

Frontotemporal Dementia, Semantic Dementia, and Alzheimer's Disease: The Contribution of Standard Neuropsychological Tests to Differential Diagnosis

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ABSTRACT

CERAD-NAB (Consortium to Establish a Registry for Alzheimer's Disease–Neuropsychological Assessment Battery) data were compared between 51 patients with frontotemporal dementia, 13 with semantic dementia, and 69 with Alzheimer's disease. There were statistically significant differences between the 3 groups. Compared with patients with Alzheimer's disease, patients with frontotemporal dementia were more impaired on Animal Fluency but not on any other CERAD-NAB subtest. Patients with semantic dementia performed worse in Animal Fluency and Boston Naming Test compared with frontotemporal dementia and Alzheimer's disease. Multiple logistic regression analysis revealed that in the differentiation between frontotemporal dementia and Alzheimer's disease, the combination of Animal Fluency and Boston Naming Test correctly classified 90.5% of patients. In segregating semantic dementia and Alzheimer's disease, the combination of Boston Naming Test and Mini Mental State Examination resulted in a correct classification of 96.3%. These findings demonstrate that the Mini Mental State Examination and the language subtests of the CERAD-NAB are valuable clinical instruments for the differential diagnosis between early frontotemporal dementia, semantic dementia, and Alzheimer's disease. (*J Geriatr Psychiatry Neurol* 2005; 18: 39–44)

Keywords: frontotemporal dementia; semantic dementia; differential diagnosis; CERAD-NAB; Boston Naming test; animal fluency

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Frontotemporal dementia (FTD) semantic dementia (SD), and progressive aphasia in typical cases represent 3 distinct clinical syndromes caused by frontotemporal lobar degeneration. FTD, originally described as dementia of the frontal lobe type,¹ later as FTD,² and more recently as frontal variant of FTD,³ is associated with bilateral and usually symmetric involvement of the frontal lobes⁴ and manifests clinically as a disorder primarily of behavior. Patients present with profound alterations of personality and social conduct, characterized either by inertia and loss of volition or by social disinhibition and distractibility with relative preservation of episodic memory.² In SD, atrophy is most severe in the anterior temporal cortex.⁵ Magnetic resonance imaging studies have shown bilateral,⁴ asymmetric left,⁶ or predominantly right temporal lobe involvement.⁷ The most prominent clinical feature of SD is a progressive semantic impairment that affects the meaning of words and visual percepts. Verbal output is fluent, effortless, and grammatically correct but often

empty.^{2,8,9} Patients with SD, however, may exhibit behavioral changes similar to those seen in FTD, particularly as the disease progresses. Moreover, deterioration of memory, attention, and executive function invariably occurs in FTD and in SD.^{3,10,11} This clinical overlap may make it challenging to distinguish between the 2 entities, particularly in the early stages of the disease,^{12,13} but also to differentiate the 2 syndromes caused by frontotemporal lobar degeneration from dementia in Alzheimer's disease (AD). Numerous recent studies have attempted to improve differential diagnosis by identifying different patterns of behavioral change and cognitive impairment.^{8,13-15} The present study aimed at distinguishing FTD, SD, and AD patients on cognitive measures that were assessed with the German version of the Consortium to Establish a Registry for Alzheimer's Disease–Neuropsychological Assessment Battery (CERAD-NAB).¹⁶ On the basis of these data, we tried to identify CERAD-NAB subtests that contribute most to differential diagnosis.

METHODS

Patients

Sixty-four consecutively referred outpatients (40 male, 24 female) were comprehensively examined at the Memory Clinic of Technische Universität in Munich, Germany. Subjects were included in the study if they met the revised Lund-Manchester criteria² for FTD or SD and if ¹⁸F-fluoro-2-deoxy-D-glucose positron emission tomography scanning (¹⁸F-FDG-PET) was compatible with the clinical diagnosis. According to these criteria, 51 patients (29 male, 22 female) were diagnosed with FTD and 13 with SD (11 male, 2 female). To compare the patterns of cognitive impairment between patients with FTD, SD, and AD, we included 69 patients with a diagnosis of probable Alzheimer's disease according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria¹⁷ who had undergone diagnostic evaluation at the same unit.

Patients with AD were matched with FTD and SD patients, regarding sex and disease severity, as assessed by the Clinical Dementia Rating (CDR).¹⁸ Patients with moderate and severe dementia (CDR 2 or 3) were excluded from analyses. Age was not used as a matching variable because the average onset of symptoms in FTD and SD typically precedes the onset of AD by at least 1 decade.¹⁹

Procedures

Because the diagnosis of FTD and SD requires significant input from caregivers or other proxies, an extensive interview with an informant was performed in all patients focusing on abnormalities of memory, language, and behavior. Informants also completed the Bayer Activities of Daily Living scale.²⁰ In patients with FTD and SD, diagnostic evaluation included the Neuropsychiatric Inventory²¹

or the Frontal Behaviour Inventory²² and the Geriatric Depression Scale.²³

Cognitive ability was evaluated using the German version of the CERAD-NAB,¹⁶ which is widely used for cognitive assessment in memory clinics.²⁴ The instrument consists of 5 subtests that are administered in 8 steps: (1) Animal Fluency (naming as many different animals as possible for 1 minute), (2) 15 items of the Boston Naming Test, German version (confrontation naming of 15 line drawings), (3) Mini Mental State Examination (MMSE),²⁵ (4) Word List Learning (learning 10 words that are presented 3 times), (5) Constructional Praxis (copying 4 geometric figures), (6) Word List–Delayed Recall (recalling the 10 words previously learned), (7) Word List–Recognition discriminability (recognizing the previously learned words from a list of 20 words [10 new words and 10 old words]), and (8) Constructional Praxis–Delayed Recall (recalling the figures that were presented earlier). The latter subtest was not available for the AD patients and was therefore omitted from the analysis.

In addition to the CERAD-NAB, neuropsychological tests of language and executive function (Frontal Assessment Battery,²⁶ Color-Word-Test,²⁷ Trail Making Test²⁸) were administered in 32 of the FTD and SD patients. Neurological examination and laboratory workup (routine chemistry, complete blood cell count, blood glucose, vitamin B₁₂, folic acid and thyroid stimulating hormone levels, and syphilis and Lyme serologies) were performed. All patients underwent either cranial computed tomography or magnetic resonance imaging. Moreover, all patients with FTD and SD as well as 24 patients with AD had ¹⁸F-FDG-PET. PET findings were used to improve the clinical differentiation between FTD and SD. Subjects were not classified as SD if they showed significant frontal hypometabolism. As a result, all patients with SD exhibited metabolic deficits predominantly of the left temporal lobe. A few patients had an additional hypometabolism in the right temporal pole. Patients with FTD showed reduced tracer uptake predominantly in frontal areas as well as additional temporal (left > right) hypometabolism in half of the cases. Each of the 24 AD patients who underwent PET scanning showed hypometabolism in the posterior cingulate, and 16 of the patients had also hypometabolism of the temporoparietal cortex (left > right).

Statistical Analysis

Data were analyzed using the SPSS 11.0 software package (SPSS Inc, Chicago, Ill). Statistical analysis proceeded in 3 steps. First, analyses of variance were performed separately for each of the CERAD-NAB variables to determine statistical differences across diagnostic groups (FTD, SD, and AD). Results are presented as group means and standard deviations. Second, post hoc *t*-tests (2-tailed) were used to examine 2-group contrasts on the CERAD-NAB variables (FTD vs AD, SD vs AD, and FTD vs SD). Results are shown as 2-tailed *P* values. Subtests that were significantly

Table 1. Demographic Characteristics, Scores on the Mini Mental State Examination (MMSE), and Clinical Dementia Rating (CDR) of the 3 Patient Groups

	FTD	SD	AD	P Value
N	51	13	69	
Sex (M/F)	29/22	11/2	32/37	.04
Age (years) ± sd	62.0 ± 10.3	65.2 ± 4.5	73.6 ± 7.7	<.001
Education (years) ± sd	12.8 ± 3.3	13.4 ± 3.8	12.1 ± 2.8	ns
MMSE ± sd	24.1 ± 3.5	23.6 ± 4.2	24.5 ± 4.5	ns
MMSE lower range	15	14	15	ns

Note: FTD = frontotemporal dementia; SD = semantic dementia; AD = Alzheimer's disease; sd = standard deviation; ns = not significant.

Table 2. Results ± Standard Deviations of the CERAD-NAB Variables for the 3 Patient Groups

	FTD	SD	AD	P Value
Animal Fluency	9.5 ± 5.0	6.4 ± 4.3	12.2 ± 4.7	<.001
Boston Naming Test	12.3 ± 2.7	5.8 ± 2.6	12.4 ± 2.4	<.001
MMSE	24.1 ± 3.5	23.6 ± 4.2	24.5 ± 3.2	.67
Word List–Learning	13.4 ± 4.5	13.0 ± 4.2	13.2 ± 4.4	.96
Word List–Delayed Recall	3.3 ± 2.2	3.6 ± 2.9	2.6 ± 2.1	.14
Word List–Discriminability	16.7 ± 3.6	15.0 ± 3.8	16.6 ± 2.5	.26
Figures–Copy	9.7 ± 1.4	10.4 ± 1.1	9.3 ± 1.9	.06

Note: CERAD-NAB = Consortium to Establish a Registry for Alzheimer's Disease–Neuropsychological Assessment Battery; FTD = frontotemporal dementia; SD = semantic dementia; AD = Alzheimer's disease.

different between diagnostic groups ($P < .05$) were included in the subsequent analysis. Third, to determine the relative contribution of the subtests for group discrimination, separate stepwise binary logistic regressions were performed for each 2-group comparison using the diagnostic classification as dependent variable and the CERAD-NAB results as predicting variables. Demographic characteristics (age in years, sex, and years of education) were included as possible confounders.

RESULTS

Demographic Data

Demographic characteristics of the 3 patient groups are depicted in Table 1. Patients with AD were significantly older than patients with FTD or SD. The proportion of male patients was significantly higher in the SD group compared with the 2 other groups. There was no statistically significant difference between the 3 groups with respect to education. The mean MMSE score was approximately 24 in all 3 groups; about 10% of the patients in each group scored lower than 20 points.

Selection of Variables for Group Differentiation

There were statistically significant differences across the 3 diagnostic groups on Animal Fluency and the Boston Naming Test (see Table 2). Post hoc demonstrated that patients with SD performed significantly worse on both tests than patients with FTD or AD. The FTD group was significantly more impaired than the AD group on Animal Fluency (see Table 3).

Table 3. 2-Group Differences on CERAD-NAB Subtests (P Values)

Variable	FTD vs SD	FTD vs AD	SD vs AD
Animal Fluency	.04	.003	<.001
Boston Naming Test	<.001	.90	<.001

Note: CERAD-NAB = Consortium to Establish a Registry for Alzheimer's Disease–Neuropsychological Assessment Battery; FTD = frontotemporal dementia; SD = semantic dementia; AD = Alzheimer's disease.

There were some nonsignificant trends: patients with SD scored higher on Figures–Copy than patients with AD. AD patients evidenced lower results on Word List–Delayed Recall compared with FTD and SD patients (see Table 2).

Group Separation by Neuropsychological Tests

Three stepwise logistic regressions were carried out to determine the contribution of the CERAD variables to diagnostic group membership. For these analyses, age, sex, and disease severity (assessed by CDR) were considered as covariates.

SD Versus FTD

In the separation between FTD and SD, the Boston Naming Test–15 Items alone achieved a correct classification rate of 88.3%. Group separation was slightly improved by including Animal Fluency in the regression model. The percentage of correctly classified patients was 90.5% (FTD 94.0%, SD 76.9%) (see Table 4). When we considered age,

Table 4. SD Versus FTD, Classification Table: Animal Fluency and Boston Naming Test (Covariates Not Considered in this Model)

	<i>Predicted Group</i>		<i>Percentage Correct</i>
	<i>FTD</i>	<i>SD</i>	
Observed group			
FTD	47	3	94.0
SD	3	10	76.9
			90.5

Note: FTD = frontotemporal dementia; SD = semantic dementia.

sex, and education as covariates, this model correctly classified 91.7% of the patients.

FTD Versus AD

In this group, discrimination on Animal Fluency alone classified 77.8% of patients correctly. The percentage of correct classifications was increased by Word List–Delayed Recall to 79.3% and was further improved by the MMSE to 81.0% (FTD 74.5%, AD 85.5%). The combination of high Animal Fluency and low Word List–Delayed Recall favored a diagnosis of AD.

SD Versus AD

Finally, in the discrimination between SD and AD, the logistic regression model including Boston Naming Test–15 Items and MMSE correctly classified 96.3% (SD 84.6%, AD 98.6%) (see Table 5). High Boston Naming Test combined with a low MMSE score predicted a diagnosis of AD.

After we added Animal Fluency, Figure–Copy, MMSE, and demographic variables as covariates to the logistic regression model, the percentage of overall correct classifications was 97.4% (SD 77.8%, AD 100%).

DISCUSSION

Differential diagnosis between frontotemporal degenerations and Alzheimer's disease as early as possible in the course of the disease is clinically important because these disorders are associated with different medical, psychological, and social needs of patients and caregivers. For the experienced clinician, the mainstay of the clinical diagnosis is the patient's typical history and clinical presentation,²⁹ supported by structural brain imaging that can be used to demonstrate frontotemporal atrophy. Functional brain imaging may be helpful if available, showing reduced cerebral blood flow or diminished glucose metabolism of frontal or temporal areas in typical cases of FTD and SD.^{24,30} To standardize and quantify the analysis and assessment of behavioral change, a number of clinical tests and interviews have been developed that refer to the specific symptom pat-

Table 5. SD Versus AD, Classification Table: Boston Naming Test and Mini Mental State Examination (Covariates Not Considered in This Model)

	<i>Predicted Group</i>		<i>Percentage Correct</i>
	<i>SD</i>	<i>AD</i>	
Observed group			
SD	11	2	84.6
AD	1	68	98.6
			96.3

Note: SD = semantic dementia; AD = Alzheimer's disease.

tern of FTD.^{26,31,32} Other studies have explored the potential of neuropsychological tests, particularly of language and frontal-executive functions, to distinguish between FTD and SD.^{15,33-37} In the present study, we were able to demonstrate that brief neuropsychological tests, which are routinely used in memory clinics, are helpful to distinguish between the 2 frontotemporal syndromes and to separate them from AD.

One advantage of our study is the relatively large sample size, particularly in the FTD and AD groups. Another strength is that the clinical diagnosis was confirmed by typical patterns of hypometabolism on ¹⁸F-FDG-PET in all patients with FTD and SD as well as in 24 patients with AD. Specifically, in patients with prominent behavioral disturbances superimposed on the features of SD, the typical pattern of temporal hypometabolism in the absence of frontal deficits in PET allowed a clear diagnostic classification. Moreover, because the diagnostic classification was primarily based on the patients' history, on extensive behavioral assessments, and on functional brain imaging, the study avoids circularity.

We found that patients with SD performed significantly worse on language tests (Animal Fluency and Boston Naming Test–15 Items) than patients with FTD or AD. Compared with AD, patients with FTD were significantly more impaired on animal fluency but not on picture naming or any other CERAD-NAB subtest. These results are consistent with previous studies that have demonstrated similar performance on confrontation naming in AD and FTD.³³⁻³⁵ Similar to other authors,¹⁵ we found that patients with AD are more impaired in tests of episodic memory (delayed recall) than patients with FTD. However, in our study this difference did not reach statistical significance. This might be a result of the fact that AD patients in our study were in an early stage of disease where a severe memory impairment is uncommon. Patients with a "frontal variant of FTD" generally perform well on tests of picture naming, word-picture matching, generation of word definition, and other semantic tasks.^{14,15} In contrast, confrontation naming is impaired in SD.^{9,38} It is also consistent

with previous reports¹¹ that there were no differences between FTD and SD on episodic verbal memory and on the visuoconstructional tasks.

From a clinical perspective, the most interesting result of our study is that patients with FTD, SD, and AD can be distinguished with regard to the pattern of their cognitive profile. Most patients with SD and some patients with AD or FTD are impaired in the Boston Naming Test–15 Items. However, in AD, low scores in the Boston Naming Test are associated with low scores in the MMSE. In contrast, in early stages of SD, a poor Boston Naming Test performance and relatively high scores in MMSE represent a typical pattern. Patients with SD score lower than FTD patients on the Boston Naming Test and on Animal Fluency. However, multiple analysis demonstrates that SD is separated from FTD by a particularly poor naming ability.

The findings of the present study demonstrate that the MMSE in combination with the language subtests Boston Naming Test and Animal Fluency of the CERAD-NAB is a valuable clinical instrument for the differential diagnosis between early FTD, SD, and AD. Although information on the patient's history and on behavioral change is most important to distinguish between these clinical entities, the pattern of cognitive impairment may facilitate differential diagnosis and should be taken into account when making diagnostic decisions. The brief tests evaluated in the present study should be included in the design of short bedside assessment batteries for the identification of frontotemporal syndromes.

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