

Neuropsychological patterns in right *versus* left frontotemporal dementia

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Abstract

Patients with frontotemporal dementia (FTD) often present with an asymmetric left or right-sided anterior cerebral perfusion abnormality that is associated with differential behavioral symptoms. However, whether patients with primarily right *versus* left FTD also have unique neuropsychological characteristics has not been previously investigated. Comparisons of 11 patients with right-sided FTD and 11 with left FTD indicated that the 2 patient groups showed relatively distinct cognitive profiles. Patients with right FTD exhibited relatively worse performance on PIQ than VIQ, and on select nonverbal executive tasks relative to their verbal analogs (e.g., design fluency < word generation; Picture Arrangement < word sequencing). In contrast, patients with left FTD showed the opposite pattern. In addition, the 2 patient groups differed on several absolute test scores; patients with right FTD demonstrated more errors and perseverative responses, and worse percent conceptual level responses, on the Wisconsin Card Sorting Test, while the left FTD patients obtained significantly worse scores on the Boston Naming Test, and Stroop word reading and color naming. Verbal and nonverbal memory, mental speed, visual perceptual–constructional skill, and IQ subtest scaled scores did not significantly differ between groups. These data indicate that FTD should not be viewed as a unitary disorder, and that neuropsychological testing holds promise for the differential diagnosis of right *versus* left FTD. (*JINS*, 1999, 5, 616–622.)

Keywords: Neuropsychological scores, Executive function, Right *versus* left frontotemporal dementia

INTRODUCTION

Diminished ability to perform executive tasks is a core feature of frontotemporal dementia (FTD), although contradictory conclusions have emerged regarding the presence of collateral deficits in constructional skill, confrontation naming, IQ, calculation, memory, and attention in mildly demented patients with this disorder (Frisoni et al., 1995; Jagust et al., 1989; Johanson & Hagberg, 1989; Miller et al., 1991; Neary et al., 1986). In a recent study comparing patients with FTD *versus* Alzheimer's disease equated for disease severity (Pachana et al., 1996), we found that most, but not

all, FTD patients showed a neuropsychological pattern in which performance on executive tasks (i.e., FAS score) was relatively poorer than performance on visual memory (Rey–Osterrieth, 3-min delay). The variability in cognitive abnormalities that has been reported in patients with FTD, as well as our own finding that not all FTD patients showed the expected executive < memory profile, suggests that FTD is a heterogeneous disorder.

Recently, we reported that behavioral patterns found in FTD differed depending upon whether left *versus* right frontal regions were the most compromised (Miller et al., 1993). Patients with primarily right anterior hypoperfusion (right FTD) displayed prominent behavioral abnormalities (disinhibition; flattened, bizarre or overmodulated affect; psychosis; and compulsions), while patients with primarily left anterior hypoperfusion (left FTD) were more likely to behave in a socially appropriate manner.

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Although behavioral differences between patients with left *versus* right FTD have now been elucidated, no study has yet compared these two groups on neuropsychological measures. It is possible that the cognitive heterogeneity documented in the literature on FTD could be due to varying levels of asymmetric cerebral hypoperfusion in the subjects studied. For example, Frisoni et al. (1995) reported more verbal than nonverbal memory difficulties in their FTD sample, but these subjects appeared to have particularly prominent left frontal hypoperfusion.

The purpose of the present study was to determine if there are differential neuropsychological patterns in FTD which correspond to asymmetries in anterior cerebral hypoperfusion.

METHODS

Participants were 27 patients determined to have FTD by a behavioral neurologist with extensive experience in FTD (B.L.M.). These cases represented consecutive testable patients referred to the clinical practice of Dr. Miller from the community over a 2-year period. All patients met research criteria for FTD set by the Lund-Manchester Group (Brun et al., 1994). All showed frontal-temporal hypoperfusion with sparing of parietal and occipital regions on single photon emission computed tomography (SPECT) brain studies on both ^{133}Xe and $^{99\text{m}}\text{Tc}$ -HMPAO scans.

As previously described (Edwards-Lee et al., 1997), two clinicians blinded to clinical history rated patient SPECT scans with regards to symmetry. Five scans showed symmetrical bifrontal hypoperfusion, 11 showed primarily left frontotemporal hypoperfusion and 11 showed primarily right-sided frontotemporal hypoperfusion. Due to the small number of participants with symmetrical hypoperfusion, these individuals were excluded from statistical analyses.

Patients were administered a comprehensive neuropsychological battery assessing general intelligence (WAIS-R, Wechsler, 1981; Satz-Mogel format except for Picture Arrangement which was administered in its entirety), language processing (Boston Naming Test, Kaplan, Goodglass, & Weintraub, 1983; Stroop A and B, Comalli format, Mitrushina et al., 1999), information processing speed (Trails A, Lezak, 1995), and pencil and paper construction skill (Rey-Osterrieth Complex Figure, Lezak, 1995; Beery Developmental Test of Visual Motor Integration, Beery & Buktenica, 1989). Verbal and nonverbal memory was assessed through the Wechsler Memory Scale-Revised (WMS-R, Wechsler, 1987) Logical Memory subtest, a 3-min delayed recall of the Rey-Osterrieth Complex figure (Boone et al., 1993), and a 10-item Shopping List test (*cereal, bread, crackers, ketchup, jelly, salt, coffee, oranges, cheese, bacon*) in which the patient reads the items aloud and then engages in free recall for five trials, followed by a 15-min delayed free recall trial and 20-item auditory recognition task involving the 10 targets and 10 foils.

In addition, several measures to assess executive-frontal lobe function were administered (Trails B, Lezak, 1995; Wis-

consin Card Sorting Test, Heaton, 1981; Stroop C, Comalli format, Mitrushina et al., 1999), including tests hypothesized to be differentially sensitive to left frontal lobe functioning (word generation-FAS, Milner, 1971) *versus* right frontal lobe functioning (Picture Arrangement subtest of the WAIS-R, McFie & Thompson, 1972; 5-min unstructured design generation task, Jones-Gotman & Milner, 1977). Also, a word sequencing task (see Appendix) was developed as a verbal analog to the Picture Arrangement subtest of the WAIS-R, and as such was postulated to be differentially sensitive to left frontal lobe functioning (Della Malva et al., 1993).

Scores used for analysis included WAIS-R VIQ, PIQ, and scaled scores for individual subtests; total score for the Boston Naming Test; immediate and 3-min delayed recall scores for the Logical Memory subtest of the WMS-R; Trial 5, 15-min delayed recall, and recognition scores for the Shopping List Test; scores for copy and 3-min delayed recall for the Rey-Osterrieth Complex figure (Boone et al., 1993); total score on the Beery (Hall et al., 1996); total words generated for FAS; total designs generated for design fluency; number of categories, perseverative responses, errors, failure to maintain set, and percent conceptual level responses documented on one deck of cards (64 trials) on the Wisconsin Card Sorting Test; time to complete Part A and Part B on the Trailmaking Test; time to complete word reading (A), color naming (B), and color-interference (C) sections of the Stroop Test (Comalli version; Mitrushina et al., 1999); and total number of correctly sequenced sentences out of a possible 10.

Given our previous observation (Pachana et al., 1996) that examination of relative performance may help to differentiate dementia subgroups, we decided, *a priori*, to compare right *versus* left FTD groups on both absolute test scores and on difference scores derived from subtracting scores on pairs of verbal ("left hemisphere") and nonverbal ("right hemisphere") analog tasks. Specifically, groups were compared on four difference scores: (1) VIQ minus PIQ, (2) verbal fluency (FAS) minus design fluency, (3) word sequencing minus picture sequencing (Picture Arrangement), and (4) verbal memory (shopping list 15-min delayed recall) minus nonverbal memory (Rey-Osterrieth 3-min delayed recall).

[*Note:* Given that the tests paired for the latter three difference scores did not have comparable metrics, difference scores were computed from *z* scores generated from control data for these six tests. The 11 controls had no history of neurologic illness, substance abuse, or major psychiatric disorder such as psychosis, major depression, or bipolar illness, and did not significantly differ from either patient group in terms of age ($M = 60.36 \pm 9.6$), years of education ($M = 14.82 \pm 3.3$), or sex distribution (5 men, 6 women).]

RESULTS

Table 1 contains the means and standard deviations or frequencies of the two patient groups for sex, age, education, and cognitive scores. As shown in the table, using a *p* value

Table 1. Demographic and test score means, standard deviations, and group comparisons

Variable	Left FTD	Right FTD	<i>t</i> or χ^2	<i>df</i>	<i>p</i>
Age	63.00 ± 8.87	59.07 ± 11.10	.91	1,20	.3722
Education	15.27 ± 3.80	15.27 ± 1.85	.00	1,20	1.000
Sex	3f/8m	6f/5m	1.62	1	>.20
Intelligence					
FSIQ	79.00 ± 11.78 <i>n</i> = 9	83.00 ± 21.05 <i>n</i> = 11	-.51	1,18	.62
VIQ	73.11 ± 13.92 <i>n</i> = 9	86.82 ± 24.35 <i>n</i> = 11	-1.50	1,18	.15
PIQ	88.00 ± 12.51 <i>n</i> = 10	79.27 ± 14.27 <i>n</i> = 11	1.48	1,19	.15
<i>VIQ minus PIQ</i>	-16.67 ± 12.53 <i>n</i> = 9	7.55 ± 13.24 <i>n</i> = 11	-4.17	1,18	.001*
Information	4.88 ± 3.52 <i>n</i> = 8	8.55 ± 2.81 <i>n</i> = 9	-2.53	1,17	.02
Digit Span	5.22 ± 2.82 <i>n</i> = 9	7.64 ± 3.72 <i>n</i> = 11	-1.60	1,18	.13
Vocabulary	3.56 ± 3.32 <i>n</i> = 9	8.36 ± 5.26 <i>n</i> = 11	-2.38	1,18	.03
Arithmetic	6.33 ± 4.03 <i>n</i> = 9	6.36 ± 4.13 <i>n</i> = 11	-.02	1,18	.99
Comprehension	3.22 ± 1.48 <i>n</i> = 9	5.09 ± 4.53 <i>n</i> = 11	-1.29	1,18	.22
Similarities	3.22 ± 2.28 <i>n</i> = 9	5.09 ± 6.01 <i>n</i> = 11	-.95	1,18	.36
Picture Completion	5.00 ± 1.94 <i>n</i> = 10	5.27 ± 2.76 <i>n</i> = 11	-.26	1,19	.80
Picture Arrangement	5.50 ± 1.78 <i>n</i> = 10	3.64 ± 1.91 <i>n</i> = 11	2.31	1,19	.03
Block Design	6.00 ± 2.45 <i>n</i> = 10	4.64 ± 2.11 <i>n</i> = 11	1.37	1,19	.19
Object Assembly	5.50 ± 1.72 <i>n</i> = 10	4.18 ± 1.99 <i>n</i> = 11	1.62	1,19	.12
Digit Symbol	4.30 ± 2.00 <i>n</i> = 10	3.82 ± 1.78 <i>n</i> = 11	.58	1,19	.57
Language processing					
Boston Naming	14.91 ± 21.42 <i>n</i> = 10	49.73 ± 6.17 <i>n</i> = 11	-5.18	1,20	.0001*
Stroop A	87.25 ± 29.07 <i>n</i> = 8	52.50 ± 9.77 <i>n</i> = 8	3.20	1,14	.01*
Stroop B	143.60 ± 31.57 <i>n</i> = 5	86.50 ± 25.69 <i>n</i> = 8	3.58	1,11	.004*
Constructional					
Rey Figure Copy	29.55 ± 6.53 <i>n</i> = 11	24.73 ± 8.81 <i>n</i> = 11	1.46	1,20	.16
Beery	29.82 ± 11.92 <i>n</i> = 11	31.20 ± 10.36 <i>n</i> = 10	-.28	1,19	.78
Information processing speed					
Trails A	83.22 ± 38.45 <i>n</i> = 11	79.20 ± 75.04 <i>n</i> = 11	.14	1,17	.89
Executive					
FAS	6.00 ± 6.96 <i>n</i> = 11	16.18 ± 15.80 <i>n</i> = 11	-1.96	1,20	.07
Design Fluency	7.46 ± 6.55 <i>n</i> = 11	6.46 ± 9.70 <i>n</i> = 11	.28	1,20	.78
<i>FAS minus Design Fluency</i>	-2.68 ± .59 <i>n</i> = 11	-1.63 ± 1.11 <i>n</i> = 11	-2.77	1,20	.01*
Word Sequencing	1.46 ± 2.88 <i>n</i> = 11	5.38 ± 4.47 <i>n</i> = 8	-2.17	1,17	.05

(continued)

Table 1. Continued

Variable	Left FTD	Right FTD	<i>t</i> or χ^2	<i>df</i>	<i>p</i>
Picture Arrangement	5.50 ± 1.78 <i>n</i> = 10	3.64 ± 1.91 <i>n</i> = 11	2.31	1,19	.03
Word Sequencing minus Picture Arrangement	-6.57 ± 2.82 <i>n</i> = 10	-2.09 ± 3.78 <i>n</i> = 8	-2.89	1,16	.01*
WCST					
Categories	1.90 ± 1.37 <i>n</i> = 10	.60 ± .97 <i>n</i> = 10	2.45	1,18	.03
Perseverative responses	16.00 ± 10.72 <i>n</i> = 8	51.14 ± 15.75 <i>n</i> = 7	-5.11	1,13	.0001*
Errors	21.00 ± 8.07 <i>n</i> = 8	41.00 ± 10.66 <i>n</i> = 6	-4.01	1,12	.002*
% conceptual level responses	59.89 ± 17.96 <i>n</i> = 8	19.53 ± 22.43 <i>n</i> = 6	3.75	1,12	.003*
Memory					
Logical Memory I	7.73 ± 7.49 <i>n</i> = 11	10.46 ± 8.58 <i>n</i> = 11	-.79	1,20	.44
Logical Memory II	4.36 ± 6.10 <i>n</i> = 11	4.46 ± 6.35 <i>n</i> = 11	-.03	1,20	.97
Shopping List					
Trial 5	4.18 ± 3.79 <i>n</i> = 11	4.64 ± 2.66 <i>n</i> = 11	-.33	1,20	.75
Delay	1.91 ± 3.11 <i>n</i> = 11	3.27 ± 3.29 <i>n</i> = 11	-1.00	1,20	.33
Recognition	8.75 ± 1.28 <i>n</i> = 8	8.90 ± 1.97 <i>n</i> = 10	-.19	1,16	.86
Rey Figure delay	7.59 ± 7.55 <i>n</i> = 10	6.05 ± 7.35 <i>n</i> = 10	.49	1,20	.63
Shopping delay minus Rey delay	-4.35 ± 1.66 <i>n</i> = 11	-3.03 ± 2.00 <i>n</i> = 11	-1.68	1,20	.11

of .05 required for statistical significance, *t*-test comparisons revealed that the two patient groups did not differ in age, education, or Full Scale IQ. Similarly, Chi-square analysis did not reveal any significant differences in sex composition. For the remainder of the *t*-test analyses, the *p* value required for statistical significance was lowered to .01 as an adjustment for the multiple comparisons, although we appreciate that this may not have entirely protected against Type 1 error.

As shown in the table, *t*-test comparisons on absolute test scores revealed statistically significant differences between groups only for scores on the Wisconsin Card Sorting Test, Boston Naming Test, and time to complete Stroop A and B. Patients with left FTD performed significantly better than patients with right FTD on number of errors, percent conceptual level responses, and perseverative responses on the Wisconsin Card Sorting Test. In contrast, the right FTD patients significantly outperformed the left FTD patients on select language processing–word-retrieval tasks. Specifically, the right FTD patients obtained significantly better scores on the Boston Naming Test, and significantly faster performance in reading words and naming colors on the Stroop test. The two groups did not significantly differ on verbal or nonverbal memory scores, visual–spatial construc-

tional skill, information processing speed, IQ scores or subtest scaled scores, or executive sequencing and generation tasks. Group comparisons could not be computed for Trails B and Stroop interference time scores due to excessive missing data: 3 left FTD and 8 right FTD patients could not execute the Trails B task, and 7 left FTD and 5 right FTD patients could not complete the Stroop C task. Chi-square analysis comparing groups on Stroop C completion was not significant [$\chi^2(1, N = 22) = .73, p > .3$], although the comparison on Trails B approached significance [$\chi^2(1, N = 22) = 4.55, p = .03$].

T test comparisons of groups on the four difference scores revealed significant differences for VIQ minus PIQ, FAS minus design fluency, and word sequencing minus picture sequencing, but not for verbal memory minus nonverbal memory.

DISCUSSION

Findings from the current study suggest that patients with right *versus* left FTD exhibit relatively distinct cognitive profiles. The patients with right FTD had more perseverative responses and errors, and poorer percent conceptual level responses, on the Wisconsin Card Sorting Test. Left

FTD patients exhibited significantly poorer scores on the Boston Naming Test, and Stroop A (word reading) and B (color naming) times. In addition to these differences in absolute test scores, patients with right FTD exhibited relatively worse performance on PIQ than VIQ, and on select nonverbal executive tasks relative to their verbal analogs (e.g., design fluency < word generation; Picture Arrangement < word sequencing), while patients with left FTD showed the opposite pattern. Groups did not significantly differ in visual-spatial constructional skill, mental speed, verbal *versus* nonverbal memory scores, IQ subtest scaled scores, and select executive tasks (Trails B, Stroop C).

Taken as a whole, the neuropsychological findings suggest that patients with asymmetric FTD show prominent deficits in sequencing and generation of either verbal or nonverbal-visual material, depending on whether the underlying perfusion abnormality primarily involves the right or left hemisphere. Sequencing and generation both require that symbolic representations be held on line to guide behavior (Stolar et al., 1994), and it is possible that a deficit in this latter supervisory activity may be a core characteristic of FTD. The left FTD patients also show worse deficits in verbal semantic knowledge (naming), reading speed, and overall verbal intellectual skills as compared to patients with right FTD, while patients with right FTD demonstrate more pronounced perseverative behavior and lowered overall nonverbal intellectual abilities as compared to patients with left FTD.

Results from the current study support our initial observation (Pachana et al., 1996) that examination of relative performance as opposed to absolute scores may be a fruitful approach to identifying cognitive profiles in dementia. While no significant group differences were documented on VIQ, PIQ, FAS, design fluency, Picture Arrangement, and word sequencing scores after adjusting for multiple comparisons, when difference scores were computed between the verbal and nonverbal analog test pairs (i.e., VIQ minus PIQ, FAS minus design fluency, word sequencing minus Picture Arrangement), significant group differences were detected. Although robust differences in test performance are typically documented between dementia patients and controls, test score differences between dementia subgroups tend to be more subtle and often appear to be better detected through analysis of relative ranking of test performances (Pachana et al., 1996), composite scores (Gregory et al., 1997), or as illustrated by the present study, comparisons on difference scores. However, the failure to detect significant differences on absolute test scores may also have been a function of small sample size and resultant Type II error. Additional research on larger samples is needed to determine whether further differences in cognitive scores between right *versus* left FTD exist.

It had been expected that the two patient groups might show a dissociation in verbal *versus* nonverbal memory given previous literature showing that the left temporal lobe is integral in the learning and recall of verbal material and that the right temporal lobe is involved in learning and recall of

nonverbal information (Milner, 1971). In fact, Frisoni et al. (1995) found verbal learning depressed relative to nonverbal learning in their sample of FTD patients with primarily left frontal hypoperfusion. However, we did not document a difference in verbal and nonverbal memory performance between our right and left FTD patients. The two patient groups both exhibited the “frontal” memory pattern of poor free recall in the context of relatively spared recognition memory (Wheeler et al., 1995). The fact that both groups performed comparably on verbal and nonverbal free recall tasks would suggest that frontal lobe disruption, regardless of lateralization, disturbs the organized retrieval of both verbal and pictorial information.

Our observation that performance on an executive task involving problem-solving-set shifting (WCST) was more perseverative in patients with right FTD was not predicted. Of interest, some investigators have reported a relationship between tests of right frontal lobe function and perseveration. Specifically, Brugger et al. (1996) observed that suppression of perseveration in random number generation was correlated with enhanced performance on a right frontal lobe cognitive task (Design Fluency) relative to performance on a left anterior cognitive task (word generation) in normal individuals. The current study provides some corroboration of these findings in that the patients who demonstrated design fluency worse than word fluency were the same individuals who exhibited the worst perseverative behavior on the WCST.

The question arises as to why perseveration would be more tied to right frontal lobe functioning. At least part of the answer may lie in emerging evidence that the two frontal lobes are lateralized in terms of select neurotransmitters. Norepinephrine systems, which are critical for response to novel situations, are overrepresented in the right hemisphere, and dopamine pathways, involved in behavioral stereotypy, are relatively lateralized to the left hemisphere (Goldberg et al., 1994; Tucker & Williamson, 1984). Goldberg and Costa (1981) hypothesized that this distinction between cognitive novelty and routinization is actually the basis for hemispheric specialization. According to Goldberg et al. (1994), “The left prefrontal system is critical to guiding behavior by a current cognitive context, and the right prefrontal system to the ability to alter the context in response to ongoing events” (p. 276). Normally, the two frontal lobes balance each other in terms of novel *versus* routinized processing, which allows for flexible and adaptive responses to the environment. However, it is hypothesized that with disruption of right frontal lobe functioning, the left frontal lobe becomes dominant, resulting in excessively routinized behavior, as exemplified by perseveration, while in disruption of left frontal lobe functioning, the right frontal lobe becomes excessively dominant, resulting in a preponderance of non-routinized behavior, as manifested by environmental dependency (Goldberg et al., 1994; Lhermitte, 1986).

Goldberg (1995) has suggested that it may be more prudent to view frontal syndromes as reflective of a lateralized imbalance rather than an absolute deficiency. Data from the

current study suggest that FTD may provide an important model for studying functional imbalance of the right and left frontal lobes.

Our findings indicate that FTD should not be viewed as a unitary disorder, and suggest that neuropsychological testing holds promise for the differential diagnosis of right *versus* left FTD. If our sample approximates the larger population of FTD patients, asymmetry is the rule rather than the exception; 82% of our patients exhibited asymmetric hypoperfusion patterns. Of interest, the original description of FTD as reported by Pick (1892/1977) involved a patient with atrophy primarily confined to the left temporal lobe. Also, Frisoni et al. (1995) reported asymmetric perfusion patterns in FTD as compared to symmetric perfusion in Alzheimer's patients, but they concluded that the asymmetry consistently reflected worse perfusion in left anterior regions in their 11 participants. In contrast, we found an equal ratio of left *versus* right asymmetry in our sample.

Recently, Hodges et al. (1999) have reported that patients with frontal lobe *versus* temporal lobe variants of frontotemporal dementia show cognitive profiles distinct from each other and from those of patients with Alzheimer's disease and controls. However, the influence of disease lateralization was not addressed. The data from the current study in conjunction with that of Hodges et al. (1999) would suggest that in future research on the neuropsychology of FTD, patients should be grouped on both hemisphere perfusion asymmetry and lobar dimensions.

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APPENDIX

WORD SEQUENCING

Instructions: Cards for each sentence are placed in front of the patient in the following scrambled order. Patients are instructed to arrange the words to make sentences using all cards. Patients are allowed up to 120 s to complete each sentence. Correct sentence orders are shown below the scrambled orders. Each sentence receives a score of 1 (correct) or 0 (incorrect).

1. orange juice he all the drank of
(he drank all of the orange juice)
2. we around parking lot walked the
(we walked around the parking lot)
3. clothes the used to she buy credit card
(she used the credit card to buy clothes)
4. bus stop at waited the they
(they waited at the bus stop)
5. was purse her in key chain the
(the [her] key chain was in her [the] purse)
6. around fastened seat belt her she the
(she fastened the seat belt around her)
7. the he hammer the found tool box in
(he found the hammer in the tool box)
8. toll booth the put she in money
(she put money in the toll booth)
9. ate they birthday cake the
(they ate the birthday cake)
10. the in eggs frying pan cooked she
(she cooked eggs in the frying pan)