

# How preserved is episodic memory in behavioral variant frontotemporal dementia?

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## ABSTRACT

**Objective:** Studies have shown variable memory performance in patients with behavioral variant frontotemporal dementia (bvFTD). Our study investigated whether this variability is due to the admixture of patients with true bvFTD and phenocopy patients. We also sought to compare performance of patients with bvFTD and patients with Alzheimer disease (AD).

**Methods:** We analyzed neuropsychological memory performance in patients with a clinical diagnosis of bvFTD divided into those who progressed (n = 50) and those who remained stable (n = 39), patients with AD (n = 64), and healthy controls (n = 64).

**Results:** Patients with progressive bvFTD were impaired on most memory tests to a similar level to that of patients with early AD. Findings from a subset of patients with progressive bvFTD with confirmed FTLN pathology (n = 10) corroborated these findings. By contrast, patients with phenocopy bvFTD performed significantly better than progressors and patients with AD. Logistic regression revealed that patients with bvFTD can be distinguished to a high degree (85%) on the immediate recall score of a word list learning test (Rey Auditory Verbal Learning Test).

**Conclusions:** Our results provide evidence for an underlying memory deficit in “real” or progressive behavioral variant frontotemporal dementia (bvFTD) similar to Alzheimer disease, though the groups differ in orientation scores, with patients with bvFTD being intact. Exclusion solely based on impaired neuropsychological memory performance can potentially lead to an underdiagnosis of FTD. *Neurology*® 2010;74:472-479

## GLOSSARY

**ACE** = Addenbrooke's Cognitive Examination; **AD** = Alzheimer disease; **bvFTD** = behavioral variant frontotemporal dementia; **CBI** = Cambridge Behavioral Inventory; **CDR** = Clinical Dementia Rating; **FTD** = frontotemporal dementia; **RAVLT** = Rey Auditory Verbal Learning Test; **RCFT** = Rey-Osterrieth Complex Figure Test; **RMT** = Recognition Memory Test.

Our study focuses on episodic memory in frontotemporal dementia (FTD). “Severe amnesia” is currently an exclusion criterion for the behavioral subtype of FTD (bvFTD),<sup>1</sup> yet 10% of pathologically confirmed cases have reported memory symptoms in the initial stages of disease,<sup>2</sup> and occasional cases have severe amnesia,<sup>3</sup> as emphasized in early descriptions of Pick's.<sup>4</sup> Recently this and other findings have put into question the reliability of current diagnostic criteria for bvFTD.<sup>5-7</sup>

To date, surprisingly few studies have investigated episodic memory in bvFTD, with inconsistent results. Such inconsistency could, at least in part, be explained by recent studies which have shown that clinically diagnosed patients with bvFTD vary in their prognosis<sup>8-10</sup>; some show rapid progression while others show little or no progression over a decade. The 2 patient groups can be discriminated on MRI and PET findings despite exhibiting equivalent degrees of behavioral disturbance.<sup>8-10</sup> This heterogeneity of bvFTD might explain previous findings: if only the progressive group shows brain atrophy, then this group is more likely to exhibit

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**Table 1** Mean (SD) scores for patients with AD, patients with bvFTD, and controls on demographics and general cognitive tests<sup>a</sup>

Demographics, cognitive and behavioral tests	AD	Progressors	Phenocopy	Controls	F values	Progressors vs AD	Phenocopy vs AD	Progressors vs controls	Phenocopy vs controls	Progressors vs phenocopy
No.	64	39	23	64	—	—	—	—	—	—
Mean age at test, y	63.4 (5.8)	61.9 (8.1)	60 (6.7)	62.8 (5.4)	NS	—	—	—	—	—
Education, y	11.4 (2.5)	11.7 (2.3)	12.1 (2.5)	13.4 (2.7)	<sup>c</sup>	NS	NS	<sup>d</sup>	NS	NS
Length of history, y	—	4.8 (4)	3.1 (2.1)	—	—	—	—	—	—	NS
Handedness, R/L	—	25/1	18/2	—	—	—	—	—	—	NS
Sex, M/F	—	27/12	21/2	—	—	—	—	—	—	<sup>d</sup>
ACE (max score = 100)	72.1 (14.8)	71.6 (15.8)	85 (16.2)	94.7 (3.2)	<sup>b</sup>	NS	<sup>c</sup>	<sup>b</sup>	<sup>d</sup>	<sup>c</sup>
Orientation	78.6 (2.7)	91.6 (1.7)	96 (1)	99.1 (0.3)	<sup>b</sup>	<sup>d</sup>	<sup>c</sup>	NS	NS	NS
MMSE (max score = 30)	24.1 (4.1)	25.9 (2.9)	28.2 (2.2)	29.2 (0.9)	<sup>b</sup>	<sup>c</sup>	<sup>b</sup>	<sup>b</sup>	NS	<sup>d</sup>
CDR (score 0-3)	0.76 (0.35)	0.91 (0.59)	0.67 (0.59)	—	NS	NS	NS	—	—	NS
CBI (max score = 316)	48.5 (31.9)	111.8 (44.1)	85.1 (43.1)	—	<sup>b</sup>	<sup>b</sup>	<sup>c</sup>	—	—	<sup>d</sup>

Abbreviations: AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; CBI = Cambridge Behavioral Inventory; CDR = Clinical Dementia Rating.

<sup>a</sup>F values indicate significant differences across groups; Tukey post hoc tests compare differences between group pairs.

<sup>b</sup>*p* < 0.000; <sup>c</sup>*p* < 0.01; <sup>d</sup>*p* < 0.05.

memory deficits, while the so-called phenocopy group will present little or no memory dysfunction.

We tested this hypothesis by classifying patients with bvFTD into progressive vs phenocopy cases based on their long-term outcome and contrasted them to a large AD patient cohort on a range of memory tests. Validation of our results was further established in the subsample of patients with confirmed FTD pathology.

**METHODS Case selection.** Patients were selected from the Cambridge Dementia Clinic database, resulting in 89 patients with a clinical diagnosis of bvFTD and follow-up for at least 3 years. All patients met core clinical diagnostic criteria for FTD<sup>11</sup> with informant substantiated changes in personality and social behavior. We allowed patients with memory complaints and impairment of episodic memory tasks if the other core diagnostic criteria were present. A senior neurologist (J.R.H.) classified the cases into progressive vs phenocopy based on the presence/absence of change over a 3-year period evident on both cognitive measures (Addenbrooke's Cognitive Examination [ACE]) and activities of daily living. The dichotomy was striking, as previously reported.<sup>8,12</sup> Crucially, memory complaints and initial neuropsychological data were not included as classifiers for progression. No significant differences in the prevalence of diagnostic features were present between the progressors and phenocopy cases.<sup>13</sup>

Of the 89 patients, 27 cases were excluded from the study for the following reasons: assessment prior to 1997 with inconsistent neuropsychological protocols (*n* = 12); combined FTD with motor neuron disease (*n* = 3); and fewer than 3 of the selected memory tests (see below) (*n* = 12). Of those excluded, 20 were progressors and 7 were phenocopy. The final sample therefore comprised 39 of 59 (66%) progressors and 23 of 30 (77%) phenocopy cases (see table 1 for demographic details). Of the pro-

gressors, 19 have died and neuropathologic investigation was available in 10 of the 19 cases (53%). In all cases, the pathologic diagnosis of FTLT was confirmed (FTLT-tau: *n* = 7; FTLT-U: *n* = 3).

The 64 patients with AD were selected from the same database and met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association diagnostic criteria for probable AD.<sup>14</sup> All had 3 or more of the neuropsychological tests. Although pathologic verification was not available in this AD cohort, earlier studies from Cambridge using the same diagnostic criteria have shown a very high rate of Alzheimer pathology in clinically diagnosed patients with AD.<sup>15</sup> Further, it is unusual for clinically diagnosed patients with AD to have underlying FTLT pathology.

All patients were assessed by a multidisciplinary team to exclude other neurologic or psychiatric (e.g., schizophrenia, depression, mania, alcohol and substance abuse) etiologies. All caregivers completed the Cambridge Behavioral Inventory (CBI)<sup>16,17</sup> to determine the severity of behavioral symptoms.

Sixty-four healthy controls, matched in age, were recruited as control subjects, via a volunteer panel, or were spouses/carers of patients.

**Standard protocol approvals, registrations, and patient consents.** All patients and their spouses gave informed consent, which was approved by the local ethics committee.

**Test selection.** The following anterograde memory tests were administered and test scores analyzed: Recognition Memory Test (RMT); Rey-Osterrieth Complex Figure Test (RCFT); Rey Auditory Verbal Learning Test (RAVLT); ACE and ACE-R memory subscores<sup>18,19</sup>; and Logical Memory I and II, Wechsler Memory Scale–Revised.

In a second step, we calculated 3 composite memory scores: 1) overall memory (all memory scores averaged), 2) overall recall (RCFT, RAVLT, ACE, and Logical Memory recall scores), and 3) overall recognition (RBMT and RAVLT recognition scores). All neuropsychological test scores were converted into percent-

age correct to allow comparison across tests and calculation of composite scores. Only test scores from the initial assessment were included in all analyses.

**Statistics.** Data were analyzed using SPSS15.0 (SPSS Inc., Chicago, IL). Parametric demographic (age, education), neuropsychological (memory and general cognitive tests), and behavioral (CBI) data were compared across the 4 groups via analysis of variance followed by Tukey post hoc tests. Prior to these analyses, variables were plotted and checked for normality of distribution by Kolmogorov-Smirnov tests. Variables revealing non-normal distributions were log transformed and the appropriate log values were used in the analyses. Clinical data were analyzed by  $\chi^2$  tests and logistic regression analyses.

**RESULTS Demographics.** Comparisons of progressors vs phenocopy cases revealed no significant difference in demographic variables. There was, however, a much higher percentage of men in the nonprogressor group ( $p < 0.05$ ) (table 1). Controls and patients with AD were not significantly different from the 2 other patient groups for age but controls had more years of education than progressors ( $p < 0.025$ ) and patients with AD ( $p < 0.01$ ). The patient groups did not differ on the Clinical Dementia Rating (CDR)

score, indicating no difference across groups in disease severity (all  $p > 0.1$ ).

**Global cognitive function.** Performance of both bvFTD groups on the ACE-R was generally worse than that of controls (table 1). The post hoc tests showed that progressors and patients with AD were equivalent, whereas they differed from phenocopy group and controls. Interestingly, though, progressors and phenocopy patients performed at control level on the orientation component of the ACE-R (max score = 10), whereas patients with AD were significantly impaired in comparison to all other groups.

Results of the CBI showed that progressors had the highest endorsements of behavioral disturbances across all 3 patient groups. Progressors and phenocopy cases had higher scores on the CBI than patients with AD, but also differed from each other.

**Memory function.** The results of the memory tests for all 4 groups are shown in table 2. Overall, memory scores across most memory test variables showed a

**Table 2** Percentage correct scores (SD) for AD, bvFTD, and controls on memory tests<sup>a</sup>

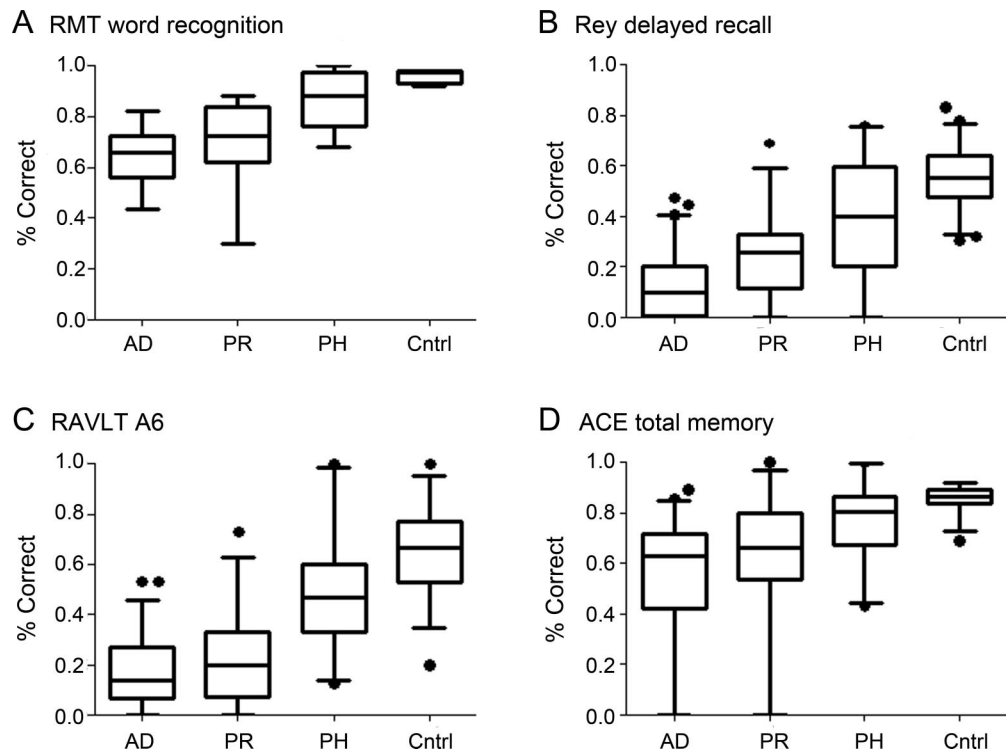
Memory tests (% correct)	AD	Progressors	Phenocopy	Controls	F values	Progressors vs AD	Phenocopy vs AD	Progressors vs controls	Phenocopy vs controls	Progressors vs phenocopy
<b>RMT</b>										
Faces	64.6 (11)	72.2 (20.3)	75.2 (9.8)	86 (9.9)	d	NS	NS	NS	NS	NS
Words	64 (11)	70.7 (17.4)	86.8 (10.8)	96 (2.8)	b	NS	b	c	NS	d
<b>RCFT</b>										
Immediate recall	13.7 (9.8)	29.7 (20.4)	37.2 (22.7)	55.9 (16.9)	b	c	c	d	NS	NS
Delayed recall	11.9 (12.3)	24.3 (17.1)	40.7 (22.8)	55.5 (12.5)	b	c	b	b	c	c
<b>RAVLT</b>										
Total Learning A	34.8 (12)	30.2 (15)	52.1 (15.2)	57.5 (23.7)	b	NS	c	b	NS	b
Immediate recall A6	16.8 (14.2)	21.3 (18.2)	47.6 (22.7)	66.9 (17.4)	b	NS	b	b	c	b
30-min recall	12 (15.4)	15.7 (20)	42.8 (22.2)	68 (19.1)	b	NS	b	b	b	b
Recognition	58.1 (24.3)	72.3 (20)	77.6 (22.2)	93.5 (8.6)	b	d	c	c	d	NS
<b>Logical memory</b>										
Immediate recall	16.2 (11.3)	32.4 (8.7)	32.9 (21.8)	55.9 (15.1)	b	d	d	c	c	NS
Delayed recall	6.5 (8.7)	20 (9.7)	23.3 (15.8)	51.9 (16.3)	b	d	d	b	b	NS
<b>ACE</b>										
Retrograde memory	58.8 (33.8)	54.5 (33.9)	81.3 (24.2)	76.5 (23)	c	NS	d	c	NS	c
Total memory score	54.8 (22.7)	61.4 (25.3)	77.6 (12.3)	85.1 (5.6)	b	NS	b	b	NS	d
<b>Composite memory scores</b>										
Overall memory	20.5 (10.5)	23.8 (9.9)	40.5 (15.5)	64.7 (9.7)	b	NS	b	b	b	b
Recall	26.7 (13.3)	36.7 (16.4)	52.5 (14.8)	65.2 (11.2)	b	c	b	b	c	b
Recognition	59.3 (21.7)	63.3 (24.8)	68.9 (19.7)	93.3 (8.4)	b	NS	NS	b	b	NS

Abbreviations: ACE = Addenbrooke's Cognitive Examination; AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; NS = non significant; RAVLT = Rey Auditory Verbal Learning Test.

<sup>a</sup>F values indicate significant differences across groups; Tukey post hoc tests compare differences between group pairs.

<sup>b</sup> $p < 0.000$ ; <sup>c</sup> $p < 0.01$ ; <sup>d</sup> $p < 0.05$ .

**Figure 1** Selected memory scores across groups



Percentage correct boxplots on (A) Recognition Memory Test (RMT), (B) Rey recall, (C) Rey Auditory Verbal Learning Test (RAVLT) A6, and (D) Addenbrooke's Cognitive Examination (ACE) memory measures across the 4 groups (AD = Alzheimer disease; PR = progressor; PH = phenocopy; Cntrl = control). Whiskers indicate 5th-95th percentile.

stepwise function (figure 1), a gradation across the 4 groups in the following pattern: controls > phenocopy > progressors > AD. More specifically, significant group effects were observed for all memory scores. Post hoc Tukey tests revealed significant differences between progressors and phenocopy on RMT word recognition, RCFT delayed recall, all RAVLT measures (with exception of the recognition component), and ACE memory scores. Importantly, the severity of the memory impairment in the progressors was very similar to that of AD. Compared to the progressors, the AD group obtained a worse performance only on RCFT recall, RAVLT recognition, and Logical Memory (being worse in AD). By contrast, phenocopy did not differ from controls on RMT word recognition, RAVLT Total, and ACE-R scores. Logical Memory test scores showed no differences for progressors and phenocopy; both groups showed impairment relative to controls.

Analyses on the composite memory scores revealed that all patient groups performed significantly more poorly than controls. More importantly, however, progressors were impaired relative to phenocopy for the overall memory and recall scores, but not for the recognition score (figure 2). In addition, phenocopy performed significantly worse than controls on all composite scores and performed better

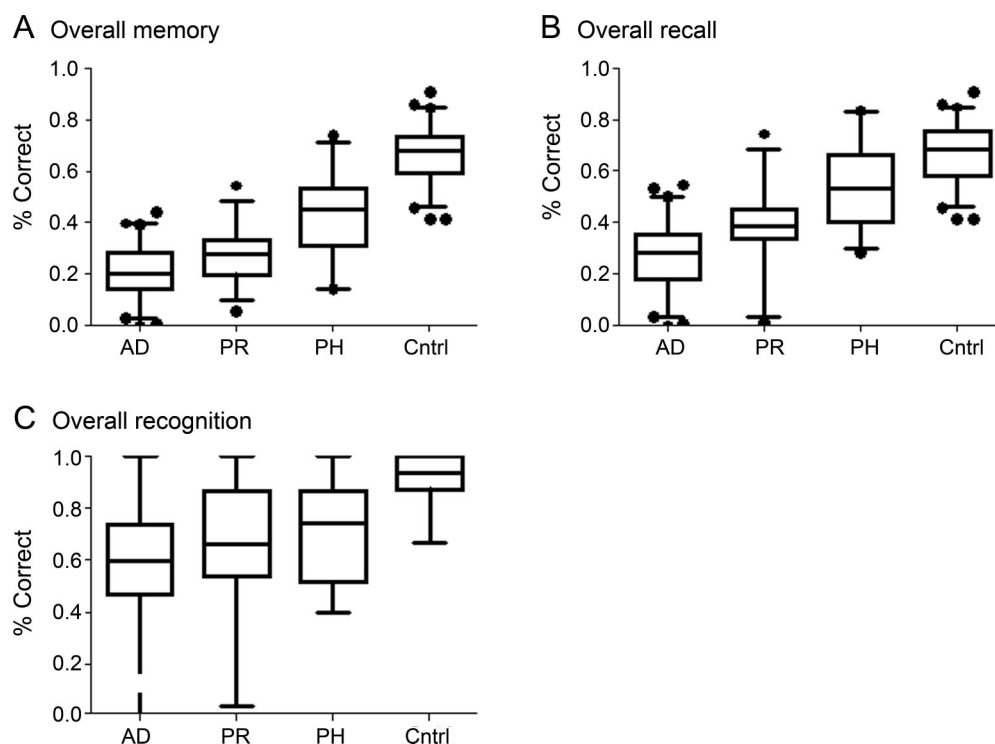
than patients with AD on the overall memory and recall scores. The overall memory and recognition scores did not differ between patients with AD and progressors but progressors obtained significantly higher scores than patients with AD on the recall composite scores. Within-group comparisons of recall and recognition measures showed significant effects for all groups, indicating an overall better performance in recognition than recall.

Importantly, a comparison of those with confirmed pathology ( $n = 10$ ) and the 29 progressors without pathology showed no differences on any measures (all  $p > 0.1$ ).

**Efficacy of test measures for bvFTD patient classification.** Classification of bvFTD subgroups was established by calculating the degree of overlap between controls and each patient group (i.e., the number of individual scores from each group within the normal range as a percentage value). We defined the normal range as scores lying within 2 standard deviations of the controls' mean.

Table 3 shows the overlap between bvFTD subgroups and controls for each memory measure. Low percentages indicate a small overlap of each patient group with the normal control range and vice versa. The overlap between phenocopy cases and controls

**Figure 2** Composite memory scores across groups



Percentage correct boxplots on (A) overall memory, (B) recall, and (C) recognition composite scores across the 4 groups (AD = Alzheimer disease; PR = progressor; PH = phenocopy; Cntrl = Control). Whiskers indicate 5th–95th percentile.

ranged from 100% (RAVLT total score) to 42% (RMT word recognition) with the majority showing at least 60% overlap. The overlap between the progressors and controls was much lower; of note is the finding of complete separation on the RMT words, indicating that all progressors were impaired. Similarly, separation on the RAVLT and RCFT was in the order of 75%.

Logistic stepwise regression analysis (enter method) was carried out after selecting the scores with the least

overlap between bvFTD subgroups (RCFT delayed recall, RAVLT immediate recall [A6], ACE retrograde memory): 85.4% of the patients could be correctly classified as progressors and phenocopy cases based upon the RAVLT immediate recall (A6) score. No other variable improved classification.

**Correlation of memory measures with behavioral disturbance.** Finally, we correlated the CBI subscores of mood, motivation, and challenging behavior with the memory scores to see whether the formal memory testing results might have been affected by the behavioral disturbance in the patients with bvFTD. None of the memory scores correlated with behavioral disturbance in progressors and phenocopy cases (all  $p > 0.1$ ).

**DISCUSSION** The most striking finding of this study is that the degree of episodic memory impairment in patients with progressive bvFTD is similar to that observed in patients with AD. This finding has important clinical and theoretical implications. Additionally, we have shown that cases with progressive bvFTD can be distinguished from the phenocopy syndrome. Virtually all of the memory tests yielded at least one score which distinguished progressors from phenocopy cases. Using immediate recall of a word list score in a logistic regression analysis

**Table 3** Percent overlap between control range scores and bvFTD groups

Memory tests	Progressors, %	Phenocopy, %	Difference score (phenocopy – progressors), %
RMT Word Recognition	0	42	42
Rey Delayed Recall	28	65	37
<b>RAVLT</b>			
Total Learning A	89	100	11
Immediate recall A6	23	74	51
30-min recall	23	62	39
<b>ACE</b>			
Retrograde memory	62	95	34
Total memory score	37	70	33

Abbreviations: ACE = Addenbrooke's Cognitive Examination; bvFTD = behavioral variant frontotemporal dementia; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey-Osterrieth Complex Figure Test; RMT = Recognition Memory Test.

achieved ~85% correct classification of patients with bvFTD. Deficits were also consistently observed across the composite memory scores, with exception of the overall recognition performance, indicating that memory scores are very sensitive in detecting progressive bvFTD cases at first presentation.

Our data show that it is difficult to distinguish patients with AD from patients with progressive bvFTD purely on the basis of neuropsychological assessment of memory at the first clinic visit. This contrasts with previous studies showing that, relative to patients with AD, patients with bvFTD have been said to perform better on recognition, recall, and associative memory tasks and not to show the accelerated forgetting typical of AD in delayed free recall conditions.<sup>20,21</sup> Verbal priming was shown to improve performance on a word completion task in FTD,<sup>22</sup> suggesting that memory dysfunction results from frontally dependent, defective retrieval strategies rather than true amnesia, though see reference.<sup>20</sup> Intact memory performance, at least in the early stages of bvFTD, has also been reported on complex associative memory tasks,<sup>23</sup> whereas such tasks are usually impaired in early AD.

In our data, both groups show deficits in memory capacities across a range of scores, although patients with AD show lower scores on some tests, notably those requiring free recall after a delay. This raises the fundamental question: on what basis should clinicians make a diagnosis of AD or FTD? The predominant and characteristic behavioral disturbances are still the best indicator of bvFTD, although such behavioral disturbances are difficult to quantify and reliable informants are not always available. There is also growing evidence that patients with bvFTD show disproportionate impairment on tests of theory of mind and social cognition, involving detection of faux pas,<sup>24</sup> sarcasm,<sup>25</sup> and emotion discrimination.<sup>26,27</sup> According to our data, it is also possible to distinguish AD and bvFTD on the orientation scores of the ACE, in that patients with AD have more impaired orientation, while even patients with progressive bvFTD had preserved orientation for time and place.

While patients with bvFTD do not demonstrate disorientation, they show substantial deficits on tests of episodic memory. Performance on such tests should be interpreted with caution. Impaired episodic memory does not exclude a diagnosis of bvFTD.

On a neuroanatomic level, pathologic studies have reported hippocampal atrophy in FTD even early in the course of the disease,<sup>4,28</sup> which could explain the observed memory deficits. Neuroimaging findings in early bvFTD have been equivocal, with

some studies reporting no medial temporal lobe atrophy<sup>29</sup> or hypometabolism in bvFTD,<sup>30</sup> whereas others have found clear changes.<sup>31</sup>

Also, atrophy does not equate with underfunctioning and further studies should explore structure and function of key memory-related structures in FTD. Similarly, it is currently not clear what the contribution is of the prominent frontal atrophy in bvFTD to the memory deficits.<sup>31</sup> Our tasks were mainly recall-based, which has been shown to place strong functional demands on prefrontal cortex areas,<sup>32</sup> and thus could have contributed to the observed memory problems. Prefrontal cortex function and, in particular, executive function have been previously shown to be impaired in progressive but not nonprogressive bvFTD.<sup>33</sup> It is, therefore, not surprising that the RAVLT immediate recall score emerged as one of the strongest predictors for the progressive group. The recall of such word lists very likely depends on the interaction between intact hippocampal structures and prefrontal cortices. Since our data were analyzed retrospectively, we were unable to address the differential contributions of prefrontal cortex and hippocampal systems to episodic memory, which clearly needs to be investigated in future studies.

Distinguishing patients with progressive bvFTD has important clinical implications. It should be noted that all patients with a clinical diagnosis of bvFTD presented with alterations of behavior and social conduct. Those who will progress over the subsequent 3 years are clinically indistinguishable from those who will remain static.<sup>13</sup> Our findings indicate, however, that the 2 groups can be distinguished to a high degree based on their memory function scores even at first presentation. If a patient shows significant and consistently low scores on memory tests, it is almost certain that this person has progressive bvFTD. By contrast, the presence of subtle or patchy memory impairment likely supports a diagnosis of the phenocopy syndrome. Further corroboration can be obtained by neuroimaging,<sup>34</sup> in that those with progressive FTD show focal orbital and mesial frontal atrophy on MRI and hypometabolism on FDG-PET.<sup>35</sup> Other indicators of progressive bvFTD are impairment in activities of daily living,<sup>12</sup> executive function,<sup>33</sup> and social cognition.<sup>25</sup>

The fact that the phenocopy group also showed reduced memory performance across most tests in comparison to healthy controls was a surprise and is difficult to explain. Subtle memory deficits can be an indicator of prefrontal cortex damage; however, previous studies report that phenocopy cases show no or very subtle executive function impairment<sup>33</sup> and little cortical prefrontal cortex atrophy.<sup>8,36</sup> Alternatively, mood and motivation disturbances could have

affected the memory performance of this group but correlational analyses of the CBI mood and motivation subscores with memory scores revealed no significant relations between the variables.

We have used the term phenocopy syndrome for patients who showed very slow or no progression over several years without apparent brain atrophy.<sup>8,9,12,13,25,33</sup> The nosology of these patients is a matter of ongoing debate. It seems unlikely that they have progressive FTD but rather a phenocopy, which mimics the behavioral symptoms of bvFTD. It is interesting that, in our sample, a large proportion of cases are male, whereas for progressive cases, sex was equally distributed, which was significantly different across groups. This factor hints toward an Asperger spectrum disorder, with possible decompensation in mid to late life. A proportion of patients may also have functional disruption of frontotemporal circuitry even though they do not reach criteria for a psychiatric disorder.

Previous inconsistent findings on memory tests in bvFTD are probably explained by the admixture of cases in prior studies. Studies containing a significant number of phenocopy patients would, therefore, yield variable results and large overlaps in the test performances between AD and FTD.<sup>37</sup> It may be that any patient with substantial memory impairment would be excluded from studies of FTD, hence perpetuating the view that memory is preserved in FTD. Clinicians should therefore take into account that patients with progressive bvFTD are very likely to present with memory disturbances but that the general orientation in these patients, in contrast to AD, is intact.

Even though the sensitivity of tests for detecting true FTD was high, the specificity of the underlying memory deficit was not explored. Furthermore, high-resolution imaging of medial temporal regions might also help to find commonalities/differences between FTD and AD. Unfortunately, suitable imaging to conduct volumetric comparison of the groups was not available in the majority of our patients, who were scanned using different protocols over a decade. Finally, our study classified cases retrospectively but, in future studies, it will be important to ascertain group membership prospectively.

#### AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. M. Hornberger.

#### DISCLOSURE

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