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Functional cognitive disorder in subjective cognitive decline—A 10-year follow-up

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Abstract

Objectives: In memory clinics, patients with significant memory complaints without objective neuropsychological findings are common. They are classified as subjective cognitive decline (SCD) and, as a group, face a heightened risk for future dementia. However, the SCD group is heterogeneous and comprises patients suffering from a somatoform condition, namely functional cognitive disorder (FCD). These patients make up at least 11% of memory clinics' attendees. The aim of this long-term follow-up study was to investigate if patients diagnosed with FCD also face a higher risk of developing dementia.

Methods: Forty-two Patients were recruited at a university hospital memory clinic. FCD was diagnosed according to the Schmidtke criteria (see Table 1). Ten years later, all were invited again. Participants were interviewed, screened for depression and given neuropsychological tests of verbal memory and information processing speed. Cognitive impairment was defined as performance below 1.5 standard deviations (SD) of the age-related mean.

Results: Twenty-eight of 42 patients (67%) took part in this follow-up. The group's mean results in both cognitive measures were stable over time. All individual performances were within 1.5 SD. With 10 patients (24%), brief contact was successful and manifest dementia could be excluded. Four patients (10%) could not be contacted.

Conclusions: In retrospect, the Schmidtke criteria for FCD safely identified memory clinic attendees with SCD who did not proceed to Mild Cognitive Impairment or dementia. None of the patients who could be contacted for this follow-up after a decade (90% of baseline participants) showed signs of dementia.

KEYWORDS
cognitive dysfunction, dementia, memory disorders, neuropsychological tests, somatoform disorders

1 | INTRODUCTION

1.1 | Subjective cognitive decline and functional cognitive disorder

In memory clinics, patients suffering from significant memory complaints but without objective findings in neuropsychological testing are a frequent phenomenon.[1] An international working group defined the term subjective cognitive decline (SCD) for this syndrome.[2] A systematic review investigated diagnoses given in memory clinics—and found mild cognitive impairment (MCI) or dementia in only 67% of the cases. Twenty-four percentage of the patients presenting with cognitive symptoms were classified as SCD without objective cognitive impairment, functional cognitive disorder (FCD) or pseudodementia.[1] The challenge around the concept of SCD is the heterogeneous etiology of cognitive symptoms among these patients and their unknown future course. Some will proceed to develop dementia and others will not. Current literature indicates that annual conversion rates among elderly patients with SCD (mean age around 75 years) to dementia lie around 2.3%, to MCI around 6.6%. Compared to controls without SCD, this corresponds to a relative risk of 2.0.[3,4] Rates differ depending on setting (lower in community-dwelling individuals vs. memory clinic attendees) and age.[5] For younger cohorts of memory clinic attendees with SCD (aged 55–65), there is sparse literature concerning their risk for future dementia. With age as the main risk factor for dementia, there is a low risk in this group, but it is not "zero." Large population based studies found significant prevalence rates of amnestic MCI in this age group of around 7%–10%.[6,7] Thus, memory complaints even in the "younger old" should be taken seriously, although the majority of patients in this age group will not proceed to develop dementia.[5,8–12] The issue is pertinent for patient selection for early intervention studies aiming at disease modification in incipient dementia. To date, there is no biomarker-based diagnostic pathway to differentiate between degenerative, other organic and nonorganic etiologies at the time of first appearance of SCD. Also, there are no established therapeutic measures.[13] Recent research into SCD has focused on the identification of patients at risk for dementia, but patients with non-degenerative etiologies constitute the larger subset. The most common causes for their amnestic complaints are psychiatric and psychological disorders like depression or FCD.[1,14–17] Cognitive complaints in depression are well-described and part of the diagnostic criteria of major depression.[18,19] The etiology of subjective memory impairment in the absence of organic disease hast been discussed in a previous contribution of ours.[20] Patients with FCD represent a relevant proportion of memory clinic attendees. Prevalences differ between institutions and countries from around 11%[20,21] to distinctly higher rates.[22] Patients with FCD suffer substantially from memory-related lapses in their daily life, despite normal neuropsychological test performances. Given the association of this disorder with relevant stress burden and neuroticism, classification of FCD as a somatoform disorder has been suggested.[23,24] Patients with FCD are genuinely concerned about their memory lapses and therefore—from a symptomatological point of view—they mostly qualify for the high-risk

> **Key points**
> - Patients with nonorganic functional cognitive disorders are a frequent phenomenon in memory clinics
> - Functional cognitive disorder (FCD) is an important differential diagnosis in patients with Subjective cognitive decline (SCD)
> - Patients with functional cognitive Ddisorder are not at heightened risk for future dementia—like it is known for patients with SCD
> - The *Schmidtke* criteria for FCD safely identify patients who will not proceed to develop dementia

subgroup of "SCDplus," as defined by the SCD Initiative Working Group.[2] This classification is based on consistent concerns about memory problems and linked to an increased risk to develop MCI later in life.[25] Such facts can lead to a false attribution of neurodegenerative etiology to genuinely functional memory symptoms. In a SCD group who fulfilled FCD criteria, different from the group examined in the present study, no increased incidence of dementia was detected[17]—although these findings are limited through the relatively short follow-up interval of 20 months. The severity of self-reported memory-related symptoms is not instrumental for the prediction of dementia.[26,27] Interactional profiles can help differentiate patients with FCD from those suffering from a manifest neurodegenerative disease as these groups show distinct patterns of communication in neurological encounters.[28,29] They might also be valuable for the challenge of separating FCD from cases of *prodromal* dementia as opposed to MCI or manifest dementia, but have not been validated for this group. The Schmidtke criteria aim to identify patients with functional cognitive symptoms and include a diagnostic tool addressing the specific and characteristic complaints found in patients with FCD.[17]

1.2 | Aims of the study

The aim of the present study was to test the hypothesis that patients diagnosed with a nonorganic memory disorder do not develop dementia over an extended period of time. To this end, we conducted a 10 year follow-up of the FCD cohort that took part in the study published by Metternich et al.[20] Comparable long-term studies investigating the risk of future dementia in patients with FCD have not yet been carried out.

2 | MATERIALS AND METHODS

In 2005 and 2006, our group designed a pilot study investigating the efficacy of a group therapy program for patients with FCD in a randomized controlled trial. The same group was now reassessed.

TABLE 1 Applied FCD criteria of the 2008 study[21]

Inclusion	Exclusion
Performance in neuropsychological memory testing within 1.5 SD of age-related mean	Dementia or MCI
Premorbid intelligence: Estimated IQ ≥ 80	History of early-onset dementia in first-grade relatives
FMD-inventory with score > 5 points	Psychiatric condition with clinical relevance at time of inclusion[a]
Clinical impression of probable FCD (e.g. relevant stress burden)	Neurological condition with clinical relevance at time of inclusion[b]
Age ≤ 69	Medication with influence on memory performance

Abbreviations: FCD, functional cognitive disorder; FMD, funtional memory disorder; IQ, intelligence quotient; MCI, mild cognitive impairment.

[a]Attention deficit hyperactivity disorder (ADHS), post traumatic stress disorder (PTSD), substance-related/addictive disorders, schizophrenia/other psychotic disorder, major depression, bipolar disorder, generalized anxiety disorder, obsessive-compulsive disorder.

[b]Traumatic brain injury, stroke, epilepsy, multiple sclerosis or other relevant neurological conditions in medical history that may affect cognitive performance at time of inclusion.

2.1 | Subjects

Recruitment took place at the Centre for Geriatric Medicine and Gerontology of the University Hospital Freiburg, Germany, in 2005 and 2006. Patients were referrals from general practitioners, neurologists, and psychiatrists. All patients presenting with memory symptoms were screened for inclusion according to the criteria shown in Table 1.

All patients who had completed baseline measures (n = 42) were contacted again for this follow-up in 2016 and invited to an appointment. Contact included a brief letter with information on the follow-up study and a subsequent telephone call by the study physician. In case of refusal to take part in an assessment, we applied the interactional profiles published by Reuber and colleges to these telephone conversations in order to analyze the probability of a potential neurodegenerative disease.[28] For those who consented to take part, assessments included medical and psychiatric history taking, neuropsychological testing, FCD symptom evaluation and screening for depression.

2.2 | Measures

FCD was diagnosed using the funtional memory disorder (FMD) Inventory, a structured interview designed and evaluated by Schmidtke and Metternich.[30] It contains 10 items assessing a range of memory complaints found to be indicative of FCD.[17] Each item/symptom is rated as absent (0 P.), mildly present (0.5 P.), or present (1 P.). The diagnostic cutoff is above 5 P.

All patients underwent neuropsychological testing of declarative memory using the German version of the Auditory Verbal Learning Test (VLMT),[31] where 15 words are presented orally over five trials and the subjects are asked to repeat as many of these words as possible on each trial, followed by a delayed free recall after 30 min. For our analysis of performance in declarative memory, we used delayed free recall.

Information processing speed was assessed using the "Zahlenverbindungstest" (ZVT), a demanding paper-and-pencil digit connection test with four trials, each requiring the test subject to connect the numbers from 1 to 90. Objective cognitive impairment was defined as a performance below 1.5 standard deviations (SD) of the age-related

mean. At baseline, verbal intelligence was estimated using the Mehrfachwahl-Wortschatztest (MWT-B, Lehrl, 2005), a widely used German vocabulary test.

Depression was assessed using the Beck Depression Inventory (BDI), where the cutoff score for clinically relevant depression is defined as >17 points.[32]

2.3 | Analysis

Statistical analysis was performed using SPSS Version 23.0. For the comparison of cognitive performance results on group level, we used paired samples t-test for both raw values and age-adapted percentile ranks (PR). Patients with clinically relevant depression were excluded from this analysis (n = 4). Individual results were controlled for the definition of cognitive decline as mentioned above (within 1.5 SD). Additionally, all individual results were examined for relevant change over time in raw values and age-adapted PR using the reliable change criterion. These individual statistics were performed for all patients.

3 | RESULTS

3.1 | Patient flow

Of 42 patients of the original study, 28 (67%) consented to take part at follow-up. With another 10 (24%) patients contact was successful, but they did not agree to participate. Four (10%) could not be contacted at all, because their addresses were unknown. There were no significant differences in main baseline demographic and memory related variables between participants and drop-outs (see Table 2). The 28 participants were 64 years old on average at the time of follow-up (SD = 7; range = 50–78 years). At follow-up 42% of participants still fulfilled diagnostic criteria for FCD as assessed in the FMD-inventory. This corresponds to a significant reduction ($p = 0.001$).

Four out of the 28 participants were excluded from testing because of a clinically relevant depression (BDI > 17 points). Two participated in a telephone interview only. In one, ZVT testing was

Baseline Data (2006)	Status at follow-up (2016)	N	Mean	SD	Sig. *p*
Age	Participants	28	54.7	6.8	0.80
	Drop-outs	14	55.5	10.4	-
Education	Participants	28	15.2	3.8	0.31
	Drop-outs	14	14.2	2.8	-
MWTB	Participants	28	31.9	3.2	0.95
	Drop-outs	14	32.0	3.5	-
VLMT (delayed recall)	Participants	28	13.0	2.0	0.46
	Drop-outs	14	12.5	2.4	-
ZVT	Participants	28	83.8	18.7	0.75
	Drop-outs	14	81.7	21.4	-
BDI	Participants	28	7.6	4.9	0.85
	Drop-outs	14	7.9	3.8	-
FMD-inventory	Participants	28	7.1	1.0	0.80
	Drop-outs	14	7.2	1.2	-

T A B L E 2 Comparison of baseline demographic variables of participants and drop-outs

Abbreviations: BDI, Beck Depression Inventory; FMD-Inventory, Functional Memory Disorder inventory; MWTB, "Mehrfach-Wortschatz-Intelligenztest B"; VLMT, German version of the AVLT (auditory verbal learning test); ZVT, "Zahlenverbindungstest."

not applicable due to visual impairment. Thus, there were 21 cases for ZVT and 24 for Auditory Verbal Learning Test (AVLT) testing.

3.2 | Cognitive performance

3.2.1 | Auditory Verbal Learning Test

There was no significant change in delayed recall of the AVLT over time (see Table 3). In total, the results at follow-up were above the age-related mean of 10.6 P (SD = 2.9; reference group aged 60–69 years[33]). Furthermore, raw data at baseline and follow-up were transformed into age-adapted PR. There was no significant change over time in these measures (see Table 3). All individual results in delayed recall of AVLT were within the range of 1.5 SD (age-adapted), defined as non-impaired cognitive performance. When comparing individual performances at baseline and follow-up, there was no case of significant change in delayedrecall of the AVLT (according to the reliable change criterion). These results were not altered significantly by the inclusion of the four cases with clinically relevant depression measures.

3.2.2 | Cognitive speed (ZVT)

In cognitive speed testing, the mean age-adapted percentile rank of the group was stable over time (according to the reliable change criterion). There was a significant decline in raw scores over time (see Table 3). All individual results were within the normal range of 1.5 SD (age-adapted), including the four cases that showed a clinically

relevant depression. Among this group of patients excluded due to depression, there was one case of significant change over time from PR 95 to PR 66.

4 | DISCUSSION

Our findings show that SCD patients who fulfill FCD criteria do not face a heightened risk of future development of dementia or MCI within a time period of 10 years. At follow-up, all individual scores remained within 1.5 SD of the age-related means. Group results in cognitive performance measures were stable and above age-related means.

There are some limitations to this study that need to be addressed. First, our cohort was rather young at baseline (mean age 55 years), thus their pretest risk for developing dementia was lower than known for elder SCD cohorts.[3–5] Population based prevalence rates of amnestic MCI in this age group are around 7%–10%.[6,7] But evidence for conversion rates from SCD to MCI/dementia in younger patients is sparse: Few studies focus on these "younger old" (55–65 years), most have small sample sizes and/or follow-up intervals are relatively short. Reisberg and colleagues showed that the follow-up interval needed to detect a later development of MCI/dementia in patients with SCD is rather long.[34] They evaluated MCI/dementia after a mean time of 5.8 years (+/− SD 3.1 years; mean age 68; n = 166). To our knowledge, there are two studies with a sufficient follow-up interval: Hessen and colleagues studied a cohort of 81 memory clinic patients with SCD for 6 years (mean age 61 years). They found annual conversion rates to MCI and dementia of 1.5% and 0.8%, respectively.[8] Eckerström and colleagues followed a cohort partly overlapping to but different from Hessen's cohort (mean age

TABLE 3 T-test for results in neuropsychological measures (raw scores and percentile ranks)

		Mean Age (years)	AVLT (n = 24)		ZVT (n = 21)	
			Mean (SD)	Sig. P two-sided	Mean (SD)	Sig. P two-sided
Raw scores	Baseline	55	13.2 (1.9)	0.90	81.5 s (17.8)	0.04
	Follow-up	64	13.1 (2.2)		88.4 s (25.6)	
Percentile ranks	Baseline	55	78[a] (24)	0.23	83.7[a] (14.4)	0.78
	Follow-up	64	83[b] (22)		84.4[b] (15.5)	

Abbreviations: AVLT, Auditory Verbal Learning Test; ZVT, Zahlenverbindungstest.

[a]according to age norm 51–60 years.

[b]according to age norm 61–70 years.

62 years; n = 122). They found higher annual conversion rates of 6.8% to MCI and 2.1% to dementia.[9] These rates are comparable to those published for elderly SCD cohorts aged around 75 years.[3] There are several studies with shorter follow-up intervals (1.8–3.5 years).[5,10–12] To sum up, annual conversion rates differ strongly among studies: for dementia they vary from 0.6% to 2.1% per year, for MCI from 1.5% to 6.8%.[5,8–12] These rates would translate to 2–5 cases of dementia and 4–14 cases of MCI in our group of 28 SCD patients after 10 years. The fact that we found no such cases at all supports our hypothesis: the Schmidtke criteria safely identified patients with FCD and long-term cognitive stability Functional cognitive symptoms can arise across the whole life span[1] and generalizability of our results to older FCD cohorts is not yet clear. Further research is needed to study long-term cognitive outcome in larger FCD cohorts that include more individuals of older age at baseline.

Second, the relatively small group of 42 patients is a limitation of our study and selection bias may have been a problem. Out of the 42 participants at baseline, 28 (67%) underwent neuropsychological testing for cognitive impairment at follow-up. To minimize the risk of missing cases with dementia in the remaining 14 (33%), we made an effort to contact these individuals. Ten (24%) patients could be contacted, but they did not agree to participate in the follow-up assessment. In all of these 10 cases, narratives indicated an absence of impairment in activities of daily living, which makes manifest dementia very unlikely: Patients explained, for example, they had no time to participate because they were busy traveling, caring for a demented partner or working. Also, the character of communication (e.g., long letter to the study physician, eloquent telephone conversation with the study physician) made an ongoing neurodegenerative process over ten years very unlikely. We applied interactional profiles for differential diagnosis of memory complaints as published by Reuber and colleagues[28] to the telephone protocols. In all cases assessed, we found characteristics typical for FCD. Of course, MCI cannot be safely excluded without neuropsychological testing. Yet, if the initial symptoms had been due to a preprodromal state of dementia, it is very probable this condition would have worsened significantly over the time span of a decade and reached a clinically manifest level[34] To sum up, 38 of 42 patients could be contacted in a way that makes manifest dementia highly unlikely. In contrast, the age-related conversion rates

for SCD patients as mentioned above would translate to 2–7 cases of dementia in a group of 38 SCD patients after 10 years. We found no such case among the 38 contacted patients, making a relevant selection bias unlikely. Only four (10%) out of the 42 original patients could not be contacted at all, because their addresses were unknown. Dementia often forces people to leave their homes and seek care in a safer setting. Thus, cases of dementia among those whom we could not reach are *one* possible explanation. Baseline data were not notably or significantly different in patients and drop-outs, supporting a nonselective response to our follow-up.

Another limitation of this study revolves around the lack of gold standard diagnostic criteria for FCD agreed upon. The definition of this entity is a topic of ongoing discussion. The criteria applied in this study identify a rather "pure" group of FCD patients as they exclude individuals with any objective cognitive deficit or major neurological or psychiatric condition. Several authors suggested a wider definition of FCD, taking into account that functional cognitive symptoms occur frequently in patients with neurological or psychiatric disorders.[35] Thus, the results presented here may not be generalizable to FCD populations with preexisting neurological or psychiatric conditions and a "functional overlay." Furthermore, we excluded all individuals showing cognitive deficits (i.e., below 1.5 SD in neuropsychological tests performed). Along with the above mentioned wider definition of FCD, patients with nonspecific cognitive impairment may be included into the FCD group.[1] There are patients with MCI—due to neurological, toxic or other causes—showing cognitive symptoms inconsistent with their neuropsychological profile that are better explained by a functional genesis, especially when considering a broader picture of psychological factors and individual medical history.[35] Of course, differential diagnosis regarding early stages of neurodegenerative diseases in these cases is a challenge. In contrast, our group of FCD patients showed normal cognitive performance indicating the absence of structural neurological damage. Our aim was to study the long-term outcome of this specific but relevant subgroup with FCD. These patients represent a considerable percentage of memory clinic attendees (i.e., around 11%, see introduction) with a potentially better cognitive prognosis than other subgroups of FCD patients. Correspondingly, Bessi and colleagues studied a large SCD population over 6 years and found that strong performance in neuropsychological testing was associated with low risk for future cognitive decline[36] Another

limitation of the group studied here is that our neuropsychological test protocol was confined to declarative memory and cognitive processing speed. There may be patterns in FCD concerning other cognitive domains we did not include or test for like symptoms regarding selective attention, verbal fluency and so on.

Another potentially confounding influence on cognitive symptoms that warrants consideration is depression. Major depressive disorder can lead to subjective memory symptoms and objective cognitive impairment and therefore was an exclusion criterion for our definition of FCD Our cohort showed slightly elevated depression scores at baseline compared to healthy controls. It did not differ in other measures linked to depression like rumination and automatic negative thoughts (see other publications on this cohort by Metternich and colleagues[20,23,37]). Affective symptoms are common in patients with MCI and dementia as well. Elfgren and colleagues compared psychiatric symptoms in patients with SCD to those with MCI/dementia—after having excluded all patients diagnosed with a major psychiatric disorder like depression. They found no significant differences between these groups concerning depressed mood.[10]

Overall, this follow-up study did not find any indications that patients presenting with SCD and an additional diagnosis of FCD face an increased risk for future MCI or dementia. In the last decade, increased scientific and clinical effort have been directed at the early diagnosis of preclinical stages of dementia among patients with SCD.[1,38,39] Patients suffering from the somatoform disorder FCD may be wrongly assigned to a group facing an elevated risk of future dementia—an issue also highlighted by Mc Whirter and colleagues in their systematic review addressing FCDs.[1] Patients with FCD often fear their memory lapses are due to a neurodegenerative process. Such a false assignment to a high-risk group may aggravate their symptoms and worsen the situation. Thus, it is relevant to differentiate safely between FCD and dementia-risk-patients among those presenting with SCD.

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CONFLICTS OF INTEREST STATEMENT

The authors of this article certify that they have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS COMMITTEE APPROVAL

The study reported on in this manuscript was approved by the ethics committee of the University Hospital Freiburg, Germany.

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