False Recognition Correlates with Amyloid- β_{1-42} but not with Total Tau in Cerebrospinal Fluid of Patients with Dementia and Mild Cognitive Impairment

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Abstract. Severe memory impairment forms the core symptom of Alzheimer's disease (AD), which is present early in the disease course. Recent studies show that AD patients not only suffer from forgetfulness, but also differ in their response bias, when having to decide whether information has been perceived recently, or whether it is only familiar or semantically related to perceived information. Changes in total tau-protein and amyloid- β ($A\beta$)₁₋₄₂ concentration in cerebrospinal fluid are also features of AD, and they predict conversion from mild cognitive impairment to dementia. In this study we correlated recognition scores with total tau and $A\beta$ ₁₋₄₂ concentrations in patients with suggested dementia. We studied 40 patients and 21 healthy controls, using an incidental recognition memory task and a neuropsychological test battery. False recognition scores correlated with delayed recall and with $A\beta$ ₁₋₄₂, and $A\beta$ ₁₋₄₂ tended to correlate with delayed recall. Total tau, however, did not correlate with memory scores or with neuropsychological performance in general. We suggest that $A\beta$ ₁₋₄₂ may indicate a reduction in the specificity of the neuronal response in the limbic cortex, due to agglomeration of plaques. This process might be more specific for AD than the increase of tau, and therefore it is stronger correlated with recognition errors.

Keywords: Amyloid- β_{1-42} , dementia, false recognition, memory, total tau

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia and the risk of AD is rising, due to increasing life expectancy. The earliest and core symptom of AD is an episodic memory deficit, which starts to aggravate during the preclinical period [1], and is accompanied by increasingly severe disturbances in language, attention, executive functions, and mood in later phases of the disease [2,3]. More specifically, AD is

characterized by impairment in delayed recall, and several studies have shown that this impairment is a sensitive and partly specific feature for patients converting from mild cognitive impairment to AD [4–7]. Therefore, neuropsychological assessment of AD in an early phase crucially depends on learning tests and on recall of to-be-learned information after a delay or following interfering information [8–10].

Recently, it has been argued that a bias to accept seemingly familiar information as actually perceived or learned might be another specific feature of the memory impairment in AD. Typically, AD patients tend to produce more false positives on recognition tests as controls, especially in response to pictures showing high frequent and meaningful objects [11–15]. They seem

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to base their decision, whether an item has been presented before, not so much on recollection of that item, but rather on a feeling of familiarity. Consequently, they accept semantically related items as target items on recognition tests. This increase in false positives has also been found in clinical studies using the California Verbal Learning Test [16–18], which contains semantically related lures in the recognition part.

Several explanations for this increase of intrusions in AD have been proposed [15]. It might be a consequence of a generally more liberal response bias, a tendency to accept all information as learned information. It might also be a consequence of the episodic memory impairment, in which the feeling of familiarity remains as the primary basis for recognition, while recollection is disturbed. The increase in recognition errors thus indicates something like a compensation of the reproduction deficit itself. And, as a third explanation, encoding of item specific information, rather than the gist (of the general semantic features), might be specifically impaired in AD. Consequently, during recognition, AD patients may base their decisions on gist information and judge semantically related information as correct. Although it is not clear which explanation is valid, the finding of a high number of false positives in AD is generally accepted [15].

Numerous studies have confirmed the decrease of amyloid- β_{1-42} ($A\beta_{1-42}$) and the increase of tau in cerebrospinal fluid (CSF) in AD patients, and recent reviews argue for a sensitivity and specificity of about 80% for each of these CSF markers in AD [19–24]. The underlying neuropathological changes in AD include degeneration of neurons and synapses in defined regions of the brain and the formation of senile plaques and neurofibrillary changes. Braak and colleagues [26, 27] have shown in postmortem studies that the concentration of senile plaques and neurofibrillary tangles with intracellular tau proteins follows a more or less fixed pathway, starting in the hippocampal and entorhinal cortex, and spreading over the temporal cortex to secondary and tertiary association areas. This origin in the hippocampal and entorhinal cortex may be the common cause of decrease of $A\beta_{1-42}$ and increase of total tau in the CSF and of deficits in memory performance as the first sign of a beginning AD. Senile plaques consist of a protein core in which the main protein is $A\beta_{1-42}$. It has been argued that this is the reason why $A\beta_{1-42}$ is reduced in the CSF of AD patients [28–30].

The $A\beta$ theory of AD further states that the increase of senile plaques leads to neuronal stress and cell death, which in turn leads to higher extracellular

concentration of tau proteins, and thus to an increase of tau in the CSF [28]. However, tau regulates intracellular traffic of vesicles and it inhibits transport of amyloid- β protein precursor ($A\beta$ PP) into neuronal extensions, which leads to accumulation of $A\beta$ PP in the cell body [31]. One might speculate that this mechanism plays a role in β - and γ -secretase of $A\beta$ PP into $A\beta_{1-42}$ and therefore might lead to agglomeration in plaques. On the other hand, many neurodegenerative diseases, like, for instance, frontotemporal dementia and dementia of Parkinson's disease, show an elevated level of total tau, but no production of $A\beta_{1-42}$ deposits [28]. Therefore, extracellular tau is not a causal factor for agglomeration of plaques. Hence, the definite link between cell death and total tau concentration in the CSF remains unclear. Irrespective of these considerations, numerous studies have confirmed the decrease of $A\beta_{1-42}$ and the increase of tau in AD patients, and recent reviews argue for a sensitivity and specificity of about 80% for each of these liquor markers in AD [32–34].

Surprisingly, the correlation of these CSF markers with neuropsychological tests has not been studied extensively. If any, these studies found significant correlations with total tau concentration, but not with $A\beta_{1-42}$ [20,33,35,36]. Stomrud et al. [37], being an exception to this rule, reported that in elderly people low levels of $A\beta_{1-42}$ correlate with subjective memory complaints, and it predicts the decline of Mini Mental Status Examination (MMSE) score three years later. A similar prediction of faster conversion to AD in mild cognitive impaired (MCI) patients with low concentration of $A\beta_{1-42}$ in CSF has also been reported [20].

The few studies, that have been published, relied on rather unsophisticated cognitive tests, like the MMSE [33,35–37] (for an exception [20]). This instrument yields a composite score of cognitive impairment and entails only one episodic memory test (testing short-delayed free recall of three words), using a single learning presentation. Moreover, it provides only a global score for classifying patients into groups with a weak, moderate or severe dementia. Therefore, the MMSE is neither sensitive, nor specific for detecting memory deficits in individuals with MCI or early stages of AD. Nevertheless, the lack of correlation is surprising because CSF markers have a moderate to high sensitivity and specificity for AD, predict conversion from preclinical impairment to dementia and neuropsychological screening of dementia often relies on the MMSE.

In this study, we analyzed memory performance and the correlation with total tau and $A\beta_{1-42}$ in the CSF

of patients, who had been admitted to the neurological department of our hospital with different neurological symptoms, but they all had a common subjective complaint of cognitive (memory) decline or a report of cognitive deficits by relatives. The reason for inclusion of patients with different forms of dementia was to ensure that variation in the CSF concentration of tau and A β_{1-42} was large enough to find a differential correlation with omissions and false positives in recognition. We developed an easy and short test, based on incidental learning, for provoking recognition errors. Following Budson and colleagues [11–14], we postulated that an increase of false positives is a specific feature of the memory impairment in AD, and it should correlate with CSF markers.

MATERIALS AND METHODS

Patients

We examined 40 patients, admitted over the last two years to the neurological department of the Hospital Bremen-Ost for cognitive, and partly for additional motor impairments. See for demographic details Table 1. Patients with definite other causes for their impairment, like inflammation or acute stroke, were excluded from the study. The clinical diagnosis recorded was based on best clinical judgment using the diagnostic criteria of ICD 10, but blind with respect to the results of experimental recognition testing (see below).

Four patients were cognitively unimpaired (based on an MMSE score higher than 28), 13 patients showed a mild cognitive impairment (MMSE range 25–28), 15 mild dementia (MMSE range 18–24), 7 moderate dementia (MMSE range 10–17), and 1 patient severe dementia (MMSE = 8). The final diagnosis was for 11 patients probable AD, for 14 patients preclinical AD or MCI, for 9 patients dementia, but not necessarily AD (vascular dementia or frontotemporal dementia were discussed as alternative diagnosis), and for the remaining 6 patients either normal pressure hydrocephalus, vascular dementia or frontotemporal dementia. According to the criteria for MCI [38], 10 of the MCI patients were of the amnesic type, 3 of a multi-domain type and 1 of a non-amnesic type.

Twenty-one healthy control subjects were recruited and they received the same neuropsychological tests as the patients (but no neurological examination and no lumbar puncture). Controls were contacted in various forms, for example, by asking relatives of patients,

hand-outs in meetings of elderly people and by contacting friends of parents. The project was approved by the Ethics committee of the University of Oldenburg, and all subjects gave informed consent to participate in the project.

Investigation of false recognition

Participants were presented 16 pictures from the Snodgrass & Vanderwart series [39] and they were asked to name them. They were not informed that they would be asked to recognize them later. After 15 minutes, the recognition test was presented, consisting of 24 trials. We used the Beck-Depressions-Inventory (BDI) [40] and the *Zahlenverbindungstest* [41] as filler tests for the period between the presentation of the pictures and the recognition task.

In the recognition task, on each trial, 3 different pictures were shown simultaneously. The three pictures were semantically related to each other (pictures of similar animals, similar furniture, etc.). On 8 trials, only new pictures were shown; on 16 trials an ‘old’ picture was shown, together with 2 distractors. The participants were asked to indicate whether they had seen one of these before, and if so, which picture, by pointing to it or naming it. If they decided incorrectly that none of the three pictures had been presented before, we counted this as an omission. If they pointed to a picture that had not been shown before, we counted this as a false positive. We used the number of omissions as indication of increased forgetting and the number of false positive errors as indication of false recognition.

Neuropsychological investigation

All patients underwent a neuropsychological examination, including the CERAD test series [42], which is composed of the MMSE, a 15-item short version of the Boston Naming Test, semantic word fluency test for animals (one minute), word list learning (10 words, three trials), word list recall after distraction, word list recognition (10 target and 10 distractor words), figure copying and delayed figure recall.

To explore language functioning even further, we used first-letter fluency from the *Leistungsprüfsystem* 50+ (Performance test) [43], which is a German version of the FAS test, comprising the generation of words with three different first letters, each for one minute. The *Mehrfachwahl-Wortschatz-Intelligenztest* (Multiple Choice Vocabulary Intelligence Test) [44] was performed as a measure for extent of and access to the vo-

Table 1
Demographic data, CSF marker, results from the recognition task

	Patient group		Controls	
	40		21	
Male/female	24/16		11/10	
	Mean	SD	Mean	SD
Age	69.4	8.6	66.1	13.1
Education in years	13.0	3.0	13.5	4.1
Mini Mental Status Examination**	22.1	6	29.5	1
Total tau	407.5	250.1	—	—
Amyloid- β_{1-42}	706.8	340.2	—	—
Recognition task – omissions**	2.7	2.5	0.3	0.5
Recognition task – false positives**	2.4	2.4	0.3	0.5

** $p < 0.01$

cabulary. To assess attention performance, we used the *Zahlenverbindungstest* of the NAI [41], which is similar to the Trail Making Test A. Participants have to follow numbers from 1 to 30 and to connect them by drawing a line. We used digit span forwards and backwards from the Wechsler Memory Scale (revised) [45] to investigate verbal working memory performance. The Beck's Depression Inventory [40] was used to investigate mood and depression.

Neurological investigation

The standard diagnostic examination protocol included medical history, physical and neurological examination, laboratory testing, brain imaging, electroencephalography (EEG) and a lumbar puncture.

The extensive blood sample analysis included blood count, erythrocyte sedimentation rate, electrolytes (sodium, potassium, chloride), creatine, urea, transaminases, blood glucose, TSH, C-reactive protein, vitamin B 12, folic acid. Optional further blood analyses included vitamins, TPPA, immunological parameter, HIV, copper metabolism, etc. An MRI/CT scan was performed for every patient to exclude other causes for cognitive impairment like strokes, tumors or inflammatory diseases.

Determination of tau protein and A β_{1-42} in CSF

Lumbar punctures were performed between lumbar vertebral body 4 and 5, by a trained neurologist, using a 22-gauge Sprotte spinal needle. Approximately 5 ml CSF was collected in polypropylene tubes and transported to an adjacent laboratory within 30 min. CSF samples were analyzed for cell count, total protein, lactate, glucose, IgG, IgA, IgM, Borrelia antibodies, A β_{1-42} and total tau. Except the specimen for the cell count, some CSF was briefly centrifuged

at low speed (4000 rpm for 7 minutes) to pellet any cellular elements, stored at a temperature of 4°C (unfrozen) and analyzed within 7 days. CSF total tau and A β_{1-42} were determined quantitatively using commercial sandwich enzyme-linked immunosorbent assays (Innotest® hTAU-Ag, Innotest® A β_{1-42} , Innogenetics, Ghent, Belgium). All tests of A β_{1-42} and total tau were performed at the Medizinisches Labor Bremen (Dr. A. Gerritzen) according to the recommendations of the manufacturer Innogenetics.

Statistical evaluation

As expected, the number of false positives and omissions was low in the control subjects and also in some of the patients. Consequently, the distribution of the recognition scores was skewed, and we used the non-parametric Spearman rank correlation for correlating cognitive scores to the CSF-markers. Group differences in memory scores were tested with the Mann-Whitney U-Test.

RESULTS

Demographic data

There were no significant differences in age, gender and education between the patients and the healthy controls.

CSF and recognition tests

Total Tau was, on average, 407.5 ng/l, A β_{1-42} 706.8 ng/l, but clearly there was a wide range for both variables (see Table 1).

Patients omitted, on average, 2.7 items and produced 2.4 false positives. Compared to the performance of the

healthy control group, both results deviate significantly at $p < 0.001$ on the Mann-Whitney U-Test. The z-score for omitted items was -5.13 , that of false positives was -4.48 .

Neuropsychological testing

Patients' mean performance on each of the neuropsychological tests was at least one standard deviation below that of the healthy control group. Mann Whitney U-tests revealed a significant $p < 0.001$ for all tests, except word list Savings CERAD-NP and digit span forward, where $p < 0.05$, and for intrusions from wordlist learning of the CERAD-NP, which did not differ significantly between groups.

Correlational analysis

No significant correlation was found between total tau and $A\beta_{1-42}$ [r : -0.111 , $p = 0.495$]. Also, no correlation was found between total Tau, age, education, BDI and any of the neuropsychological scores. $A\beta_{1-42}$ correlated significantly with the number of false positives in the experimental recognition test [r : -0.434 , $p = 0.005$], but not with omissions. The correlation between $A\beta_{1-42}$ and number of recalled items from the Wordlist of the CERAD-NP was also significant [r : 0.354 , $p = 0.032$], and also for the savings of word list recall [r : 0.344 , $p = 0.04$], for the number of recalled figures from the figure drawing task [r : 0.359 , $p = 0.029$] and savings from figure drawing recall [r : 0.374 , $p = 0.023$]. Moreover, $A\beta_{1-42}$ correlated significantly with processing time from the *Zahlenverbindungstest* [r : -0.463 , $p = 0.007$]. An exploratory analysis with Pearson's parametric correlation test did not yield other results.

To analyze the meaning of $A\beta_{1-42}$ in more detail, we used a split-half method dividing the patient group in patients with a relatively low and patients with a high $A\beta_{1-42}$ concentration. Patients with a low concentration (average $A\beta_{1-42}$ concentration of 386.2 ng/l) produced 3.0 omissions and 3.3 false positives. Patients with a high concentration (average $A\beta_{1-42}$ concentration of 964.6 ng/l) produced 2.3 omissions and 1.4 false positives. The difference for false positive errors but not for omissions is significant (z : -2.360 , $p = 0.02$). The patient groups also differ in figure copying savings [z : -2.227 , $p = 0.029$] and in attention/psychomotor speed [z : -2.187 , $p = 0.029$].

The number of omissions in the recognition task was correlated with several scores from the neuropsychological

battery (see Table 2). Interestingly, omissions were not correlated with word list recall of the CERAD-NP, but a significant correlation was found with attention (*Zahlenverbindungstest*), digit span backwards and copying performance of the CERAD-NP. On the other hand, false positives in the recognition task did correlate with word list learning, word list delayed recall and word list savings, i.e., with memory tasks and not with executive tasks.

Analysis of sub-groups

As mentioned the clinical diagnosis was probable AD for 11 patients, preclinical AD or mild cognitive impairment for 14 patients, dementia, but not necessarily AD for 9 patients, and for the remaining 6 patients either normal pressure hydrocephalus, vascular dementia or frontotemporal dementia. Furthermore, to examine the impact of different clinical diagnoses on our results, we compiled three groups: patients with probable AD, MCI patients and all other patients (not AD dementia patients). Note that the inclusion of all not probable AD patients into one group of not AD dementia was done to have a reasonable group size, but at the same time might have led to the inclusion of AD patients in the not AD group.

The three groups did not differ significantly from each other on tau and $A\beta_{1-42}$ (probably because of the small number of patients per group), although probable AD patients documented in absolute terms clearly decreased level of $A\beta_{1-42}$ (see Table 3). There were also no significant correlations between false errors, omissions and $A\beta_{1-42}$ or tau in the single subgroups.

Comparing patients with probable AD and patients with no definite indication for AD, the false positives in recognition were significantly increased in AD patients [z : -2.16 , $p = 0.035$], but not the number of omissions. Probable AD patients differed in false positive from MCI patients [z : -2.031 , $p = 0.044$], and in omitted items [z : -2.080 , $p = 0.044$]. MCI patients omitted significantly fewer items than patients with no definite indication for AD [z : -2.576 , $p = 0.012$], but there was no difference in false positives.

DISCUSSION

In this study, we concentrated on the question whether recognition errors correlate with total tau or $A\beta_{1-42}$. Forty patients were recruited from our neurological department with different diagnoses, but pri-

Table 2
Rank correlation of omissions and false positives of the cognition task with neuropsychological test results

	Recognition task			
	Omissions		False positives	
Neuropsychological test results etc.	Spearman r	p	Spearman r	p
Recognition – false positives	0.307	0.054		
Age	0.230	0.153	0.156	0.335
MMSE	–0.336	0.042	–0.349	0.034
Zahlen-Verbindungs-Test	0.412	0.017	0.327	0.063
Digit span backwards	–0.363	0.030	–0.091	0.597
CERAD-NP				
Wordlist learning	–0.346	0.036	–0.451	0.005
Wordlist recall	–0.253	0.131	–0.485	0.002
Wordlist savings	–0.174	0.311	–0.363	0.03
Copying performance	–0.407	0.012	0.066	0.696

Only test scores with at least one significant correlation are shown. Figures in bold and italics indicate correlations that are only significant for either omissions or errors.

Table 3
Subgroup characteristics

	Probable AD		Not AD dementia		MCI		Group differences
N	11		14		15		
	Mean	SD	Mean	SD	Mean	SD	
Age	68.5	11.0	72.1	5.0	67.8	9.0	ns
MMSE	16.7	5.5	21.4	3.9	26.1	2.9	pAD < NpAD < MCI
Tau	444.0	163.9	358.1	235.1	422.5	311.8	ns
A β	592.6	299.9	699.7	265.5	791.1	409.0	ns
Recognition – omissions	3.2	2.5	3.7	3.1	1.4	1.3	pAD = NpAD < MCI
Recognition false positives	3.5	2.4	1.6	1.6	2.1	2.8	pAD < NpAD = MCI

Abbreviations: AD = Alzheimer's disease, MCI = Mild cognitive impairment, MMSE = Mini Mental State Examination, SD = Standard deviation, pAD = Probable AD, NpAD = Not probable AD dementia.

Fig. 1. Patients with high level concentration of A β_{1-42} did not differ from patient with low level concentration of A β_{1-42} in omissions but in false positives of the recognition task. Both groups differed from healthy controls in either omissions and in false positives.

marily with deficits in memory and concentration, reported by themselves or by their relatives. Most patients fulfilled the criteria of a preclinical AD, actually classified as mild cognitively impaired, or they received a diagnosis of a dementia with unclear aetiology (ICD-10: F03). The heterogeneity of the final diagnoses of our patients reflects the heterogeneity of patients admitted to a neurological department for complaints about cognitive functioning.

A β_{1-42} and total tau did not correlate in our patient group. This may be a consequence of the small number of patients. Unfortunately, most of the studies [23,37, 46] on liquor marker in AD do not report on the correlation between these markers. One exception is the study of Sunderland et al. [36], who investigated 131 patients with AD and 72 controls. They found a correlation of 0.3 between A β_{1-42} and total tau, which is a weak to moderate correlation. Interestingly, a separate analysis

of the AD patients and the controls showed that only in the controls the correlation was significant. In the AD patients the correlation was -0.08 , which is near to zero. We conclude that total tau and $A\beta_{1-42}$ measure neuropathological changes, that are not closely linked to each other, at least not in time. Hence, in principle, deficits in different neuropsychological processes may be associated with either an increase of total tau or a decrease of $A\beta_{1-42}$ in the CSF, although both indicate a neurodegenerative process resulting in global cognitive decline and in dementia.

As far as we know, this is the first study reporting a relation of cognitive performance with $A\beta_{1-42}$, but not with total tau in the CSF. Even more interestingly, these correlations concerned primarily recognition errors. This suggests that false recognition is sensitive to neuropathological processes particularly associated to a decrease of $A\beta_{1-42}$ in CSF. Dividing the group of patients in patients with high levels of $A\beta_{1-42}$ and patients with low levels, revealed two groups with either a normal level or with a level, which is indicative for AD (less than half of the level of the group with high level of $A\beta_{1-42}$, as defined by Blennow [34], and also below a level of 400 ng/l as found by De Jong and colleagues [22]). The group with a low level of $A\beta_{1-42}$ differed from the group with a normal level of $A\beta_{1-42}$ concentration in false positives but not in omissions. Splitting up the patients into subgroups with different clinical diagnoses corroborated this result, because patients with probable AD differed from non-AD patients and MCIs in false positives, but not in omissions.

The number of omissions on the recognition test correlates with neuropsychological test scores like attention digit span backwards and copying performance from CERAD-NP, indicating that this variable measures decline of cognitive functions related to executive functions rather than memory. False positives in the recognition task, on the other hand, were correlated with word list learning, word list recall, and word list saving (all from the CERAD-NP). These scores concern quite specifically memory, and they are known to be particularly predictive for medio-temporal lobe pathology and also for predicting Alzheimer dementia [1,5,16]. Moreover, intrusions of CERAD word list learning did not correlate with false positives from the recognition task, and also neither with $A\beta_{1-42}$. This pattern of correlations suggests that two different mechanisms causing errors may be distinguished and that would argue against a globally increased liberal response bias as an explanation for the higher number of false recognitions in AD.

Schacter and Slotnick [47] related the fact that some disorders result in a bias of relying on a feeling of familiarity rather than on recollection of an episode during recognition, to hippocampal pathology. This pathology, presumably, forces subjects to use non-hippocampal structures for remembering events. The crucial significance of the hippocampus for item-specific recall ("recollection") has been shown in patients with short hypoxic episodes and isolated hippocampal lesions, but also in fMRI-studies in healthy controls [48,49]. The specific role cortical structures play in familiarity judgment is still not fully understood, and there is a debate about whether secondary and tertiary association areas of the temporal, parietal and occipital lobe or the entorhinal cortex contribute to this process. What than may be the explanation for the fact that $A\beta_{1-42}$, and not total tau, correlated with false positives in the recognition test? One may speculate that the accumulation of plaques, adjacent to axons and dendrites of the limbic system, *diminish the specificity of neuronal responses*, leaving the general ability to respond intact [29,30]. In this case, differential processing of information content is eliminated, while only the "general message" of the information is stored or can be retrieved [28]. Tau pathology, on the other hand, may reflect functional cell loss due to $A\beta_{1-42}$ aggregation [29,30]. As an indication of cell *destruction*, tau may be related to a complete lack of retrieval and not of degradation of fine-grained information storage and retrieval. Such an interpretation would explain the closer association between total tau, the MMSE and the ADAS-cog reported in the literature [20,31,33,37], compared to $A\beta_{1-42}$, because the MMSE and ADAS-cog measure global cognitive impairment. In our study, this rather weak correlation might not have shown up, because of the relatively small number of patients. On the other hand, the decrease of specificity of axonal and dendrite processing starts earlier and is concentrated in the limbic system. Therefore, the relation between recognition errors and $A\beta_{1-42}$ might be close enough to become significant already in a small group of patients. This specific relation might also explain why decrease of $A\beta_{1-42}$ in CSF correlates with subjective memory complaints [37], and also with decreased recall performance (Table 2). Moreover, in the PET ligand study of Pike and colleagues [50], memory impairment was associated with enhancement of radiotracer in $A\beta_{1-42}$ plaques, especially in the early stages of AD, i.e., in MCI patients, but not in the later stages. This points in the same directions as the explanation described above.

Clearly, this is somewhat speculative, and only future studies can show, whether this line of reasoning is

correct. For example, longitudinal studies of memory performance and tau and $A\beta_{1-42}$ concentration will be necessary to corroborate the findings. Such longitudinal studies would also be helpful to decide whether there are different time courses in CSF changes (for example, early decrease of $A\beta_{1-42}$ and later increases of tau). Our study used a cross-sectional design, which is of limited value to investigate causal relations between functional impairment and neurodegenerative processes. But from a clinical point of view, it seems to be important to note that the close link between $A\beta_{1-42}$ and recognition errors may enable us to screen patients for a specific neurodegenerative process in an early stage. Moreover, it would enable us to identify patients at risk with a fast, easily applicable and cheap instrument, namely a recognition test eliciting false positives, which may then be assessed with lumbar puncture, to verify the indication from the cognitive evaluation. But only future studies, including more subjects with primarily a diagnosis of probable AD, will be able to answer whether such a goal can be achieved.

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