).

Discrimination accuracy of neuropsychological tests between CSF groups and GDS subgroups

In patients with GDS scores ≤10, the neuropsychological tests with the highest specificity and sensitivity in differentiating between CSF positive and CSF negative were the MMSE (AUC = 0.72), Constructional Praxis Recall (0.71), and Wordlist Total (0.71). In patients with GDS scores between 11–20, the Trail Making Test-B (0.77), Wordlist Discriminability (0.75), and Wordlist Recall (0.75) showed the highest specificity and sensitivity. The neuropsychological tests with the highest specificity and sensitivity to differentiate between CSF groups

Table 3
AUC of neuropsychological tests

	AUC all	AUC GDS ≤10	AUC GDS 11–20	AUC GDS 21–30
WL_R	0.737 (305/182) [0.69,0.784]	0.706 (112/99) [0.634,0.777]	0.752 (122/69) [0.678,0.826]	0.783 (71/14) [0.659,0.906]
CPR	0.732 (307/190) [0.687,0.778]	0.714 (112/102) [0.644,0.783]	0.733 (124/73) [0.662,0.804]	0.776 (71/15) [0.639,0.912]
CPS	0.728 (306/189) [0.681,0.775]	0.706 (111/102) [0.635,0.777]	0.738 (124/72) [0.666,0.81]	0.733 (71/15) [0.573,0.893]
WL_total	0.719 (307/190) [0.673,0.765]	0.714 (112/102) [0.645,0.783]	0.723 (124/73) [0.648,0.798]	0.735 (71/15) [0.587,0.884]
WL_3	0.719 (307/190) [0.672,0.766]	0.705 (112/102) [0.635,0.775]	0.737 (124/73) [0.662,0.811]	0.721 (71/15) [0.565,0.876]
MMSE	0.713 (307/190) [0.667,0.758]	0.72 (112/102) [0.653,0.788]	0.68 (124/73) [0.603,0.756]	0.761 (71/15) [0.634,0.887]
TMT-B	0.708 (307/190) [0.663,0.754]	0.643 (112/102) [0.569,0.717]	0.766 (124/73) [0.7,0.831]	0.816 (71/15) [0.704,0.928]
WL_2	0.68 (307/190) [0.632,0.728]	0.667 (112/102) [0.596,0.739]	0.68 (124/73) [0.601,0.759]	0.751 (71/15) [0.603,0.898]
WL_discr	0.677 (307/190) [0.629,0.726]	0.645 (112/102) [0.571,0.72]	0.753 (124/73) [0.684,0.823]	0.592 (71/15) [0.447,0.738]
WL_1	0.673 (307/190) [0.625,0.721]	0.678 (112/102) [0.607,0.749]	0.668 (124/73) [0.589,0.747]	0.671 (71/15) [0.508,0.834]
WL_sav	0.669 (304/182) [0.616,0.721]	0.638 (111/99) [0.561,0.715]	0.683 (122/69) [0.597,0.768]	0.752 (71/14) [0.62,0.883]
CDT	0.664 (307/190) [0.618,0.71]	0.633 (112/102) [0.563,0.703]	0.665 (124/73) [0.59,0.739]	0.786 (71/15) [0.67,0.902]
TMT-A	0.639 (307/190) [0.589,0.688]	0.634 (112/102) [0.56,0.708]	0.702 (124/73) [0.628,0.776]	0.619 (71/15) [0.434,0.804]
TMT-B/A	0.63 (307/190) [0.581,0.68]	0.552 (112/102) [0.475,0.63]	0.657 (124/73) [0.581,0.734]	0.762 (71/15) [0.626,0.897]
WL_I	0.626 (307/190) [0.574,0.678]	0.627 (112/102) [0.552,0.703]	0.635 (124/73) [0.55,0.719]	0.521 (71/15) [0.352,0.69]
SF	0.622 (302/189) [0.572,0.672]	0.618 (112/101) [0.542,0.694]	0.623 (120/73) [0.544,0.701]	0.641 (70/15) [0.463,0.82]
BNT	0.592 (307/190) [0.54,0.644]	0.553 (112/102) [0.475,0.632]	0.6 (124/73) [0.519,0.682]	0.752 (71/15) [0.608,0.895]
CP	0.556 (307/189) [0.502,0.61]	0.521 (112/102) [0.442,0.6]	0.581 (124/72) [0.493,0.668]	0.581 (71/15) [0.371,0.79]

Area under the curve (AUC) as well as number of subjects (CSF negative/positive) and [confidence interval] of each neuropsychological test in respective GDS score groups and irrespective of GDS score. WL_1, Wordlist 1st trial; CPR, Constructional Praxis Recall; CPS, Constructional Praxis Savings; WL_3, Wordlist 3rd trial; WL_R, Wordlist Delayed Recall; MMSE, Mini-Mental Status Examination; TMT-A, Trail-Making Test A; WL_I, Wordlist Intrusions; WL_S, Wordlist Savings; WL_discr, Wordlist Discrimination; WL_2, Wordlist 2nd trial; CDT, Clock Drawing Test; SF, Semantic Fluency; TMT-B, Trail-Making Test B; WL_total, Wordlist Total of immediately recalled words; TMT-B/A, Ratio of TMT B/A; BNT, Boston Naming Test; CP, Constructional Praxis.

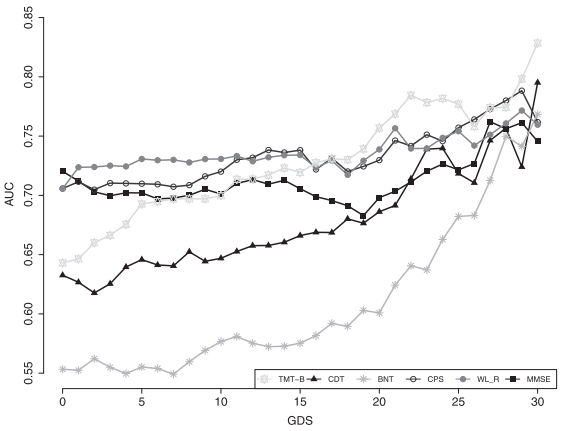

Fig. 1. AUC of selected neuropsychological tests with increasing GDS. TMT-B, Trail-Making Test B; CDT, Clock Drawing Test; BNT, Boston Naming Test; CPS, Constructional Praxis Savings; WL_R, Wordlist Delayed Recall; MMSE, Mini-Mental Status Examination.

with GDS scores between 21–30 were the Trail Making Test-B (0.82), CDT (0.79), and Wordlist Recall (0.78) tests. An overview of AUC values for all neuropsychological tests by GDS subgroup is presented in Table 3.

When analyzing the discriminatory power throughout GDS scores (0–30), we find a rise in the AUC values of several neuropsychological tests with increasing GDS scores. In Fig. 1, we present six CERAD-NP subtests we selected because of their significant rise in AUC with increasing GDS values. In particular, the TMT-B and especially the Boston Naming Test (BNT) test exhibit a marked rise in AUC values with higher GDS scores. There are significant differences when comparing AUCs of the TMT-B (AUC: 0.64 versus 0.82, $p < 0.02$) and the BNT (AUC: 0.55 versus 0.75, $p < 0.02$) between the two groups with low (≤10) and high (≥21) GDS scores.

No significant differences can be found when comparing the cognitive domains Recall (AUC: 0.71 versus 0.76, $p = 0.52$) and Executive Function (AUC: 0.65 versus 0.75, $p = 0.23$) between high and low GDS score groups (Supplementary Table 1).

DISCUSSION

Cognitive impairments in old age have numerous causes. Better understanding the etiology of cognitive decline is a prerequisite for appropriate treatment. Here, we explored the sensitivity and specificity of different neuropsychological tests to identify cognitive impairments typical of AD pathology in the presence of varying degrees of depressive symptoms in patients verified for AD-typical CSF biomarkers. Our

findings support our hypothesis that depending on the number of depressive symptoms, neuropsychological tests will vary in their ability to differentiate between subjects with and without AD-typical changes in CSF. We found that in subjects with a moderate to high number of depressive symptoms, assessing executive function with the TMT-B has the highest power to discriminate between CSF-positive and CSF-negative patients. Furthermore, we observed an increasing discriminatory power of several CERAD-NP subtests over the course of rising GDS scores.

Upon closer examination of different neuropsychological subtests and their ability to discriminate between CSF-positive and negative subjects, the CDT showed to be a valuable instrument in patients with high GDS scores between 21–30. However, differentiation accuracy was lower in patients with lower GDS scores. Although the CDT is largely used to assess AD-typical cognitive impairments and has shown acceptable sensitivity and specificity in patients with depression [17], its clinical value remains controversial. It has also been shown that the CDT lacks sensitivity in mildly impaired patients [18] and is not well suited to differentiate between AD patients and patients suffering from other types of dementia [30].

The MMSE is known to have limitations in detecting cognitive impairments in early AD [31], which appears to be mainly due to its ceiling and floor effects and due to the marked impact of age and education on test results [32]. Interestingly, our results showed that the MMSE had the highest power (AUC = 0.72) in distinguishing between CSF positive and CSF negative patients in the low GDS subgroup. This is most likely due to the broad range of cognitive domains that are covered by the MMSE. However, it seems that in patients with higher GDS scores, other tests outperform the MMSE.

The TMT-B test was best at differentiating between CSF positive and negative patients with moderate to high GDS scores (11–30). The TMT-B assesses, among others, executive function, which has been shown to be impaired not only in mild AD [33] but also in earlier stages of AD (i.e., MCI due to AD) [34] and there is evidence the TMT-B may help distinguish between cognitively healthy controls, AD, and depressed patients [35, 36]. Our results are inline with these previous findings. Hence, we can confirm the value of testing patients' executive function to establish a differential neuropsychological diagnosis.

Interestingly, with increasing GDS scores, we observed a broad rise in the AUC values of a few CERAD-NP subtests. It has been shown before that comorbid depression influences AD patients' test performance in the TMT-B [20]. In our data, higher depressive symptoms in CSF positive patients seem to more strongly influence test performance than in CSF negative patients. Since being at risk for AD as defined by CSF-typical biomarker changes typically leads to a significant difference in test performance compared to CSF negative patients [37], a concurrent high number of depressive symptoms might lead to an even more pronounced difference in test performance. This can be seen as a "double hit", resulting in the higher power of a few neuropsychological tests to differentiate between the two CSF groups. This might also explain the difference between the AUCs of the TMT-A and TMT-B tests. The higher cognitive demand of the TMT-B compared to the TMT-A test might lead to worse performance in CSF patients with higher GDS scores compared to CSF negative patients.

Our findings stress the differential diagnostic value of specific neuropsychological test results of old age patients presenting with depressive symptoms. Indeed, depending on the level of depressive symptoms, traditionally used tests like the MMSE and the CDT showed less power than other tests such as the TMT-B test in discriminating between patients with and without AD-typical CSF pathology. Therefore, for patients presenting to a memory clinic with suspected or clinically manifest depression, we recommend focusing on tests that assess executive function rather than the MMSE, CDT, or verbal memory tests for higher diagnostic differentiation. Doing so can help guide clinicians in their decision of whether further diagnostic measures are warranted.

We consider the high number of patients with available CSF data a strength of this analysis. To the best of our knowledge, we are not aware of any published data of monocentric databases with a similar amount of CSF data available. Furthermore, using patients' CSF data and neuropsychological test results rather than their diagnosis reduces the risk of being biased by their clinical diagnosis when interpreting our findings. Moreover, few publications regarding neuropsychological test performance in early AD patients with moderate or high depressive symptoms are available, as mood disorders are often exclusion criteria in studies on neurodegenerative disorders.

The cross-sectional nature of the study may be seen as a limitation. Since no follow-up examinations were conducted, it remains unclear whether the observed CSF abnormalities resulted in neuropsychological and GDS score changes or whether these changes were present before CSF abnormalities. Furthermore, no phosphorylated tau (*p*-Tau) data was available, which together with Aβ defines AD according to the NIA-AA research framework [29]. Moreover, since the GDS is a self-reported measure, scores might not accurately reflect the severity of depressive symptoms as would be obtained by a trained clinician. This may have under- or overestimated the actual degree of depressive symptoms in some patients, which might additionally be influenced by antidepressant or anxiolytic medication. Lastly, the unequal GDS subgroups and CSF group sizes limit statistical power, thus results presented here must be interpreted with caution. These differences are noticeable especially in the ratio of CSF positive versus negative subjects in the group of GDS scores $\geq$21. This is likely due to the fact that the majority of our patients presenting with memory concerns who have high GDS scores suffer only from depression and less likely from an additional underlying neurodegenerative process. Furthermore, we suspect that patients with high GDS scores who at the same time suffer from a neurodegenerative disease would be more severely impaired and thus have an MMSE score below 24, which we excluded in this study.

Our results support previous studies identifying neuropsychological tests that more accurately differentiate between patients with MCI, mild AD, or MDE. However, especially in mildly cognitively impaired individuals, differentiation based on neuropsychological tests alone is difficult [38, 39]. Our findings strengthen existing results regarding which neuropsychological tests used in clinical routine practice are best at differentiating between CSF positive and CSF negative patients while considering varying degrees of depressive symptoms.

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SUPPLEMENTARY MATERIAL

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8.2. Value of a Panel of 6 Serum Biomarkers to Differentiate between Healthy Controls and Mild Cognitive Impairment Due to Alzheimer Disease

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8.3. Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study

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Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study

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Abstract

Background: Subjective cognitive decline (SCD) has been proposed as a pre-MCI at-risk condition of Alzheimer's disease (AD). Current research is focusing on a refined assessment of specific SCD features associated with increased risk for AD, as proposed in the SCD-plus criteria. We developed a structured interview (SCD-I) for the assessment of these features and tested their relationship with AD biomarkers.

Methods: We analyzed data of 205 cognitively normal participants of the DELCODE study (mean age = 68.9 years; 52% female) with available CSF AD biomarkers (Aß-42, p-Tau181, Aß-42/Tau ratio, total Tau). For each of five cognitive domains (including memory, language, attention, planning, others), a study physician asked participants about the following SCD-plus features: the presence of subjective decline, associated worries, onset of SCD, feeling of worse performance than others of the same age group, and informant confirmation. We compared AD biomarkers of subjects endorsing each of these questions with those who did not, controlling for age. SCD was also quantified by two summary scores: the number of fulfilled SCD-plus features, and the number of domains with experienced decline. Covariate-adjusted linear regression analyses were used to test whether these SCD scores predicted abnormality in AD biomarkers.

Results: Lower Aß-42 levels were associated with a reported decline in memory and language abilities, and with the following SCD-plus features: *onset of subjective decline within 5 years*, *confirmation of cognitive decline by an informant*, and *decline-related worries*. Furthermore, both quantitative SCD scores were associated with lower Aß42 and lower Aß42/Tau ratio, but not with total Tau or p-Tau181.

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Conclusions: Findings support the usefulness of a criterion-based interview approach to assess and quantify SCD in the context of AD and validate the current SCD-plus features as predictors of AD pathology. While some features seem to be more closely associated with AD biomarkers than others, aggregated scores over several SCD-plus features or SCD domains may be the best predictors of AD pathology.

Keywords: Preclinical Alzheimer's disease (AD), Subjective cognitive decline (SCD), Cerebrospinal fluid (CSF), Aß42, Preclinical AD, CSF biomarkers

Background

Subjective cognitive decline (SCD), the subjective experience of worsening cognitive performance among cognitively normal older individuals, can indicate an at-risk stage of Alzheimer's disease (AD) [1, 2]. Several studies, using a variety of assessments, found SCD to predict objective cognitive decline [3, 4], incident mild cognitive impairment (MCI) [5] and incident AD dementia [5, 6].

Furthermore, in several cross-sectional studies, cognitive complaints were found to correlate with biomarkers of early AD pathology such as amyloid-ß (Aß). For example, Amariglio and colleagues [7] found an association of Aß deposition in the brain and a memory complaint composite score in cognitively normal older adults. Higher baseline memory complaint scores in participants screened positive for Aß were also found to predict faster cognitive decline [8].

These and other studies have established that some form of SCD can be a clinical indicator of early AD (stage 2, according to the NIA-AA research framework [9]).

Based on the evidence accrued until 2014, a group of researchers forming the SCD-Initiative proposed the "SCD-plus criteria" as an enrichment strategy for the likelihood of preclinical AD in individuals with SCD [9], comprising (a) *Subjective decline in memory rather than other domains*, (b) *onset of SCD within the last 5 years*, (c) *age of onset ≥ 60 years*, (d) *particular concerns associated with SCD*, (e) *the feeling of worse performance than others of the same age group*, (f) *confirmation of perceived cognitive decline by an informant*, and (g) the *presence of the APOE e4 genotype*.

These criteria were not meant to be final but were considered to be in need of further refinement and validation in research studies. For example, recent studies suggest that consistency of complaints over time may be another feature associated with the presence of AD risk [6].

Current assessments differ widely regarding administration (interview with a physician versus questionnaire), content, number of items, and scaling, leading to a large variety of methods [10, 11]. While some SCD studies used single questionnaire items [12] or items from different SCD questionnaires [13–15], others were using one out of many questionnaires [7, 11] or even composites derived from several questionnaires (e.g., [16]). Psychometric analyses are ongoing to extract from existing data those single SCD questions or features contributing most to the prediction of AD [17].

One potential limitation of most current SCD assessments is that they only refer to memory [11]. Subjective memory concerns are highly prevalent in older adults (e.g., around 53% in a large population-based sample [18]) and may therefore be highly sensitive but of insufficient specificity regarding the detection of preclinical AD. Thus, current research suggests involving additional cognitive domains in SCD assessment [2], e.g., subjective complaints in executive function which have also been associated with Aß deposition in cognitively normal individuals [7]. Irrespective of the cognitive domains, studies have also highlighted specific features of SCD which are associated with AD biomarkers, objective cognitive decline, or incident MCI. Perrotin and colleagues [19] for example found an association between the comparison of memory function to peers with Aß deposition using Pittsburgh compound B positron emission tomography (PiB-PET) imaging.

Another feature replicated in several studies is the presence of worries associated with the subjective worsening in function.

A recent study on the validity of SCD-plus criteria in cognitively unimpaired patients of the Amsterdam memory clinic [20] could not find significant relationships between amyloid biomarkers and any of the examined subjective cognition features ("memory specific decline", "onset of complaints within 5 years", "worse performance than others of the same age", and "informant reports decline"). Amyloid was only predicted by higher age (> 60) and ApoE4 in this study, in line with established knowledge [21]. Apart from sample size limitations in this study, the apparent insensitivity of the subjective cognition features in the SCD-plus criteria could have been due to the relatively young age of the memory clinic subjects (64 years on average) and to the measurement of SCD with two different questionnaires which were not designed to fully capture the SCD-plus criteria.

Importantly, there is no straightforward, interview-based assessment of SCD criteria, and a single validation

study of SCD-plus features is still missing. In clinical settings, structured interviews offer an advantage over questionnaires as they rely on personal contact to the patient, thus improving acceptance, and may allow an informed clinical rating of participants' complaints according to diagnostic categories. They are an established strategy for reducing information variance [22, 23].

In the present study, we aimed to provide further validation of the SCD-plus features while also testing the usefulness of an interview-based assessment for AD-related SCD. We developed a new, semi-structured interview for detailed SCD assessment (SCD-I) which includes assessment of perceived decline in different cognitive domains as well as the SCD-plus criteria mentioned above. We examined cognitive complaints as measured by the SCD-I in a sample of cognitively normal older adults and tested for associations of individual SCD features as well as composite scores derived from the interview with biomarkers of AD pathology, respectively.

Methods

Study design

The DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) is an observational longitudinal memory clinic-based multicenter study in Germany with the aim to improve characterization of the early, preclinical stage of AD with a focus on SCD patients. The study protocol was approved by Institutional Review Boards of all participating study centers of the DZNE [24]. All patients provided written informed consent.

Participants

We included 205 participants (age M = 68.9; SD = 5.4) from an interim data release of the DELCODE study. Here, we analyzed only data from cognitively normal individuals. These included healthy controls (HC, $n = 76$) who all had denied any worrisome subjective cognitive impairment during an initial telephone screening for study eligibility, first-degree relatives of patients with AD dementia (AD relatives, $n = 24$), and memory clinic patients with unimpaired test performance but with a report of worrisome subjective cognitive decline at the initial screening (SCD patients, $n = 105$).

The diagnostic criteria for group definition and the study protocol have been described in detail previously [24]. The HC and the AD relatives group were both recruited via local newspaper advertisement and conducted a telephone interview to screen for suitability. The SCD patient group was recruited via the memory clinics of all participating DELCODE sites. These individuals sought diagnostic evaluation of subjectively experienced a decline in cognitive functioning. It was required that they expressed concerns to the physician of the memory clinic regarding their self-perceived cognitive decline while their test performance was above −1.5 SD of age-, sex-, and education-adjusted normal performance on all subtests of the CERAD neuropsychological assessment battery. Subsequent to these different screening procedures, subjects in all groups were enrolled into the DELCODE study and underwent a uniform baseline assessment including the semi-structured SCD interview described below.

Subjective cognitive decline interview (SCD-I) and scoring procedures

The SCD-I allows assessment of subjective cognitive decline in five different cognitive domains *(memory, language, planning, attention, any other cognitive decline)* and comprises all five SCD-plus features which refer to subjective experience [2]. All interviews were administered face to face by trained study physicians and lasted approximately 5 min. The interview consists of 3 parts including an open question at the beginning as well as a structured part for the participant and the informant. In this study, we are only focusing on the structured part. The whole interview procedure is shown in Additional file 1. For each domain, the physician asked the patient if he/she had noticed any worsening in function (e.g., "do you feel like your memory has become worse"). If the participant answered this question with yes, the physician added more in-depth questions about the domain to assess the presence/absence of SCD-plus features, i.e., specific questions about associated worries ("Does this worry you?"), onset ("How long ago did you start to notice the decline?"), and the performance in comparison to peers ("Compared to other people of your age, would you say that your performance is worse?"). Furthermore, participants were asked whether they had talked to a physician about their subjective cognitive decline (this information was not analyzed in the present study as by design all SCD subjects had been referred to a memory clinic). In addition, a modified SCD-I was administered to a study partner (usually a relative or spouse) of all participants, asking for an *observed* decline in any of the same five domains. Study partners were not asked the in-depth SCD-plus questions but were also asked about whether they had observed any behavioral changes in the participant (this was not analyzed in the present study).

The quantification of response data allows derivation of the total number of domains with a reported decline as well as the total number of fulfilled SCD-plus features. This scoring was executed as follows:

Number of fulfilled SCD-plus features: Reported as number of fulfilled SCD-plus features ranging from 0 to 5 (decline in memory, onset within the last 5 years, worries associated with a decline in a cognitive domain, feeling of

worse performance than others of the same age group, confirmation of perceived cognitive decline by an informant).

Number of reported SCD domains: Sum of the number of cognitive domains (memory, language, planning, attention, others) in which the participant endorses a worsening in function (maximum score = 5).

Neuropsychological and clinical assessment

The DELCODE test battery included an extensive neuropsychological and clinical assessment which covers tests for global cognitive function and different cognitive domains (described in detail previously [24]) as well as a structured medical history and a standardized physical examination [24]. Here, we focus on the assessment relevant to the present study. The Mini-Mental State Examination (MMSE) is used to describe the global cognitive function in all subgroups, and the 15-item short form of the Geriatric Depression Scale (GDS) to measure and control for depressive symptomatology. In a previous memory clinic study [25], we had found that questions on SCD (different from those in the SCD-I) were associated with CSF AD biomarkers, and this was still true after controlling for delayed recall memory performance (an established, strong predictor of CSF AD biomarkers [26]). We analyzed the present data in the same manner with the ADAS delayed recall as covariate.

CSF AD biomarker measures

CSF samples were collected according to previously described standard operating procedure [24] by using commercially available kits according to vendor specifications (V-PLEX Aβ Peptide Panel 1 (6E10) Kit (Intra Plate variance of 3.0 and inter plate variance of 8.8), K15200E and V-PLEX Human Total Tau Kit (intra plate variance of 4.5 and an inter plate variance of 17.1), K151LAE (Mesoscale Diagnostics LLC, Rockville, USA), and Innotest Phospho-Tau (181P) (intra plate variance of 1.7 and inter plate variance of 11.4), 81581, Fujirebio Germany GmbH, Hannover, Germany).

We used the continuous variables of Aß-42 level, the p-tau-181, and the total Tau level as outcomes. In addition, we calculated a CSF amyloid/tau ratio score (Aβ42/(240 + 1.18 × tau) which has been established as a specific marker for AD [27]. We decided to use continuous biomarker values (rather than categorical variables based on cutoffs) in order to explore associations of SCD within the complete spectrum of AD pathological change, especially Aβ accumulation, in cognitively normal individuals, i.e. without loss of information due to dichotomization. This is supported by recent study results, which showed that Aβ accumulation, in cognitively normal older participants still classified as Aß-negative, was associated with longitudinal changes in memory function [28].

Statistical analysis

All analyses were performed using SPSS Version 23.0 (IBM) for Windows. For descriptive statistics, we used x^2 test for categorical and analyses of variance for continuous variables as well as post hoc t tests or chi-square tests for single contrasts. Group differences in CSF level were reported as age-adjusted results based on ANCOVA. Linear regression models were used to examine the relationship between different SCD score and the CSF biomarker outcome variables described above. We performed separate analyses for the number of fulfilled SCD-plus features as well as for the number of reported SCD domains. In step 1, we entered one of the SCD scores as a single predictor. In a second step, we adjusted for age, sex, and education. In order to gauge the "added benefit" of SCD questions over and above memory testing, we controlled for objective memory performance by using the world list delayed recall score as a covariate. All cases with missing data in any variables were excluded. Since we included just participants with CSF biomarkers, we tested whether our sample differed significantly from cognitively normal DELCODE participants without biomarkers ($n = 291$). The samples did not differ in terms of age ($t(493) = -1.84$; $p = .067$), sex ($X^2 = .441$; $p = .507$), and education ($t(491) = -.304$; $p = .761$) and neither regarding the number of fulfilled SCD plus features ($t(493) = -.288$; $p = .774$) or the number of reported SCD domains ($t(493) = .969$; $p = .333$).

Results

Sample descriptive statistics and group differences in demographic, clinical, cognitive, and biomarker data

The 205 included participants (of whom 107 (52.2%) were female) had a mean age of 69 years ($SD = 5.4$) and mean education of 14.7 years ($SD = 2.95$). Demographic, neuropsychological, and clinical characteristics of the sample as well as detailed group differences are shown in Table 1. HC, AD relatives, and SCD patients did not differ with regard to sex, education, MMSE, and word list delayed recall score, although we note SCD patients and AD relatives had slightly worse memory performance. AD relatives were younger than SCD patients and HC, while SCD patients had slightly higher scores in the GDS, which however where in the normal range (GDS < 6) in most cases (97.3%).

The three groups differed significantly in the CSF-Aß42 level and the Aß42/Tau ratio (see Table 1) after adjusting for age. The SCD group had a significantly lower Aß-42 concentration and a significantly lower Aß42/tau ratio relative to the HC group. There was no significant group difference in p-tau-181 level and in t-tau level (see Table 1).

Prevalence and group differences of SCD-plus features and SCD domains

An overview of the prevalence and the group differences in SCD-plus features is given in Table 2. Reported

Table 1 Sample characteristics and group differences in CSF biomarkers

N = 205	Total Sample	HC (*n* = 76)	HC vs. SCD[b]	SCD (*n* = 105)	SCD vs. Rel[b]	Relatives of AD (*n* = 24)	HC vs. Rel[b]	*F* value/chi^2 value[c]
Age (in years, mean, SD)	68.9 (5.4)	68.3 (4.9)	*	70.4 (5.5)	***	64.5 (3.7)	**	14.2***, $p < 0.001$
Sex (female; *n*, %)	107 (52.2)	42 (55.3)		48 (45.7)	*	17 (70.8)		5.4, $p = .07$
Education (in years, mean, SD)	14.7 (2.9)	14.6 (2.8)		15.0 (3.1)		13.6 (2.5)		2.1, $p = .12$
MMSE (mean, SD)	29.26 (0.95)	29.4 (0.9)		29.2 (0.9)		28.9 (1.2)		2.38, $p = .09$
Word list recall (mean, SD)	7.5 (1.7)	7.9 (1.6)		7.3 (1.7)		7.1 (2.2)		2.97, $p = .053$
GDS (mean, SD)	1.27 (1.6)	0.7 (1.3)	***	1.8 (1.8)	**	1.0 (1.5)		13.05***, $p < 0.001$
APOE genotype								
APOE4 genotype of all APOE (*n*, %)	53 (25.9)	15 (21.4)		31 (33.7)		7 (43.8)		4.50, $p = 0.105$
CSF biomarkers[a]								
Aß42 (pg/ml; mean, SD)	768.55 (313.89)	851.80 (301.55)	**	708.64 (316.88)		767.00 (289.93)		4.23*, $p < .05$
Aß42/Tau ratio (mean, SD)	1.15 (0.48)	1.28 (0.47)	**	1.06 (0.49)		1.14 (0.40)		4.02*, $p < .05$
Total Tau (mean, SD)	393.46 (175.63)	384.73 (165.199)		404.506 (195.333)		372.799 (103.895)		0.081, $p = .923$
p-Tau-181 (pg/ml; mean, SD)	51.00 (20.82)	51.22 (18.51)		51.73 (23.94)		46.81 (12.32)		0.94, $p = .940$

Bonferroni adjusted *p* values; *p* value = .05, two-tailed sign
SD standard deviation, *MMSE* Mini-Mental State Examination, *GDS* Geriatric Depression Scale, *HC* Healthy Controls
*Significant results on the $\alpha < .05$ level
**Significant results on the $\alpha < .01$ level
***Significant results on the $\alpha < .001$ level
[a]Tests of CSF biomarkers are adjusted for age
[b]Post hoc *t* tests for continuous and chi^2 tests for categorical variables (sex and APOE4)
[c]*F* values were presented for continuous variables, chi^2 values for categorical variables (sex and APOE4)

Table 2 Prevalence and group differences in SCD-plus features and SCD-I domains

N = 205	Sample					Chi^2/*F* value; *p* value
		Total Sample	HC (*n* = 76)	SCD (*n* = 105)	Relatives of AD (*n* = 24)	
SCD-plus features						
Decline in memory	Yes, *n* (%)	129 (62.9)	20 (26.3)	98 (93.3)	11 (45.8)	88.285***, $p < .001$
	No, *n* (%)	76 (37.1)	56 (73.7)	7 (6.7)	13 (54.2)	
Onset of SCD in any domain within the last 5 years	Yes, *n* (%)	120 (58.5)	24 (44.5)	85 (81.0)	11 (45.8)	46.088***, $p < .001$
	No, *n* (%)	85 (41.5)	52 (68.4)	20 (19.0)	13 (54.2)	
Particular concerns/worries in any domain	Yes, *n* (%)	113 (55.1)	11 (14.5)	95 (90.5)	7 (29.2)	110.351***, $p < .001$
	No, *n* (%)	92 (44.9)	65 (85.5)	10 (9.5)	17 (70.8)	
The feeling of worse performance than others in any domain	Yes, *n* (%)	35 (17.1)	1 (1.3)	31 (29.5)	3 (12.5)	25.179***, $p < .001$
	No, *n* (%)	170 (82.9)	75 (98.7)	74 (70.5)	21 (87.5)	
Confirmation of decline in any domain by an informant[a]	Yes, *n* (%)	81 (39.5)	15 (39.47)	59 (57.84)	7 (43.75)	25.731***, $p < .001$
	No, *n* (%)	124 (60.5)	61 (60.53)	46 (42.16)	17 (56.25)	
Number of fulfilled SCD-plus features	*M (SD)*	2.33 (1.73)	0.9 (1.27)	3.5 (1.08)	1.63 (1.71)	99.81***, $p < .001$
SCD-I domains						
Decline in memory	Yes, *n* (%)	129 (62.9)	20 (26.3)	98 (93.3)	11 (45.8)	88.285***, $p < .001$
	No, *n* (%)	76 (37.1)	56 (73.7)	7 (6.7)	13 (54.2)	
Decline in language	Yes, *n* (%)	127 (62.0)	28 (36.8)	87 (82.9)	12 (50)	41.251***, $p < .001$
	No, *n* (%)	78 (38.0)	48 (63.2)	18 (17.1)	12 (50)	
Decline in attention	Yes, *n* (%)	62 (30.2)	6 (7.9)	49 (46.7)	7 (29.2)	31.430***, $p < .001$
	No, *n* (%)	143 (69.8)	70 (92.1)	56 (53.3)	17 (70.8)	
Decline in planning	Yes, *n* (%)	20 (9.8)	2 (2.6)	22 (21.0)	2 (8.3)	13.827***, $p < .001$
	No, *n* (%)	6 (2.9)	74 (97.4)	83 (79.0)	22 (91.7)	
Decline in other	Yes, *n* (%)	48 (23.5)	5 (6.6)	39 (37.1)	4 (16.7)	24.045***, $p < .001$
	No, *n* (%)	156 (76.1)	71 (93.4)	65 (61.9)	20 (83.3)	
Number of reported SCD domains	*M (SD)*	1.91 (1.47)	0.80 (0.98)	2.81 (1.17)	1.50 (1.44)	70.17***, $p < .001$

*$p < .05$
**$p < .01$
***$p < .001$
[a]This refers to participants reporting a decline in at least one domain including a total of *n* = 156 (76.1%) individuals (HC: *n* = 38 (50%); SCD: *n* = 102 (97.1%); AD relatives *n* = 16 (66.7%))

domains in the total sample are shown in Fig. 1. Out of the 205 individuals, 76.1% reported a cognitive decline in at least one domain, and among those experiencing a decline, 72% also endorsed worries associated with the decline. Most complaints were reported in the memory (n = 129; 62.9%) and language domain (n = 127; 62%).

As expected, due to the inclusion criteria, the three participant groups differed in the endorsement of decline in SCD domains and SCD-plus features (see Table 2). Unsurprisingly, most (93.3%) SCD patients reported a decline in memory, but a sizeable proportion of the other participants also did, although less frequently (HC 26.3%; comparison with SCD, X^2 = 87.26; p < .001; AD relatives 45.8%; comparison with SCD X^2 = 33.65; p < .001). The same pattern was observed for experienced decline in language abilities (SCD = 82.9%, HC = 36.8%, pairwise comparison X^2 = 40.29; p < .001; AD relatives = 50%, pairwise comparison to SCD X^2 = 11.82; p < .001).

The *number of domains with* a reported decline differed significantly across the groups (F(2,202) = 70.17, p < .001). On average, the SCD group mentioned a decline in two domains, while the number of impaired domains was 0.8 in the healthy control group ($p_{\text{(bonf. adj.)}} \leq .001$) and 1.5 in the AD relatives' group ($p_{\text{(bonf. adj.)}} \leq .001$).

Group differences also emerged regarding the reported onset of decline in participants reporting any such decline. Around 80% of SCD patients reported an onset of cognitive worsening (in any domain) within the last 5 years. This was significantly more often than in the HC group (44.5%; X^2 = 44.87; p < .001) and in the AD relatives (45.8%; X^2 = 12.66; p < .001), who more often reported a more distant onset of decline. There was no significant difference between HC and AD relatives (X^2 = 1.63; p = .20).

The feeling of worse performance than others (in any domain) was also most frequently reported in the SCD group (29.5%) compared to healthy controls (1.3%) (X^2 = 24.10; p < .001) and relatives of AD patients (12.5%; X^2 = 2.92; p = .088). AD relatives also reported this slightly more often than HC (X^2 = 5.94; p = .042).

Interestingly, although all HC participants had negated a worrisome cognitive decline during the initial telephone screening, a worrisome decline (in any domain) was reported by 14.5% of HC during the physician-led personal interview. In AD-relatives, where the absence of worrisome cognitive decline was not an exclusion criterion, the prevalence was 29.2%. As expected because of the inclusion criteria, SCD patients reported concerns much more frequently (90.5%) compared to both at-risk groups (SCD vs. HC: X^2 = 104.58; p < .001; SCD vs. AD relatives: X^2 = 44.37; p < .001), which did not differ from each other.

The informant also reported (i.e., confirmed) a decline in at least one domain for the majority (57.8%) of the SCD patients who reported a decline by themselves in at least one domain, while such a confirmation occurred less often in the HC group (39.5%, X^2 = 24.24; p < .001) and in AD relatives (43.8%, X^2 = 5.710; p < .05).

The number of fulfilled SCD-plus features differed highly significantly between the three groups (F(2,202) = 99.807; p < .001). Participants in the SCD group fulfilled more SCD-plus features (M = 3.5) than participants in the HC group (M = 0.93, $p_{\text{(bonf. adj.)}} \leq .001$) and in the AD relatives (M = 1.63, $p_{\text{(bonf. adj.)}} \leq .001$), which also differed from each other ($p_{\text{(bonf. adj.)}} \leq .05$).

Relationship between AD biomarkers and SCD plus features and SCD domains

In the combined sample of all three groups, lower age-adjusted CSF-Aß-42 levels were found in those fulfilling the SCD-plus features *of a decline in memory* (F(1,

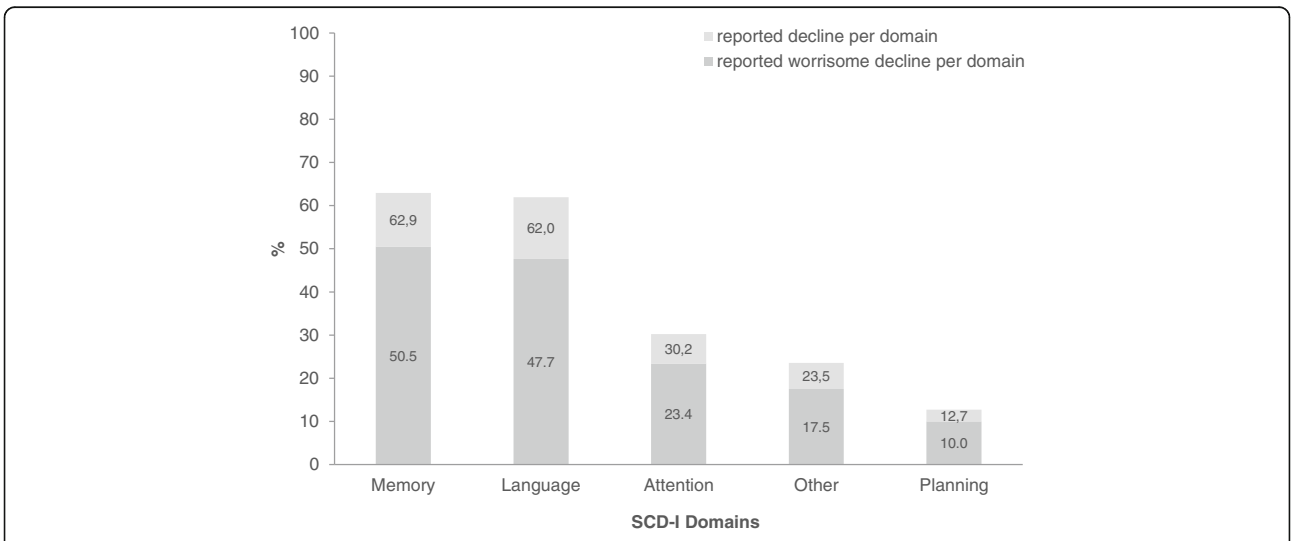

Fig. 1 Frequency of domains reported with an experienced decline and associated worries, respectively

202) = 7.65, $p < .01$, $\eta_p^2 = .036$), *onset within the last 5 years* ($F(1,202) = 6.07$, $p < .05$, $\eta_p^2 = .029$), and the *confirmation by an informant* ($F(1,202) = 4.19$, $p < .05$, $\eta_p^2 = .032$, Table 3). The association of lower CSF-Aß-42 with *worries in any domain* approached significance ($F(1,202) = 3.68$, $p = .056$, $\eta_p^2 = .018$).

Hierarchical linear regression analysis showed that the number of fulfilled SCD-plus features was a significant predictor of a reduced (more pathological) CSF-Aß-42 level ($ß = -.225$, $p < .005$) (Fig. 2) and of a reduced (more pathological) CSF Aß-42/tau-ratio ($ß = -.189$, $p < .01$) independent of age, sex, and education. In contrast, the relationship between the number of fulfilled SCD-plus features and CSF total Tau ($ß = -.055$, $p > .05$) and p-tau-181 ($ß = -.077$, $p > .05$) was not significant.

Using objective memory performance (word list delayed recall) as an additional covariate to control for subtle group deficits in cognition, we found that the SCD-plus score was still a significant predictor, explaining more variance than objective memory performance (as seen by the contribution to R^2 in the prediction model) in CSF-Aß42 and CSF Aß-42/tau ratio (Table 4).

We further observed that participants endorsing a *decline in memory or language* had significantly lower age-adjusted Aß-42 levels than those who did not report a decline in these domains (Table 3). Interestingly, a reported decline in the other domains (which occurred less often than a reported decline in memory and language) was not significantly associated with Aß-42.

The *number of reported domains* with experienced decline was also a significant predictor of lower CSF-Aß42 level ($ß = -.209$, $p < .01$) and lower CSF Aß42/tau-ratio ($ß = -.146$, $p < .05$) after including age, sex, education, and the delayed recall score to the model. For CSF-p-tau18 and total Tau, only age (total Tau $ß = .260$, $p < .001$; p-tau: $ß = .215$, $p < .01$) and delayed recall score

Table 3 Associations between endorsement of SCD-plus features and SCD-I domains with CSF-Aß-42 level

N = 205	CSF-Aß-42 level (pg/ml)						p^a
			M	(SD)	*F*	η_p^2	
SCD-plus features							
Decline in memory	*Yes*	*n* = 129	720	− 316	7.65**	.036	.006
	No	*n* = 76	849	− 293			
Onset of SCD within the last 5 years	*Yes*	*n* = 120	722	− 312	6.07*	.029	.015
	No	*n* = 85	833	− 306			
Particular concerns/worries	*Yes*	*n* = 113	727	− 309	3.68	.018	.056
	No	*n* = 92	819	− 313			
The feeling of worse performance than others	*Yes*	*n* = 35	695	− 308	2.488	.012	.116
	No	*n* = 170	783	− 313			
Confirmation by an informant	*Yes*	*n* = 81	695	− 315	4.19*	.032	.017
	No	*n* = 124	816	− 304			
SCD-I domains							
Decline in memory	*Yes*	*n* = 129	720	− 316	7.65**	.036	.006
	No	*n* = 76	849	− 293			
Decline in language	*Yes*	*n* = 127	727	− 312	5.18*	.025	.024
	No	*n* = 78	835	− 306			
Decline in attention	*Yes*	*n* = 62	738	− 349	.751	.004	.387
	No	*n* = 143	781	− 297			
Decline in planning	*Yes*	*n* = 26	704	− 326	1.049	.005	.307
	No	*n* = 179	777	− 312			
Decline in other	*Yes*	*n* = 48	716	− 302	1.65	.008	.201
	No	*n* = 156	780	− 313			

M mean, *SD* standard deviation
*$p < .05$
**$p < .01$
***$p < .001$
[a]Adjusted for age for the SCD-I domains and for age and education for the SCD-plus features, $\eta_p^2 > .01$ = small effect; $\eta_p^2 > .06$ = average effect; $\eta_p^2 > .14$ = large effect (according to Cohen 1988)

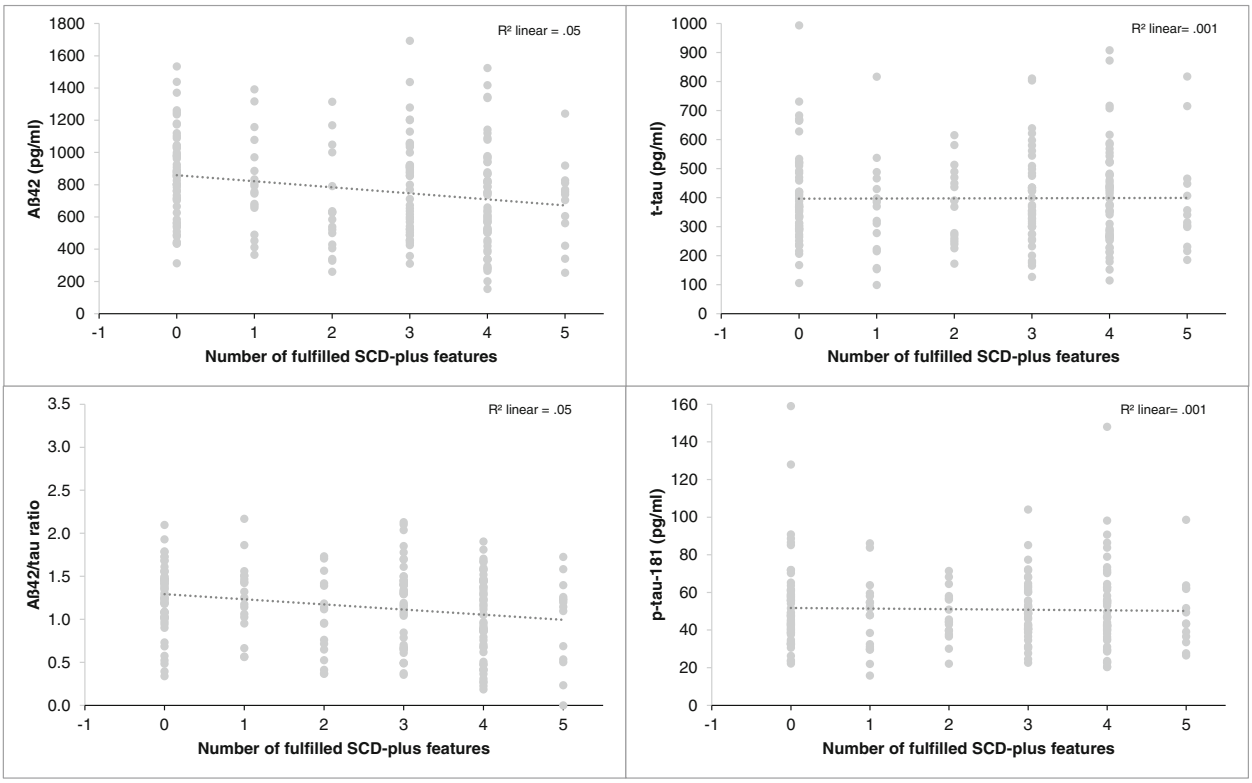

Fig. 2 Relationship between CSF biomarkers and the number of fulfilled SCD-plus features in cognitively normal individuals ($n = 205$)

(total tau: $ß = -.167$, $p < .05$; p-tau: $ß = -.151$, $p < .05$) were significant predictors (Table 4, Fig. 3).

Discussion

In the present study, we demonstrate the feasibility and validity of a short semi-structured interview (SCD-I) designed to capture important aspects of SCD in the context of preclinical AD. In particular, the SCD-I captures all current experiential SCD-plus criteria within a single instrument. We here used the SCD-I to explore the quantitative and qualitative diversity of subjective cognitive decline in cognitively normal subjects at clinical or familial risk for AD, and in cognitively normal controls screened for the absence of either risk. We also established the association of SCD-plus items and of two quantitative SCD-I scores with CSF biomarkers.

Prevalence of SCD domains and SCD-plus features

Across all three groups of these cognitively normal older adults, *memory* and *language* complaints were most frequent while complaints in the domain *planning* were relatively rare with only 10% of participants reporting them. As expected, due to the inclusion criteria, almost all SCD patients reported a decline in one or more cognitive domains within the last years. However, two thirds of the AD relatives and about half of the HC group also endorsed at least some cognitive decline. The latter is in line with community studies reporting prevalence rates from 25 to 50% of memory complaints increasing with age [29]. This indicates that SCD can be caused by other non-AD etiologies including personality traits [30], physiological aging, or the research setting [31], highlighting the need to further investigate the features characterizing SCD in the context of preclinical AD.

A *worrisome cognitive decline* was reported by most of the SCD subjects, again, an expected finding given that a worrisome decline reported during the memory clinic screening was required for inclusion. Interestingly, 29.2% of the AD relatives and even 14.5% of the HC group reported at least one worrisome cognitive decline during the baseline SCD interview. The latter finding was contrary to our expectations since these "control" individuals had negated a question regarding any worrisome self-perceived cognitive decline during the initial telephone screening. Yet, they expressed some concern to the clinician during the SCD interview. In contrast, 10% of the SCD patient group did *not* report worries in the SCD-I although expression of concerns regarding the self-perceived cognitive decline to the physician of the memory clinic at screening was a mandatory inclusion criterion. These discrepancies may be due to several reasons, including temporal instability of measurements

Table 4 Linear regression with the number of fulfilled SCD-plus features and the number of reported SCD domains predicting AD biomarkers

Predictor variables	Dependent variables											
	CSF Aß-42-level (pg/ml)			CSF Aß-42/tau-ratio			CSF-p-tau-181 (pg/ml)			CSF total Tau (pg/ml)		
	B	*SE (B)*	ß	*B*	*SE (B)*	ß	*B*	*SE (B)*	ß	*B*	*SE (B)*	ß
Unadjusted model												
SCD-plus features	R^2 = .054, *F* for change in R^2 = 11.49***			R^2 = .047, *F* for change in R^2 = 10.024***			R^2 = .006. *F* for change in R^2 = 1.139			R^2 = .001. *F* for change in R^2 = .001		
	− 0.059	0.017	− 0.233***	− 0.056	0.019	− 0.217**	− .006	0.016	− 0.028	2.798E−05	0.018	0.000
SCD-I domains	R^2 = .044, *F* for change in R^2 = 9.213**			R^2 = .029, *F* for change in R^2 = 6.015*			R^2 = .006, *F* for change in R^2 = 1.139			R^2 = .003. *F* for change in R^2 = .610		
	− .062	0.020	− 0.209**	− 0.056	0.023	− 0.170*	− 0.020	0.019	− 0.077	− .016	.020	− .055
Covariate-adjusted model (age, sex, education)												
SCD-plus features	R^2 = .076, *F* for change in R^2 = 1.57			R^2 = .110, *F* for change in R^2 = *4.679***			R^2 = .067, *F* for change in R^2 = 4.488**			R^2 = .091. *F* for change in R^2 = 6.548***		
	− 0.057	0.018	− 0.225***	− 0.053	0.022	− 0.189**	− .016	0.016	− 0.074	− 0.011	0.017	− 0.043
SCD-I domains	R^2 = .067, *F* for change in R^2 = 1.64			R^2 = .096, *F* for change in R^2 = 4.953**			R^2 = .075, *F* for change in R^2 = 4.731**			R^2 = .097. *F* for change in R^2 = 6.816***		
	− 0.060	0.020	− 0.203**	− 0.048	0.022	− 0.146*	− 0.030	0.018	− 0.118	− 0.026	0.020	− 0.090
Covariate-adjusted model (age, sex, education, and delayed recall)												
SCD-plus features	R^2 = .109, *F* for change in R^2 = 7.35**			R^2 = .135, *F* for change in R^2 = 5.657*			R^2 = .088, *F* for change in R^2 = 4.298*			R^2 = .115. *F* for change in R^2 = 5.430*		
	− 0.053	0.017	− 0.210**	− 0.050	0.019	− 0.177**	− 1.037	0.863	− 0.083	− 0.014	0.017	− 0.056
Delayed recall	0.048	0.018	0.194**	0.046	0.019	0.167*	− 1.964	.895	− 0.152*	− 0.041	0.017	− 0.166*
	R^2 = .103, *F* for change in R^2 = 7.908**			R^2 = .123, *F* for change in R^2 = 6.040*			R^2 = .095, *F* for change in R^2 = 4.257*			R^2 = .122. *F* for change in R^2 = 5.524*		
SCD-I domains	− 0.057	0.020	− 0.193**	− 0.045	0.022	− 0.138*	− 0.031	0.018	− 0.122	− 0.028	0.020	− 0.098
Delayed recall	0.050	0.018	0.201**	0.048	0.020	0.174*	− 0.033	0.016	− 0.151*	− 0.041	0.017	− 0.167*

Full models are shown in the Additional file 1: Table S1 and Table S2
SE standard error, *B* unstandardized beta, ß standardized beta
*$p < .05$; **$p < .01$; ***$p < .001$

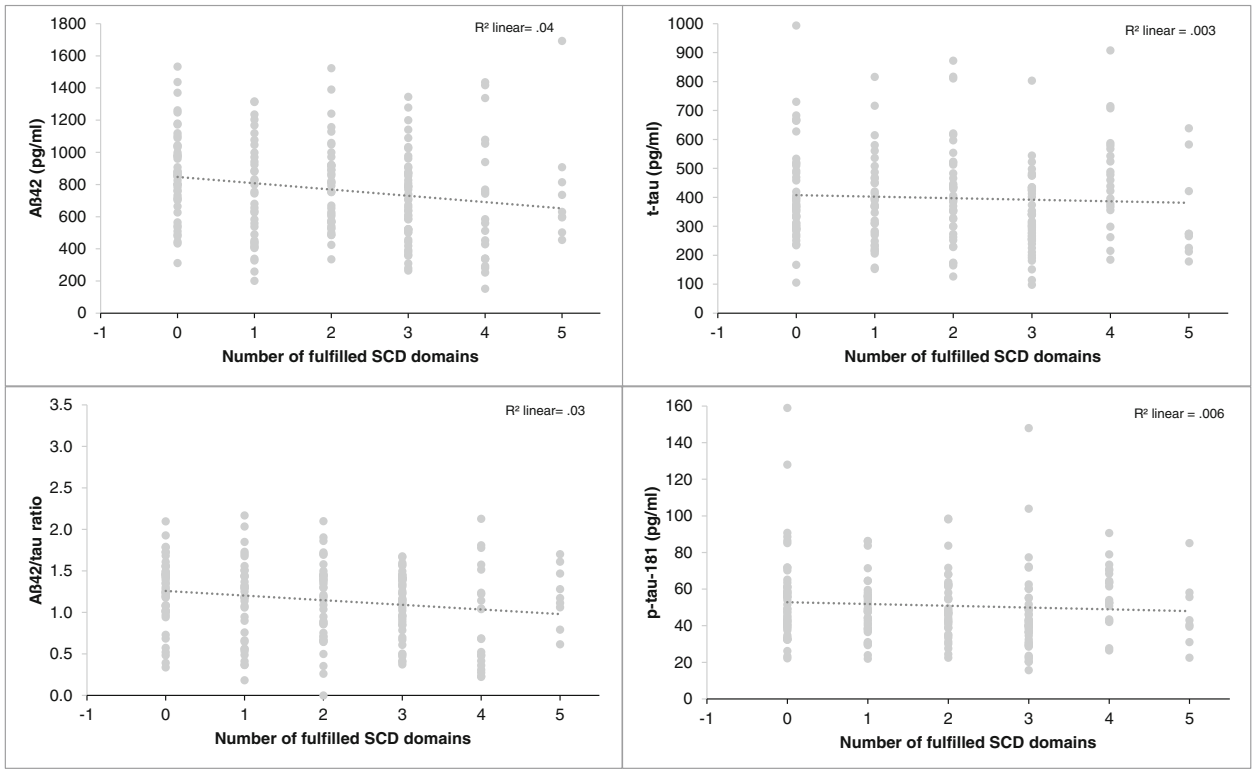

Fig. 3 Relationship between CSF-biomarkers and the number of fulfilled SCD domains in cognitively normal individuals ($n = 205$)

and subjective reports in general, the difference between settings, and possibly an undeclared interest of some healthy volunteers to participate in a study which they imagine to confer some health benefit [32]. Consistency of worries over time has been shown to relate to clinical progression [6] and thus will be an interesting issue for future analyses of longitudinal SCD-I data.

Most SCD participants (81%) reported an onset of a decline *within the last 5 years.* This is perfectly in line with the reported onset in the SCIENCE SCD-cohort, where 83% reported an onset within the last 5 years [33]. Interestingly, those HC and AD relatives who reported any decline frequently indicated a more distant onset. This suggests a different pattern of perceived onset of decline in cognitively unimpaired memory clinic patients.

The SCD-plus feature *performing subjectively worse than others* was reported least frequently, endorsed by 30% of the SCD patients but only by 1% in the healthy control. Finally, the *confirmation of any complaints by an informant* occurred for the majority of SCD participants (58%). Interestingly, 38% of informants of those controls who reported any decline also confirmed an observed decline in at least one domain, as did 44% of the informants of AD relatives endorsing any cognitive decline. Thus, there is a considerable overlap between groups not only regarding any self-reported decline, but also regarding the degree of confirmation by the informants.

Relation of SCD-I items and SCD-I scores with AD CSF biomarkers

In line with the first interim report from the DELCODE study based on a smaller sample [28], we found that SCD participants had lower age-adjusted CSF-Aß42 levels and lower CSF-Aß42/Tau ratios than HC, while the total Tau level and the p-Tau-181 level did not differ between groups.

The SCD-plus sum score and the SCD-I domain score were significantly and specifically associated with measures of amyloid pathology, and to the same extent with a derived amyloid/Tau ratio, but not with p-Tau181 or t-tau level alone. The associations with amyloid are in line with previous studies using either CSF amyloid measures [14, 25] or amyloid PET [16, 34]. Like in the present study, CSF-Tau was not associated with quantitative SCD in the studies of [14, 25]. However, significantly positive associations between quantitative SCD and regional Tau measured with flortaucipir PET have been reported [16, 35]. This discrepancy may be due to the low correlation between CSF Tau and flortaucipir tracer uptake in early disease stages [36].

Three of the suggested SCD-plus features were significantly associated with amyloid pathology: *experienced decline in memory*, *onset of subjective decline within the last 5 years*, and *confirmation by an informant.* The association with worries was almost significant ($p = .056$), which bears mentioning because a recent study with

cognitively normal memory clinic patients [33] and a community-based study [20, 37] also reported an association of worries with amyloid pathology. To our knowledge, only the Amsterdam SCIENCe cohort has tested associations of all SCD-plus criteria with amyloid pathology, using different questionnaires plus some questions similar to those of the SCD-I interview to reflect the criteria. Two studies from this cohort [20, 33], in contrast to our own study, did not find associations with "decline in memory" and "onset within 5 years". Apart from differences in assessment, this may be due to the younger age of the SCIENCe cohort as compared to the DELCODE cohort (64 versus 69 years on average). However, an association of subjective memory decline (e.g., [7]) and cognitive ratings by informants [38] with amyloid pathology has been found before. Our study appears to be the first one directly testing and validating the SCD-plus criterion "onset within the last 5 years".

The biomarker associations of the single SCD domains revealed that perceived decline in the memory and language domain showed the highest associations with AD biomarkers, which is in line with studies suggesting that memory complaints are the best predictor of incident MCI [37] or that memory-related complaints are associated with PIB retention in healthy older adults [7]. However, to our knowledge, this is the first study reporting an association of Aß42 with subjectively experienced decline in the domain of language abilities. This pattern is consistent with the earliest neuropsychological deficits in AD starting with decline in episodic memory followed by deficits in language [39].

We also observed a relationship between objective memory performance and CSF-Aß42 level irrespective of the subjective complaints. While subtle objective cognitive decline can be expected in "late" preclinical AD [40], we showed that subjective cognitive decline is equally and independently predictive of amyloid abnormality in cognitively normal individuals. This extends findings of a previous study which also found an independent association of subjective and objective cognitive performance with CSF-Aß in patients with MCI [25].

Strengths and limitations

The current brief SCD interview has been derived from the assessment routine in memory clinics and standardizes the assessment of those SCD features which are currently considered relevant for assessing suspected preclinical and prodromal AD. Aside from establishing the presence or absence of each of these features, it offers summary measures of quantitative SCD, which in the current study predicted the presence of amyloid pathology.

The SCD-I is a direct operationalization of the SCD-plus criteria and therefore has high content validity. While this is not the only conceivable operationalization, it is one which is frequently used in clinical assessment, e.g., in DSM-based interviews, like the SCID [41], or in questionnaires directly based on diagnostic criteria (like the PHQ-9 [42]). The SCD-I discriminated well between the HC and SCD groups in our study. This is somewhat circular for the items of cognitive decline and related concerns, as these SCD-plus criteria were used for group definition at inclusion. However, also the other SCD-plus items assessed at baseline with the SCD-I markedly differ between the groups. Furthermore, most SCD-I items, and both SCD-I summary scores, were associated with CSF-amyloid, implicating that it captures, to some degree, AD-related cognitive concerns. In sum, this provides a first validation of the SCD-I as a measure for SCD. This does not imply that this assessment method is superior to others, e.g., questionnaire-based methods. For example, the SCD-Q [43] captures many of the SCD-plus items (it lacks the question of comparison with others of the same age, and asks for perceived decline in the last 2 years, rather than 5 years). In an elderly population sample enriched for family history of AD, larger SCD-Q scores were associated with objective cognitive impairment and confirmation of decline by an informant predicted cerebral volume reduction in AD-related brain areas [44]. More data are needed to compare the prediction of the same outcomes by different SCD assessment methods.

One limitation of the present SCD-I is that it directly asks for an experienced or observed decline in five neuropsychological domains, using global and commonly used terms like memory, language, or planning. Whether subjects "correctly" identify their specific problems as being related to one of those domains is unknown. However, subjects can endorse deficits in many domains as opposed to only one or two, and the domain score, like the SCD-plus score, seems to capture SCD severity, as it is related to AD pathology. The SCD domain scores can be calculated for reports of patients and informants alike, so that the difference between both scores could be used to examine the shift from a hyperawareness to hypoawareness of cognitive deficits with the progression of AD [45].

Current research suggests that other specific aspects or higher-order thinking, e.g., self-reports of confusion, are also related to AD pathology in cognitively normal individuals [15]. To identify alternative descriptions of experienced and possibly pathological cognitive change, we have added an open initial question in the SCD-I asking for *any* observed cognitive change during recent years. The recorded answers will be analyzed with the help of qualitative methods [46, 47] and may give rise to the identification of new AD-related SCD features not captured by this first iteration of the SCD-I.

Furthermore, it should be noted that individuals included in the present study were recruited in the

memory clinic (SCD patients) as well as from the community (HC and relatives). Evidence suggests that the active process of seeking medical help due to self-perceived cognitive decline is a factor with potential prognostic value for the presence of AD pathology [12, 13]. Validation of the SCD-I in other samples will be another research goal of the future.

Conclusion

Findings support the use of interview-based approaches for the assessment of AD-related subjective cognitive decline. In this study, detailed questions on perceived decline in different cognitive domain and on the presence/absence of the SCD-plus features were related to AD biomarkers in cognitively normal participants of the DELCODE study. Combining information on perceived decline in multiple cognitive domains and SCD-plus features is useful for prediction of underlying AD pathological change in these individuals. The consistent report of worries/non-worries is possibly an additional SCD-plus feature to be considered in future SCD studies.

Additional file

Additional file 1: Subjective Cognitive Decline Interview (SCD-I). **Table S1.** Linear regression with the number of fulfilled SCD-plus features predicting AD biomarkers. **Table S2.** Linear regression with the number of reported SCD-I domains predicting AD biomarkers. (PDF 137 kb)

Abbreviations

AD: Alzheimer's disease; ANOVA: Analysis of variance; APOE: Apolipoprotein E; Aß: ß-Amyloid; CDR: Clinical Dementia Rating; CDR-SOB: Clinical Dementia Rating-sum of boxes; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CSF: Cerebrospinal fluid; DELCODE: DZNE-Longitudinal Cognitive Impairment and Dementia Study; DZNE: German Centre for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen); eCRF: Electronic case report form; FBB: 18F-Florbetaben; FDG: 18F-Fluordesoxyglucose; fMRI: Functional magnetic resonance imaging; GDS: Geriatric Depression Scale; HC: Healthy controls; ICD-10: International Classification of Diseases; MAC-Q: Memory Assessment Clinic-Questionnaire; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination; MRI: Magnetic resonance imaging; p-Tau-181: Tau phosphorylated at position 181; SCD: Subjective cognitive decline; SCD-I: Subjective cognitive decline interview; SD: Standard deviation; SOP: Standard operation procedure; SPSS-23: Statistical Package for the Social Sciences, 23rd Edition

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Authors' contributions

The following authors contributed to the overall design and implementation of the study: LM, SW, MW, OP, JP, AS, JW, FJ, ED, KB, RP, ST, CL, MW, MH, AR, AS, and NR. The following authors were responsible for the conduction of the study at the respective sites: MW, FJ, FM, ES, KF, CB, DM, CM, CC, IK, MB, AP, FB, LD, KL, JU, SA, PK, DJ, and EI. The following authors were responsible for the methodological core central data management and data analyses: LM, SW, MW, FJ, AS, NR, ED, AS, and KF. All authors contributed to the drafting of the manuscript and approved the final version.

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Availability of data and materials

The data, which support this study, are not publically available, but may be provided upon reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the ethical committees of the medical faculties of all participating sites. These were as follows: The ethical committees of Berlin (Charité, University Medicine), Bonn, Cologne, Göttingen, Magdeburg, Munich (Ludwig-Maximilians-University), Rostock, and Tübingen. The process was led and coordinated by the ethical committee of the medical faculty of the University of Bonn. The registration number of the trial at the ethical committee in Bonn is 117/13. All patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

9. Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

10. List of publications

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Congress posters and lectures

Coraline D. Metzger, Martin Dyrba, Daniel Bittner, Xiaochen Hu, Stefan J. Teipel, Michel J. Grothe, Oliver Peters, **Felix Menne**, Manuel Fuentes, Josef Priller, Eike Spruth, Christiana Franke, Anja Schneider, Klaus Fliessbach, Barbara Kofler, Jens Wiltfang, Claudia Bartels, Katharina Bürger, Cihan Catak, Ingo Kilimann, Christoph Laske, Martina Buchmann, Annika Spottke, Manuela Thelen, Michael T. Heneka, Frederic Brosseron, Alfredo Ramirez, Michael Wagner, Steffen Wolfsgruber, Sandra Roeske, Ingo Frommann, Alexandra Polcher, Laura Dobisch, Frank Jessen, Emrah Düzel, DELCODE consortium. RELATIONSHIP BETWEEN GLOBAL CONNECTIVITY, AMYLOID AND TAU IN DIFFERENT STAGES DURING THE DEVELOPMENT OF ALZHEIMER'S DISEASE AS DEMONSTRATED IN THE DZNE DELCODE COHORT. AAIC Sunday Poster Abstract, Volume 15, ISSUE 7, SUPPLEMENT, P415-P416, July 01, 2019

E.N. Marzban, S. Teipel, S. Altenstein, C. Bartels, F. Brosseron, M. Buchmann, K. Buerger, C. Catak, L. Dobisch, K. Fließbach, M. Heneka, E.I. Incesoy, D. Janowitz, P. Kalbhen, I. Kilimann, C. Laske, S. Li, D. Meiberth, **F. Menne**, C. Metzger, O. Peters, A.A. Polcher, J. Priller, J. Rudolph, A. Schneider, E.J. Spruth, M. Wagner, J. Wiltfang, E. Düzel, F. Jessen, M. Dyrba. "Intuitive visualization for convolutional neural networks detecting brain diseases in MRI scans", Organization for Human Brain Mapping (OHBM), Rome, Italy, 2019.

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Carola G. Schipke, **Felix Menne**, Stefan J. Teipel, Katharina Buerger, Anja Schneider, Josef Priller, Laske Christoph, Jens Wiltfang, Annika Spottke, Michael Heneka, Frederic Brosseron, Michael Wagner, Emrah Düzel, Frank Jessen, Oliver Peters, DELCODE Study Group. LEVELS OF THE ASTROCYTE-DERIVED PROTEINS GFAP AND S100B IN THE CEREBROSPINAL FLUID OF HEALTHY INDIVIDUALS AND ALZHEIMER'S DISEASE PATIENTS AT DIFFERENT DISEASE STAGES. Abstract only. Volume 14, ISSUE 7, SUPPLEMENT, P1458-P1459, July 01, 2018

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