Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease

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ABSTRACT

Objective: To compare cued recall measures with other memory and nonmemory tests regarding their association with a biomarker profile indicative of Alzheimer disease (AD) in CSF among patients with mild cognitive impairment (MCI).

Methods: Data were obtained by the German Dementia Competence Network. A total of 185 memory clinic patients fulfilling broad criteria for MCI (1 SD deficit in memory tests or in nonmemory tests) were assessed with an extended neuropsychological battery, which included the Free and Cued Selective Reminding Test (FCSRT), the word list learning task from the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD-NP), and the Logical Memory (LM) paragraph recall test from the Wechsler Memory Scale–Revised. CSF was obtained from all patients.

Results: A total of 74 out of 185 subjects with MCI (40%) had a CSF profile consistent with AD ($A\beta_{1-42}$/tau ratio; CSF AD+ group). FCSRT measures reflecting both free and cued recall discriminated best between CSF AD+ and CSF AD− patients, and significantly improved CSF AD classification accuracy, as compared with CERAD delayed recall and LM delayed recall.

Conclusions: Cued recall deficits are most closely associated with CSF biomarkers indicative of AD in subjects with MCI. This novel finding complements results from prospective clinical studies and provides further empirical support for cued recall as a specific indicator of prodromal AD, in line with recently proposed research criteria. *Neurology*® 2012;78:379–386

GLOSSARY

AD = Alzheimer disease; **aMCI** = amnestic mild cognitive impairment; **CERAD-NP** = Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery; **DCN** = Dementia Competence Network; **ERC** = entorhinal cortex; **FCSRT** = Free and Cued Selective Reminding Test; **LM** = Logical Memory; **MCI** = mild cognitive impairment; **PHC** = parahippocampal cortex.

Abnormal processing of the β-amyloid peptide, giving rise to amyloid depositions in the brain and subsequent neuronal loss, is an early event in the pathophysiology of Alzheimer disease (AD).[1] Increased CSF tau protein, not specific for AD, reflects neuronal injury and loss and is assumed to occur in temporal succession, before cognitive and finally functional impairment occur. The ratio of (reduced) CSF $A\beta_{1-42}$ and (increased) CSF tau has been established as a signature both sensitive and specific to AD.[2,3]

An impairment of episodic memory is generally considered as a core requirement for defining mild cognitive impairment (MCI) due to AD.[4,5] Since recall deficits can be caused by conditions different from AD (e.g., depression, or frontotemporal lobar degeneration), the

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Supplemental data at www.neurology.org

Supplemental Data

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Study funding: Funding information is provided at the end of the article.

Disclosure: Author disclosures are provided at the end of the article.

recently proposed Research Diagnostic Criteria for the Diagnosis of AD suggested a more specific memory signature as the core clinical symptom of AD, consisting of a recall deficit which does not improve with cueing.[6,7] Semantic cued recall tests, like the Free and Cued Selective Reminding Test (FCSRT),[8,9] predict conversion from MCI to AD dementia within 18–36 months.[10,11] However, it is unclear whether cued recall tests more closely reflect AD pathology, or more accurately predict future AD dementia, than other verbal learning tests frequently employed for assessing MCI.[12]

Longitudinal studies which compare the accuracy of diagnostic measures in predicting AD dementia face sample attrition, possibly insufficient follow-up times, and the problem that the categorical conversion from MCI to AD rests on clinical criteria only. We therefore compared several verbal episodic memory tests, including the FCSRT, with regard to their cross-sectional association with biomarker pathology in the CSF of subjects with broadly defined MCI. Using a validated cutoff for the $A\beta_{1\text{-}42}$/total tau ratio,[13,14] we tested the hypothesis that cued recall measures would be most strongly associated with a biomarker signature of prodromal AD.

METHODS

Subjects. Subjects were recruited between 2003 and 2007 at 14 University memory clinics collaborating within the multicenter German Dementia Competence Network (DCN). The DCN aims at defining the diagnostic and prognostic power of a range of clinical, laboratory, and imaging methods with regard to AD. The procedures for recruitment and assessment have been published previously.[15]

Briefly, subjects aged 50 years or older who had approached one of the memory clinics underwent a uniform set of clinical, neuropsychological, and laboratory assessments. Subjects screened for participation were usually referred by general physicians, neurologists, or psychiatrists because of their reported cognitive problems when no obvious medical or psychiatric condition was detected. Exclusion criteria were substance abuse or dependence, major depression, insufficient German language skills, multimorbidity, comorbid condition with excess mortality, or lack of an informant.

Diagnoses of MCI and dementia were made on the basis of clinical and neuropsychological data, without reference to CSF results (see below).[15]

Standard protocol approvals, registrations, and patient consent. The study was approved by the Ethics Review Board of the Erlangen medical faculty (coordinating center) and by the Ethics Committees at each individual center, and was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent.

Neuropsychological measures and definition of MCI. Subjects were assessed by trained neuropsychologists following standardized procedures.[15] The assessment included the Logical Memory Test of the Wechsler Memory Scale–Revised, the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD-NP), the Trail Making Test, and the FCSRT. The FCSRT first employs a study phase to ensure semantic encoding of all 16 items, directly followed by 3 identical recall trials, which involve a sequence of interference (counting backwards), free recall, cued recall, and selective reminding of items not recalled.[9,16] One additional delayed free and cued recall trial 15 minutes later was also employed.

The DCN study deliberately employed a broad definition of MCI.[17] Subjects scoring more than 1 SD below age- and education-adjusted norms in either subtest of the CERAD-NP battery (verbal memory, visual memory, word fluency, naming, constructional praxis) or in the Logical Memory II (delayed recall) or in either the Trail Making Test A or B were considered MCI cases, if they had no or only minor impairments in instrumental activities of daily living (Bayer ADL score <4).[18]

We here focus on episodic memory measures commonly employed for the assessment and definition of MCI. The Logical Memory II (LM) subtest from the Wechsler Memory Scale–Revised measures how many items a subject can remember from 2 stories verbally presented to her or him 30 minutes earlier.[19] The CERAD-NP contains a 10-word list which is read and immediately recalled 3 times.[20] About 15 minutes later, filled with other tasks, subjects have to recall the items presented and then to recognize them among distractors. The primary measures derived from the FCSRT are the sum of words correctly recalled with or without cues during the 3 recall trials (FCSRT total recall) and the sum of words recalled without cues (FCSRT free recall). We also explored whether the first FCSRT recall trial, which is less affected by ceiling effects than the subsequent FCSRT recall trials 2 and 3, would be particularly sensitive to an AD CSF profile. Similarly, we tested whether the delayed FCSRT free and cued recall trial would be superior to the FCSRT free and cued recall directly following the study phase. For purposes of comparison, we also examined how strongly a number of nonmemory measures would be associated with a CSF AD+ profile.

CSF measures. CSF was collected by lumbar puncture from the L3/L4 or L4/L5 intervertebral region, sampled in polypropylene test tubes with intermediate storage at site (−80°C), and then shipped on dry ice to the biobank in Erlangen without undergoing any thawing/refreezing cycles. The CSF biomarkers $A\beta 1\text{–}42$, tau, and ptau181 (Innogenetics, Ghent, Belgium) were measured by ELISA.[15]

We employed the formula $A\beta_{42}/(240 + [1.18 \times \text{t-tau}])$ to classify the CSF profile as either indicative of AD (CSF AD+, $n = 74$, AD-profile ratio <1) or not (CSF AD−, $n = 111$). This formula was developed by Hulstaert et al.[13] and discriminated patients with AD from controls with high sensitivity (85%) and specificity (87%). The formula has been applied in several subsequent independent cohorts and also identified patients with potential AD-type dementia among patients with MCI with high diagnostic accuracy.[14]

Statistical analysis. For the current article, we analyzed all 185 MCI cases from the DCN study with quality-controlled

Table 1 Sociodemographic data of the MCI sample, split according to presence (CSF+) or absence (CSF−) of a CSF biomarker profile indicative of AD, as determined by reference 13

	MCI, CSF+ (n = 74), mean (SD)	MCI, CSF− (n = 111), mean (SD)
Age[a]	69.9 (7.7)	63.3 (8.1)
Years of education[b]	12.8 (3.2)	12.5 (3.1)
MADRS[b]	6.9 (5.4)	9.2 (7.2)
Female, n (%)[a]	31 (41.9)	40 (36.0)
*APOE*4 genotype, n (%)[a]	40 (54.1)	30 (27.0)
$A\beta_{1\text{-}42}$[a]	506.5 (150.2)	989.0 (309.2)
Tau[a]	626.0 (261.5)	264.1 (110.3)
p-Tau181[a]	85.7 (31.0)	46.1 (17.5)
AD profile[13a]	0.56 (0.22)	1.87 (0.73)

Abbreviations: AD = Alzheimer disease; MCI = mild cognitive impairment.
[a] $p < 0.01$.
[b] $p < 0.05$.

CSF data and complete neuropsychological data from the tests mentioned above.

The performance of CSF AD+ and CSF AD− subjects was compared in a series of analyses of covariance with age, sex, and years of education as covariates. Effect sizes (Cohen *d*) were derived from the means and SDs for the adjusted scores. Logistic regression analyses tested whether the FCSRT total recall, as predicted, would significantly improve prediction of a biomarker pathology beyond the prediction achieved by LM and CERAD verbal delayed recall. We examined by multiple regression analyses how closely $A\beta_{42}$ and total tau, respectively, are associated with the cognitive measures. Age, sex, and years of education were entered first into all analyses, which were performed with SPSS 17. *APOE*4 was not entered because we wanted to compare the specific contribution of clinical neuropsychological information for predicting CSF biomarkers, irrespective of genetic information. Supplementary analyses with *APOE*4 as an additional predictor did not change the pattern of results (results not shown).

RESULTS MCI CSF AD+ subjects were older, better educated, had fewer depressive symptoms, were more likely to be female, or to carry at least 1 *APOE*4 allele, than MCI CSF− subjects (table 1).

As expected, all episodic memory measures were highly significantly related to a CSF AD+ signature (table 2). Among the memory measures, scores from the FCSRT discriminated best between groups (e.g., FCSRT total recall, $d = 0.91$), while LM (d = 0.74) and CERAD delayed recall ($d = 0.71$) achieved smaller effect sizes.

Logistic regression analyses confirmed the superior ability of cued recall measures to predict the likelihood of an CSF AD+ profile among MCI subjects (table 3).

Table 2 Neuropsychological raw test scores and group differences by analysis of covariance (adjusted for age, sex, and education) of MCI subjects with a CSF profile indicative of AD (CSF+) and MCI subjects without such a CSF risk profile (CSF−)[a]

	MCI, CSF+ (n = 74)	MCI, CSF− (n = 111)	$F_{1,180}$	*p*	Effect size (*d*)
Memory measures					
FCSRT total recall trial 1–3	41.72 (±5.35)	46.61 (±5.38)	35.02	<0.001	0.91
FCSRT free recall trial 1–3	20.07 (±8.34)	24.76 (±8.40)	13.31	<0.001	0.56
FCSRT total recall trial 1	13.42 (±2.02)	15.38 (±2.03)	39.65	<0.001	0.97
FCSRT delayed total recall	14.04 (±1.91)	15.68 (±1.92)	21.01	<0.001	0.87
FCSRT delayed free recall	7.36 (±3.86)	9.09 (±3.89)	8.40	0.004	0.45
Logical memory delayed recall	8.12 (±7.44)	13.59 (±7.49)	22.70	<0.001	0.74
CERAD verbal delayed recall	4.22 (±1.99)	5.63 (±2.00)	21.01	<0.001	0.71
CERAD verbal delayed recognition	8.13 (±2.11)	8.41 (±2.13)	0.74	0.389	0.13
CERAD visual delayed recall	6.01 (±3.11)	7.29 (±3.13)	7.07	0.009	0.41
Other measures					
CERAD word fluency	18.78 (±6.12)	18.08 (±6.16)	0.54	0.463	0.11
CERAD praxis	10.07 (±1.41)	10.10 (±1.42)	0.02	0.901	0.02
CERAD naming	13.52 (±1.84)	13.46 (±1.85)	0.03	0.855	0.03
Trail making A, s	65.57 (±31.90)	57.37 (±32.08)	2.78	0.097	0.26
Trail making B, s	169.96 (±60.60)	138.91 (±60.95)	11.03	0.001	0.51

Abbreviations: AD = Alzheimer disease; FCSRT = Free and Cued Selective Reminding Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; MCI = mild cognitive impairment.
[a] Cohen *d* effect sizes were derived from adjusted estimates to give a readily understandable metric of the relative power of each test score to discriminate between the groups. FCSRT total recall is the sum of free and cued recall. CERAD visual delayed recall is the number of visual elements recalled from the CERAD constructional praxis trials.

Table 3 Results of logistic regression analyses for models with different sets of predictors: Best fit requires FCSRT

Model[a]	−2 LL[b]	Difference χ^2	p	Nagelkerke R^2
1a	200.447			0.312
1b	180.509	19.938	<0.001	0.418
2a	198.382			0.324
2b	182.126	16.256	<0.001	0.410
3a	184.188			0.400
3b	180.509	3.679	0.055	0.418
4a	184.188			0.400
4b	182.126	2.062	0.151	0.410

Abbreviation: FCSRT = Free and Cued Selective Reminding Test.
[a] Model 1a with age, gender, years of education, and CERAD delayed recall. Model 1b with age, gender, years of education, CERAD delayed recall, and FCSRT total recall. Model 2a with age, gender, years of education, and logical memory delayed recall. Model 2b with age, gender, years of education, logical memory delayed recall, and FCSRT total recall. Model 3a with age, gender, years of education, and FCSRT total recall. Model 3b with age, gender, years of education, FCSRT total recall, and CERAD delayed recall. Model 4a with age, gender, years of education, and FCSRT total recall. Model 4b with age, gender, years of education, FCSRT total recall, and logical memory delayed recall.
[b] Lower scores indicate better model fit.

We first ran 3 separate forward logistic regressions, with CSF AD+ and CSF AD− as a criterion, with age, sex, and education as standard predictors, and with CERAD delayed recall, LM delayed recall, or FCSRT total recall as single cognitive predictors. The model 3a including the FCSRT total recall achieved a good model fit (Nagelkerkes $R^2 = 0.400$), while the model fit was poorer for the models employing either the CERAD delayed recall (model 1a, Nagelkerkes $R^2 = 0.312$) or the LM delayed recall (model 2a, Nagelkerkes $R^2 = 0.324$). Importantly, adding the FCSRT total recall as a predictor to the models 1a or 2a significantly increased the model fits (table 3, models 1b and 2b). However, the reverse was not true: the model employing the FCSRT total recall could not be significantly improved by either CERAD delayed recall or LM delayed recall (models 3b and 4b).

We repeated these analyses for a restricted group of amnestic MCI (aMCI) patients, classifying subjects with either CERAD word list or LM delayed recall more than 1.5 SD below age- and education-corrected norms as aMCI (n = 125). Not surprisingly, more subjects in the CSF AD+ group (84%) than in the CSF AD− group (57%) could be characterized as aMCI (χ^2 [$df = 1$] = 14.8, $p < 0.001$). Importantly, the logistic regression analyses for aMCI yielded the same results as for the full sample, with best model fits always requiring FCSRT total recall (Nagelkerkes $R^2 >= 0.43$).

This implies that among all memory measures employed, the FCSRT total recall reflects CSF AD pathology and best predicts the probability of presence or absence of a CSF profile indicative of AD, even in a sample selected for the presence of aMCI.

Additional regression analyses examined which neuropsychological variables best predicted either $A\beta_{1\text{-}42}$ or tau levels, respectively. Both CSF markers appeared to have a unimodal distribution (figure e-1 on the *Neurology*® Web site at www.neurology.org). In general, the relationship between cognitive variables was stronger with tau than with $A\beta_{1\text{-}42}$, memory variables were more closely linked to CSF variables than nonmemory variables, and FCSRT measures were most closely linked both with tau and $A\beta_{1\text{-}42}$ (table e-1 and table e-2). This confirms that the association of FCSRT measures with CSF is independent from the specific formula chosen to define CSF AD+ subjects, but is present across the range of variation of both $A\beta_{1\text{-}42}$ and tau in MCI. For CSF AD+ subjects or CSF AD− subjects treated as separate groups, none of the regressions remained significant.

DISCUSSION The main finding of this study is that cued recall measures were more closely related to a biomarker signature of AD than 2 delayed free recall measures which are frequently employed in diagnosing MCI. The FCSRT total recall (i.e., the sum of free and cued recall) outperformed not only FCSRT free recall, but also delayed free recall measures derived from verbal list learning (CERAD) or paragraph recall (LM), in predicting the likelihood of a pathologic CSF profile. This novel finding complements results from prospective clinical studies which have shown that conversions from MCI to AD dementia can be predicted by cued recall measures (FCSRT and MIS-plus, respectively) with high sensitivity and specificity.[10,11] Our data provide new biological support for the emphasis on cued recall as a specific neuropsychological marker for early AD pathology.[6,7]

It may seem surprising that a recall measure without several minutes of delay should be most closely related to AD pathology. However, the FCSRT (but not the other memory tests of this study) employs a controlled distraction procedure (counting backwards) before each recall trial, thus ensuring that items cannot be recalled from working memory, but require episodic memory. Erasing working memory for items is probably more relevant than a mere temporal delay between encoding and recall, which is inherently variable with regard to the events during

the interval (e.g. patients' reactions to difficult tests administered before delayed recall).

All episodic memory measures discriminated well between subjects with MCI with and without an AD CSF profile and were significantly correlated with $A\beta_{1-42}$ and tau, independent of age, sex, and education. Some studies have described associations of tau with memory measures, while previous results were inconclusive with regard to $A\beta_{1-42}$, possibly because of smaller sample sizes and different subject selection criteria.[21–23] In our sample, the association between $A\beta_{1-42}$ or tau, respectively, and episodic memory recall measures was both significant and specific, in that no associations (with the exception of the Trail Making B test) were found with nonmemory measures. This fits with other studies which found significant correlations between episodic memory performance and $A\beta_{1-42}$ burden in the brain measured with PIB-PET.[24–26]

Abnormal CSF $A\beta_{1-42}$ reaches a plateau earlier than CSF tau during the prodromal phase of AD, and memory impairment occurs even later, according to current theory.[1] This temporal sequence could explain why memory measures generally correlate more strongly with CSF tau than with CSF $A\beta_{1-42}$.

Is the FCSRT more predictive for the presence or absence of CSF AD pathology than CERAD delayed recall or LM delayed recall for psychometric reasons, e.g., because of having more trials (3×16 items) than the CERAD (3×10 items) or because of single item learning being more demanding than memorizing contextually linked stories (in the LM)? Such increased sensitivity possibly underlies the differential sensitivity of different free recall tasks, e.g., the CVLT-2, a 16-item word list recall test, being more sensitive to classify and predict progression of MCI than the LM.[27] However, in terms of items recalled, the FCSRT (free plus cued recall) was less difficult than both CERAD and LM delayed recall (93%, 51%, and 23% items recalled, respectively). As the (more difficult) FCSRT free recall was not particularly predictive, it is more likely the qualitative feature of cueing which sets the FCSRT total recall apart, possibly because patients with mediotemporal AD pathology have particular difficulties in using semantic cues.

Two neuroanatomic hypotheses could be proposed to account for the relative superiority of cued recall in predicting CSF AD pathology. First, cued recall may be most effective to isolate AD-typical hippocampal pathology from other memory retrieval deficits.[7] Indeed, cued recall procedures discriminate well between depression and MCI,[28] consistent with the view that the memory deficit in AD is an encoding deficit, rather than a retrieval deficit. The average MADRS depression score was slightly, but significantly higher in our AD− subjects, suggesting that somewhat depressed memory complainers with MCI, but without AD pathology, can be well detected with cued recall measures.

Cued recall might also be more sensitive for dysfunction of the parahippocampal (PHC) and entorhinal cortex (ERC). While the hippocampus is critical for binding of information to context and for recollection, the PHC, connected to the hippocampus via the ERC, supports recollection by retrieving contextually associated information.[29] Neurofibrillary tangles in the ERC occur early in the development of AD.[30] ERC volume is reduced in patients with MCI and predicts transition to AD dementia.[31–33] In support of the differential sensitivity hypothesis, the FCSRT total recall score correlates with both hippocampal and PHC/ERC volumes in patients with MCI,[34] while delayed free recall measures vary with hippocampal volume only.[35] FCSRT recall is strongly correlated with ERC volume in subjects with memory complaints.[31] Furthermore, frontal brain activation during associative retrieval correlates with left ERC volume in healthy elderly subjects, independent of hippocampal volume.[36] Thus, cued recall may capture aspects of memory subserved by ERC/PHC where AD pathology results in structural and functional loss. Further structural and functional imaging studies of cued recall in subjects with prodromal AD are needed to test this conjecture.

The 2 groups of patients did not differ with regard to verbal recognition in the CERAD, the only recognition task employed. This confirms that cueing and recognition are not interchangeable procedures and that, in line with the most recent "new lexicon" criteria[7] of prodromal AD, only a lack of normalization by cueing is sensitive to prodromal AD. However, recognition paradigms which avoid ceiling effects might be more sensitive to AD-typical memory decline than the CERAD recognition measure.[37]

Reduced ceiling effects may also be the reason why the first trial of the FSCRT discriminated best between CSF AD+ and CSF AD− patients. In contrast, a delayed FCSRT recall trial did not add discriminative power relative to postdistractional FCSRT recall directly after the study phase. These observations could highlight opportunities for further refinement of memory assessment in early AD detection. Brain imaging and neurochemical biomarkers of early AD now provide for an important biological validation strategy for neuropsychological methods, in addition to prospective clinical validation.

The strengths of the study include the large sample size, a quality controlled CSF measurement, an

extended neuropsychological battery, and the multicenter design which resulted in increased statistical power and generalizability of the findings. The broad inclusion criteria for MCI are a strength with regard to the variance in cognitive and biological measures and their possible covariance in our cross-sectional analyses. However, it should be kept in mind that the results are derived from subjects who had been screened with the CERAD and the LM II tests for the presence of MCI. The data therefore do not allow for the conclusion that the FCSRT alone is the "best test" for all diagnostic decisions. Rather, cued recall measures like the FCSRT seem to capture unique variance of the episodic memory deficit resulting from mediotemporal AD pathology in the prodromal phase of AD. Neuropsychological characterization of suspected prodromal AD in research settings should therefore include such cued recall measures. In clinical settings, cued recall measures (more than recognition measures from frequently applied list learning tasks) likely add specificity with regard to the memory deficit indicative of prodromal AD, while free recall measures may be the most sensitive screening tools. Further research will have to determine which combination and sequence of cognitive and biomarker measures will be most sensitive and specific in identifying prodromal AD.

AUTHOR CONTRIBUTIONS

Dr. Wagner: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. S. Wolf: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Reischies: study concept or design, analysis or interpretation of data, study supervision. M. Daerr: analysis or interpretation of data, statistical analysis. S. Wolfsgruber: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Dr. Jessen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, obtaining funding. Dr. Popp: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. Maier: drafting/revising the manuscript, study concept or design, study supervision, obtaining funding. Dr. Hüll: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Frölich: drafting/revising the manuscript, study concept or design, acquisition of data, study supervision. Dr. Hampel: drafting/revising the manuscript, writing of manuscript, proofing, discussion and design of paper concept and goals. Dr. Perneczky: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Peters: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. Jahn: drafting/revising the manuscript, acquisition of data. Dr. Luckhaus: study concept or design, acquisition of data, study supervision. Dr. Gertz: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Schröder: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Pantel: drafting/revising the manuscript, acquisition of data. Dr. Lewczuk: drafting/revising the manuscript. Dr. Kornhuber: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, study supervision, obtaining funding. Dr. Wiltfang: drafting/revising the manuscript, contribution of vital reagents/tools/patients.

STUDY FUNDING

Supported by the German Ministry of Research (Bundesministerium für Bildung und Forschung), grant 01GI0420 awarded to the dementia network "Kompetenznetz Demenzen."

DISCLOSURE

Dr. Wagner receives research support from German Ministry of Education and Research (BMBF) and German Research Foundation (DFG). S. Wolf has received speaker honoraria from Merz Pharmaceuticals, LLC; has served as a consultant for Servier and Æterna Zentaris Inc; and has received research support from UCB and Novartis. Dr. Reischies has received speaker honoraria from Janssen, Eli Lilly and Company, Lundbeck Inc., AstraZeneca, and Servier. M. Daerr and S. Wolfsgruber report no disclosures. Dr. Jessen has served on scientific advisory boards for GE Healthcare Johnson & Johnson, and AC Immune SA; has received speaker honoraria from Eisai Inc, Pfizer Inc, and Johnson & Johnson; and receives research support from BMBF, DFG, and BfArM. Dr. Popp serves as an Associate Editor for the *Journal of Alzheimer's Disease*. Dr. Maier serves on scientific advisory boards for Bayer Schering Pharma, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GE Electric; has received speaker honoraria from AstraZeneca, Janssen, Lundbeck Inc, Merck Serono, Merz Pharmaceuticals, LLC, Novartis, Pfizer Inc, sanofi-aventis, and Schering-Plough Corp.; serves on editorial advisory boards for *Nevenarzt* and *European Archives*; and serves on speakers' bureaus for AstraZeneca, Bayer Schering Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GE Healthcare, Janssen, Lundbeck Inc., Merck Serono, Merz Pharmaceuticals, LLC, Novartis, Pfizer Inc, sanofi-aventis, and Schering-Plough Corp. Dr. Hüll has received speaker honoraria from Wyeth/Pfizer Inc, Merz Pharmaceuticals, LLC, and Novartis; and receives research support from Pfizer Inc/Wyeth, Medivation, Inc., BMBF, BMG WHEDA, and DFG. Dr. Frölich has served on scientific advisory boards for Eisai Inc., Elan Corporation/Wyeth, Eli Lilly and Company, GE Healthcare, Janssen, Lundbeck, Inc., Merz Pharmaceuticals, LLC, Novartis, Pfizer Inc, and Schering-Plough Corp; serves on editorial advisory boards for *Psychiatry Research–Neuroimaging*, *Journal of Alzheimer's Disease*, and *Drug Research Education*; has served as a consultant for AstraZeneca, Merz Pharmaceuticals, LLC, Myriad Genetics, Inc., Neurochem Inc., Novartis, Pfizer Inc, and Schering-Plough Corp.; has served as legal expert for Apotex Inc.; and has received speaker honoraria or funding for travel from Allergan, Inc., Eisai Inc., Elan Corporation/Wyeth, Janssen, Lundbeck, Inc., Merz Pharmaceuticals, LLC, Neurochem Inc., Novartis, and Pfizer Inc. Dr. Hampel serves on scientific advisory boards for BRAHMS AG, Bristol-Myers-Squibb, Novartis, Janssen, and Merz Pharmaceuticals, LLC; has received funding for travel or speaker honoraria from Eisai Inc., Pfizer Inc, Janssen, Novartis, Merz Pharmaceuticals, LLC, and Schwabe Pharmaceuticals; serves on the editorial boards of *Brain Aging*, *Neuroscience Imaging*, *Journal of Alzheimer's Disease*, *World Journal of Biological Psychiatry*, *Journal of Medical Psychology*, *Pharmacopsychiatry*, *World Journal of Neurology*, *World Journal of Pharmacology*, and *Journal of Diagnostics*; is listed as author on several pending patents; and receives research support from BRAHMS AG, Novartis, Janssen, GlaxoSmithKline, German Federal Office of Education and Research (BMBF), State of Hess, Germany, Katharina-Hardt-Foundation, and Thea-Göring-Foundation. Dr. Perneczky has received speaker honoraria from Janssen; and serves on the editorial boards of the *Journal of Alzheimer's Disease*, *Open Journal of Nuclear Medicine*, and *Open Longevity Science*. Dr. Peters has received speaker honoraria from Medivation, Inc., Bayer Schering Pharma, Bristol-Myers Squibb, and Janssen; serves as an Associate Editor for the *Journal of Alzheimer's Disease*; serves as a consultant for Medivation, Inc.; and has received research support from AC Immune SA, AFFiRiS AG, Bayer Schering Pharma, Bristol-Myers Squibb, Janssen, Eli Lilly & Company, Merz Pharmaceuticals, LLC, Novartis, Medivation, Inc., Pfizer Inc, Roche, Servier, and Wyeth. Dr. Jahn serves as Co-Editor of the *German Journal of Psychiatry* and as a consultant for the French Agence Nationale de la Recherche; and receives research support from the European Union ERA-NET Neuron (www.neuron-eranet.eu), Eli Lilly and Company, Servier, Pfizer Inc, Janssen, and AFFiRiS AG. Dr. Gertz, Dr. Schröder, and Dr. Pantel report no disclosures. Dr. Lewczuk serves as a consultant for and receives research support from Innogenetics. Dr. Kornhuber has received speaker

honoraria from Lundbeck Inc. and GlaxoSmithKline; serves on editorial advisory boards for *Journal of Neural Transmission*, *Neuropsychobiology*, *Fortschritte Neurologie, Psychiatrie & Psychotherapie*, and *UpToDate*; is listed as author on patents re: Substituted piperidines or pyrrolidine compounds for treating sigma-receptor modulated disorders, Method of differentially diagnosing dementias, Soluble amyloid precursor proteins in cerebrospinal fluid as biomarkers of Alzheimer disease, Immunoglobulin-bound Aβ and immunoglobulins-binding Aβ peptides in diagnosis and therapy of Alzheimer disease, and Method of diagnosing acute cerebral ischemia; receives research support from Siemens Health Care, Deutsche Forschungsgemeinschaft (DFG), Bundesministerium für Bildung und Forschung (BMBF), and Bayerische Forschungsstiftung (BFS); and has served as an expert legal consultant to Merz Pharmaceuticals, LLC. Dr. Wiltfang reports no disclosures.

Received March 15, 2011. Accepted in final form July 18, 2011.

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