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Comparison of neuropsychological functioning in Alzheimer's disease and frontotemporal dementia

NANCY ANN PACHANA,[1] KYLE BRAUER BOONE,[2] BRUCE L. MILLER,[3] JEFFREY L. CUMMINGS,[4] AND NANCY BERMAN[5]

[1]Department of Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Los Angeles, CA 90024
[2]Department of Psychiatry, Harbor-UCLA Medical Center, Torrance, CA 90509
[3]Department of Neurology, Harbor-UCLA Medical Center, Torrance, CA 90509
[4]Departments of Neurology and Psychiatry, and Biobehavioral Sciences, UCLA School of Medicine, and Behavioral Neuroscience Section, Psychiatry Service, West Los Angeles Veterans Affairs Medical Center, Los Angeles, CA 90024
[5]Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA 90509

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Abstract

Neuropsychological changes distinguishing mild Alzheimer's disease (AD) from frontotemporal dementia (FTD) have been described, but empirical verification of differential cognitive characteristics is lacking. Archival neuropsychological data on 15 FTD patients, 16 AD patients, and 16 controls were compared. Controls outperformed both patient groups on measures of verbal and nonverbal memory, executive ability, and constructional skill, with AD patients showing more widespread memory decline. No differences were found between the 3 groups in confrontation naming, recognition memory, or basic attention. Patient groups differed only in nonverbal memory, with FTD patients performing significantly better than AD patients. However, patient groups also differed in pattern of performance across executive and memory domains. Specifically, AD patients exhibited significantly greater impairment on memory than executive tasks, whereas the opposite pattern characterized the FTD group. These findings suggest that examination of relative rankings of scores across cognitive domains, in addition to interpretation of individual neuropsychological scores, may be useful in differential diagnosis of FTD *versus* AD. (*JINS*, 1996, 2, 505–510.)

Keywords: Frontotemporal degeneration, Alzheimer's disease, Executive functions, Memory

INTRODUCTION

In Alzheimer's disease (AD), deficits in memory, constructional skills, and naming are characteristic of the early stages of the disease, while early deterioration in personality and social behavior, judgment, and executive system functions are typical of frontotemporal dementia (FTD; Cummings & Benson, 1992). However, documentation of the validity of the differing neuropsychological and neurobehavior profiles of FTD and AD has been sparse.

Neary et al. (1986) described a unique neuropsychological profile of reduced executive skills in the context of variable memory and attention, but normal language (except for a mild anomia), manual skill, constructions, and IQ in 4 FTD patients with prominent behavioral and personality changes. Similarly, Jagust et al. (1989) observed reduced executive skills relative to memory ability in 4 FTD patients, and the opposite pattern in 20 AD patients; confrontation naming and constructions were depressed and equivalent in both groups. Johansen and Hagberg (1989) also described reduced executive skills, as well as constructional impairment, variable memory, impaired calculation, and echolalic speech in 20 FTD patients.

Given the small sample sizes in the above studies, statistical comparisons of groups were generally not feasible, and the conclusions regarding the neuropsychological differences between FTD and AD were based on clinical interpretations of individual test protocols. The one paper statistically comparing 6 FTD patients with elderly controls revealed that FTD subjects had significantly poorer per-

Reprint requests to: Kyle B. Boone, Harbor-UCLA Medical Center, Department of Psychiatry, Box 498, 1000 W. Carson Street, D-5 Annex, PO Box 2910, Torrance, CA 90509-2910.

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formance on executive skills, IQ, and attention; confrontation naming, memory, and visuospatial skills were found to be comparable between groups (Miller et al., 1991). As other forms of dementia were not studied, no conclusions could be drawn regarding whether these findings were unique to FTD. In fact, Kumar et al. (1990) have raised questions about the specificity of deficient executive skills in FTD, observing no disproportionate impairment in frontal lobe cognitive abilities in FTD in their statistical analysis of the patterns of scores of FTD and AD. However, their requirements for significant group differences were exceedingly stringent (i.e., FTD neuropsychological indices had to differ by more than 2 *SD*s from AD scores).

Thus, while the available studies suggest that patients with FTD show a statistically significant departure from normal performance in executive skills, it remains unclear whether this profile is specific to FTD. In addition, while the descriptive reports have been relatively consistent in reporting decline in executive functioning in FTD, contradictory conclusions have emerged regarding the presence of collateral declines in constructional skill, confrontation naming, memory, and attention.

The purpose of the present study was to examine group differences between AD and FTD patients and controls on neuropsychological measures obtained from archival data.

METHOD

Research Participants

Archival data for participants chosen for inclusion in the study were obtained from Harbor-UCLA Medical Center records as well as the Alzheimer's Disease Center database at the University of California at Los Angeles. Single photon emission computed tomography brain studies were obtained on all patients using both ^{133}Xenon and ^{99m}Tc-hexamethylpropyleneamine oxime. For a diagnosis of FTD, patients were required to show frontal–temporal hypoperfusion with relative sparing of the parietal and occipital regions. In contrast, AD patients were required to exhibit temporal–parietal hypoperfusion with either normal, or only mildly decreased, perfusion in the frontal and anterior temporal regions.

For all FTD patients, the clinical diagnosis of FTD was made at the time of the original evaluation by two behavioral neurologist physicians with special interest and expertise in this condition (JLC and BLM). All FTD patients included in our sample met the diagnostic research criteria for FTD set by the Lund-Manchester Group (Brun et al., 1994). Specifically, to diagnose FTD, we required that, in addition to frontal hypoperfusion, all patients have a gradual cognitive decline and show prominent personality changes such as disinhibition, antisocial behaviors, hyperorality, compulsions, or apathy. Neuropsychological test scores were not used in deriving a diagnosis. Six of the FTD patients have subsequently had pathologic confirmation according to the Lund-Manchester Research Criteria for pathology; 4 showed Pick bodies, frontal gliosis, and neuronal loss, while 2 were found to have frontal gliosis and neuronal loss but no Pick bodies.

All AD patients met the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) diagnostic criteria for probable AD (McKhann et al., 1984). Although only 1 of our patients from this study has come to autopsy and been confirmed to have AD, we recently published a paper that demonstrates that a diagnosis of probable AD is corroborated with pathology in more than 90% of our cases (Read et al., 1995).

Patients with medical, substance abuse, neurologic or psychiatric disorders other than AD or FTD that could account for their abnormal mental status were excluded. Magnetic resonance imaging (MRI) was performed in all patients to rule out stroke or other lesions that could have caused dementia. In addition, because participants in more advanced stages of dementia are essentially unable to perform neuropsychological tests, a Mini Mental State Examination (MMSE; Folstein et al., 1975) score of at least 18 was required in all patients.

Nine men and 7 women with AD, and 7 men and 8 women with FTD, met the above criteria. Sixteen control participants (8 men and 8 women) were chosen from an ongoing study at Harbor-UCLA of healthy, normal older adults. All control participants had normal neurological exams; had no history of major affective or psychotic disorder, head injury, stroke, seizures or other neurologic disorders; and had no history of substance abuse within the past 5 years. In addition, all control subjects underwent MRI brain scanning to rule out any significant structural abnormalities. In Table 1 are shown the mean ages and educational levels for the three groups, as well as the mean MMSE scores for the two patient groups; all control participants had MMSE scores above 26.

Procedures

Neuropsychological tests were chosen to reflect the following cognitive domains:

- *Attention*: Digit Span subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler, 1981)
- *Visuoconstructional*: Rey–Osterrieth Complex Figure (Lezak, 1983)
- *Verbal and nonverbal memory*: (1) Rey Auditory Verbal Learning Test (RAVLT; Lezak, 1983); (2) WHO-UCLA Auditory Verbal Learning Test (Maj et al., 1994); (3) Wechsler Memory Scale–Revised (WMS–R; Wechsler, 1987), Logical Memory subtest; (4) Rey–Osterrieth Complex Figure delayed recall (Boone, et al., 1993)
- *Language:* Boston Naming Test (BNT; Kaplan et al., 1978)
- *Executive Functioning*: Verbal Fluency (FAS; Benton & deS Hamsher, 1976; Boone et al., 1990); Stroop Test (Stroop, 1935; Boone et al., 1990)

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Table 1. Neuropsychological and demographic variables for FTD, AD, and controls

Variable	Group		
	FTD *M* ± *SD*	AD *M* ± *SD*	Controls *M* ± *SD*
Age	63.9 ± 8.3	70.3 ± 10.0	70.4 ± 5.2
Education	15.2 ± 2.9	14.6 ± 2.7	14.8 ± 2.2
MMSE	25.4 ± 3.2	23.5 ± 3.1	n/a
Executive			
FAS	17.3 ± 15.1 (n = 15)	26.5 ± 11.6 (n = 16)	43.4 ± 10.6 (n = 16)
Stroop time	214.1 ± 65.3 (n = 8)	242.9 ± 162.3 (n = 7)	129.1 ± 24.4 (n = 16)
Stroop errors	40.5 ± 46.0 (n = 6)	3.9 ± 3.2 (n = 7)	1.4 ± 1.8 (n = 16)
Attention			
Digit Span	8.7 ± 2.6 (n = 15)	9.2 ± 3.3 (n = 16)	9.9 ± 2.7 (n = 16)
Language			
Boston Naming	47.2 ± 15.1 (n = 11)	50.1 ± 12.1 (n = 15)	55.9 ± 4.5 (n = 16)
Visuoconstructional			
Rey–Osterrieth	23.8 ± 8.1 (n = 14)	18.7 ± 10.5 (n = 12)	32.8 ± 2.2 (n = 16)
Verbal memory			
LM percent retention	41.0 ± 40.7 (n = 13)	33.1 ± 27.4 (n = 8)	76.6 ± 13.3 (n = 16)
AVLT			
Trial 5	6.7 ± 2.8 (n = 6)	6.6 ± 2.6 (n = 11)	10.4 ± 2.2 (n = 16)
Delayed recall	4.8 ± 4.2 (n = 6)	1.8 ± 2.8 (n = 11)	7.1 ± 3.1 (n = 16)
Recognition	11.5 ± 2.4 (n = 6)	11.5 ± 3.3 (n = 11)	12.9 ± 1.7 (n = 16)
Nonverbal memory			
Rey–Osterrieth	31.3 ± 24.5 (n = 14)	10.0 ± 12.8 (n = 12)	55.8 ± 16.9 (n = 16)

The choice of tests was limited by the constraints of existing data sets, and not all subjects completed all tests.

Test variables used for analyses included (1) the scaled score for the Digit Span subtest of the WAIS–R; (2) number of items recalled on the fifth trial, 30-min delayed recall, and delayed recognition on the RAVLT or WHO-UCLA AVLT; (3) percent retention (delayed recall/immediate recall) at 30-min delayed recall on the Logical Memory subtest of the WMS–R; (4) copy score and memory score (percent retained on delayed recall) for the Rey–Osterrieth Complex Figure; (5) time (in s) to complete the color-interference section of the Stroop, and total number of errors on this section; (6) number correct on the BNT; and (7) total number of words generated for the letters "f," "a," and "s" on FAS.

RESULTS

Sample Characteristics

Education level was not significantly different among the groups [$F(2, 43) = .24$, $p = .79$]. Groups did differ by age [$F(2, 44) = 3.31$, $p < .05$], with FTD patients slightly younger than the other two groups, but posttest analyses did not reveal any significant differences between pairs of groups, and the age discrepancies were judged not to be clinically significant. No significant differences between AD and FTD groups were observed on MMSE [$t(28) = -1.62$, $p = .12$].

Group Comparisons on Neuropsychological Data

Analysis of variance (ANOVA) statistics were used for comparisons of the three groups on neuropsychological variables that were found to be normally distributed based on Shapiro and Wilk's statistic, with Kruskal–Wallis one-way ANOVAs used for the remaining group comparisons. Significant group differences were documented on 8 of 11 neuropsychological variables:

1. FAS (K–W = 19.84, $p = .00001$),
2. Stroop time (K–W = 11.30, $p = .0035$),
3. Stroop errors (K–W = 6.96, $p = .03$),
4. Logical Memory (K–W = 11.26, $p = .004$),
5. Rey–Osterrieth copy [$F(2, 39) = 13.26$, $p = .00001$],
6. Rey–Osterrieth Memory score (K–W = 21.66, $p = .00001$),
7. 5th trial on the AVLT [$F(2, 30) = 9.98$, $p = .0005$], and,
8. delayed recall on the RAVLT (K–W = 12.45, $p = .002$).

Groups did not significantly differ on Digit Span (K–W = 1.50, $p = .47$), Boston Naming Test (K–W = 4.83, $p = .09$), or recognition on the AVLT (K–W = 1.91, $p = .39$). Group means and standard deviations for neuropsychological variables are shown in Table 1.

Posttest analyses indicated that controls performed at a significantly higher level than both AD and FTD patients ($p < .05$) on FAS, Stroop time, Logical Memory, Rey–Osterrieth copy, and Rey–Osterrieth memory score. In addition, controls significantly outperformed AD patients on the fifth learning trial ($p < .05$) and delayed recall trial of the AVLT. No significant differences were detected between patient groups on any of the neuropsychological measures. However, when the two patient groups were compared on standardized test scores (i.e., z scores calculated on the mean and standard deviation of the control sample), a single significant difference was observed on the Rey–Osterrieth memory score [$t(21) = -2.83$, $p = .01$], with FTD patients scoring significantly better than AD patients.

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Neuropsychological Profile Analyses

To facilitate comparison of patient groups on neuropsychological test profiles, mean z scores were calculated separately for each patient group for all test variables. Using the mean z scores, the test scores were arranged hierarchically from best to worst for each patient group (see Table 2).

Visual inspection of Table 2 suggests that the two patient groups differed in their respective rankings on memory (particularly, nonverbal and rote verbal) and executive skills; FTD patients generally performed better on the memory tests and worse on the executive tasks, whereas the AD group tended to show the opposite pattern. In contrast, scores on basic attention, constructional skill, story recall, recognition memory, and speed aspects of executive performance appeared to be similarly ranked across groups.

Although a statistical comparison of rank ordering for all measures was desirable, missing data limited such analyses. Since FAS and Rey–Osterrieth Memory data were available for most participants, these tests were employed as representative measures for the executive and memory domains, respectively, in further analyses. Twelve of 12 AD patients were found to have lower z scores for Rey–Osterrieth Memory than for FAS, while 10 of 14 FTD patients showed FAS z scores that were either lower than ($n = 9$) or equal to ($n = 1$) z scores on Rey–Osterrieth Memory, ($n = 26$, $\chi^2(df = 1) = 13.93, p < .001$). Paired t tests comparing the FAS z scores and Rey–Osterrieth Memory z scores within each subject were computed for each patient group separately. The AD patients scored significantly better on FAS (mean $z = -1.36 \pm 1.13$) than Rey–Osterrieth memory (mean $z = -2.71 \pm .75$) [$t(11) = 4.54, p = .0009$]. In contrast, the FTD group showed a nearly significant trend to score better on Rey–Osterrieth Memory (mean $z = -1.45 \pm 1.45$) than FAS [mean $z = -2.43 \pm 1.48$; $t(13) = -2.01, p = .07$]. Comparison of the two patient groups on difference scores [i.e., (FAS z score) − (Rey–Osterrieth Memory z score)] was significant [$t(24) = 3.91, p = .0007$].

Table 2. Rank ordering of mean neuropsychological *Z* scores for AD and FTD groups

Rank order		Group	
		FTD	AD
Best	1	Digit Span	Digit Span
	2	AVLT–delayed recall	AVLT–recognition
	3	AVLT–recognition	Boston Naming Test
	4	Rey–Osterrieth memory	Stroop errors
	5	AVLT–5th trial	FAS
	6	Boston Naming Test	AVLT–delay recall
	7	FAS	AVLT–5th trial
	8	Logical Memory	Rey–Osterrieth memory
	9	Stroop time	Logical Memory
	10	Rey–Osterrieth copy	Stroop time
Worst	11	Stroop errors	Rey–Osterrieth copy

DISCUSSION

Comparison of neuropsychological test scores obtained on retrospective chart review on FTD and AD patients and normal controls revealed that both patient groups performed significantly below controls in verbal and nonverbal free recall, construction ability, and executive skills, with AD patients exhibiting more widespread declines in memory. Patients and controls did not differ significantly in basic attention, confrontation naming, or recognition memory.

Patient groups were found to differ on a single neuropsychological variable: FTD patients performed significantly better than AD patients in delayed recall of the Rey–Osterrieth figure. The lack of additional significant differences between FTD and AD patients may be partially an artifact of small sample size and missing data, as several of the mean scores of the two patient groups appeared to be substantially discrepant (e.g., FAS, AVLT delayed recall, Rey–Osterrieth Copy).

In addition to the single significant difference between FTD and AD groups in nonverbal memory performance, the two patient groups exhibited different patterns of performance on executive versus nonverbal memory tasks. Specifically, within the AD sample, a significantly worse performance was observed on nonverbal memory relative to executive functioning, while FTD patients demonstrated an opposite pattern of skills. Twelve of 12 AD patients demonstrated standardized scores (i.e., z scores based on control means and standard deviations) that were higher for FAS than Rey–Osterrieth recall, while only 4 of 14 FTD patients showed this pattern.

Functional neuroimaging studies of AD and FTD patients have documented distinct abnormalities, with AD patients showing bilateral posterior temporal–parietal hypometabolism (Duara et al., 1991) and hypoperfusion (Neary et al., 1987), but relative sparing of more anterior areas. Patients with FTD display bilateral frontal and anterior temporal hypoperfusion with relatively normal parietal and occipital blood flow (Neary et al., 1988; Miller et al., 1991; Risberg et al., 1993). This distribution of functional abnormalities fits with the findings from the present study, which show differing cognitive patterns for the AD and FTD groups. Specifically, AD patients exhibit abnormalities primarily in cognitive abilities mediated by the temporal–parietal lobes (e.g., free recall), whereas FTD patients show abnormalities primarily in cognitive abilities mediated largely by the frontal lobes (i.e., executive skills).

The results from the present study help clarify some of the contradictory findings in the existing literature regarding the neuropsychological characteristics of FTD. Neary et al. (1986), Jagust et al. (1989), and Johansen and Hagberg (1989) observed that FTD patients performed more poorly than AD patients in executive function tasks, but better than AD patients in memory, although their reports did not allow statistical verification of group differences. However, Kumar et al. (1990) failed to detect any significant differences between FTD and AD patients in executive skills, and concluded that impairment in executive skills, while

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present in FTD, was not specific to FTD. Our data indicate that both sets of observations are accurate. Specifically, FTD and AD patient groups both show impairment in executive skills, and exhibit similar absolute scores on executive tasks; however, when relative patterns of cognitive scores are considered, FTD patients perform disproportionately more poorly on executive tests.

Contradictory findings have also been reported regarding the presence of impairment in constructional skills, memory, language (confrontation naming), and attention in FTD. Decreased memory has been reported in some studies (Neary et al., 1986; Johansen & Hagberg, 1989) but not others (Jagust et al., 1989; Miller et al., 1991), while attentional losses have been observed by some investigators (Neary et al., 1986), but not others (Miller et al., 1991). Similarly, evidence for (Jagust et al., 1989; Johansen & Hagberg, 1989) and against (Neary et al., 1986; Miller et al., 1991) the presence of decreased constructional skill, and for (Neary et al., 1987; Jagust et al., 1989) and against (Miller et al., 1991) language (i.e., confrontational naming) disturbance in FTD has also emerged. In the present study, FTD patients showed significant impairments in constructional skill and free recall relative to controls, while attention and confrontation naming were spared.

The discrepancy among studies regarding the neuropsychological characteristics of FTD could stem in part from the fact that FTD may not be a uniform condition. The 4 FTD participants in the present study who did not exhibit better visual memory (i.e., Rey–Osterrieth Memory) than executive (i.e., FAS) scores had reductions in cerebral blood flow that were most prominent in right frontotemporal areas. Future research is needed to determine if there are differential neuropsychological patterns in FTD that correspond to asymmetries in anterior cerebral hypoperfusion.

Additional research is also required to determine if neuropsychological tests other than those used in this study might be more sensitive to the cognitive dysfunction present in FTD *versus* AD. Given the retrospective nature of the present investigation, the choice of cognitive tasks was constrained by test scores available in the archival files. Some of the purportedly nonexecutive tasks available for analysis in the present study may have in fact required executive skills, thus leading FTD patients to perform at a substandard level. For example, copy of the Rey–Osterrieth figure, the constructional task employed in the present study, is often performed poorly by patients with frontal lobe dysfunction, due to the organizational requirements (Lezak, 1983). It is possible that the AD and FTD patients in our study performed at comparable levels on this test for different reasons, with FTD patients failing due to the organizational demands, but AD patients scoring poorly due to the loss of parietal anatomic structures that subserve spatial skills. For the purpose of clinical discrimination of FTD from AD, less complex constructional tasks, in which organizational skills are minimized, may be more useful for differential diagnosis.

Conversely, performance by AD patients on some executive tasks may have been sabotaged by impairments in purportedly nonexecutive skills. For example, time to complete the Stroop test, an executive task, was actually slower on average in the AD patients than in the FTD patients. It is possible that declines in psychomotor speed associated with AD (Storandt & Hill, 1989), rather than impairment in executive ability *per se*, lowered performance on this measure. In line with the recommendations put forth by Stuss (1993), the executive tasks used in future research examining FTD *versus* AD need, as much as possible, to tap selective executive abilities independent of other cognitive skills, such as mental speed, memory, language, and visuospatial ability, known to deteriorate in early AD.

In conclusion, neuropsychological differences between FTD and AD patient groups appear to be rather subtle, and patient groups certainly mirror each other much more than they resemble normal controls on cognitive scores. Examination of relative rankings of scores across cognitive domains, in addition to interpretation of individual neuropsychological scores, may be the best psychometric approach to the differential diagnosis of FTD *versus* AD.

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