

# Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia

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## ABSTRACT

**Background:** Recent studies suggest that behavioral variant frontotemporal dementia (bv-FTD) patients differ in their prognosis with fast-progressing and very slow-progressing cases. We investigated executive and behavioral profiles of progressive and nonprogressive bv-FTD patients to establish diagnostic markers discriminating the two groups.

**Methods:** A range of neuropsychological and behavioral tests were used. Mean overlap-based statistical analyses and logistic regression analyses were performed to distinguish progressive from nonprogressive bv-FTD cases.

**Results:** Although progressors and nonprogressors showed similar behavioral profiles, they were distinguishable by their performance on executive tasks. The nonprogressors' performance on all tests was within the normal range, whereas the progressors were consistently impaired on four tests: Digit Span Backward, Hayling Test of inhibitory control, Letter Fluency, and Trails B. Logistic regression showed that 86% of patients could be classified on the basis of Digit Span and Hayling subscores.

**Conclusions:** Contrary to some prior reports, behavioral variant frontotemporal dementia (bv-FTD) patients who progress over time are typically impaired on executive tasks at first presentation, although an important minority of true FTD patients perform normally. Previous inconsistencies are explicable by the mixture of patients with progressing FTD and phenocopy cases. *Neurology*® 2008;71:1481-1488

## GLOSSARY

**ACE** = Addenbrooke Cognitive Examination; **AD** = Alzheimer disease; **BADS** = Behavioral Assessment of the Dysexecutive Syndrome; **bv-FTD** = behavioral variant frontotemporal dementia; **CBI** = Cambridge Behavioral Inventory; **FTD** = frontotemporal dementia; **MMSE** = Mini-Mental State Examination; **NPI** = Neuropsychiatric Inventory; **NS** = not significant.

Frontotemporal dementia (FTD), the second commonest cause of young-onset dementia (<65 years),<sup>1</sup> has received a surge of renewed interest after recent genetic discoveries.<sup>2</sup> Clinical diagnostic criteria have been proposed,<sup>3</sup> but the differentiation from other dementias remains difficult with current neuropsychological and imaging tools.<sup>4</sup> This is in particular true for the behavioral subtype of FTD (bv-FTD), in which patients present with behavior and personality changes,<sup>5</sup> including change of mood, motivation, and inhibition, with severe implications for social conduct and increased impact on carers. Neuroimaging and pathologic studies have suggested that the brain regions mostly consistently involved are mesial and orbitofrontal followed by dorsolateral prefrontal cortices.<sup>6-8</sup> The question arises of how well standard neuropsychological tests of executive function discriminate bv-FTD from healthy controls and Alzheimer disease (AD) patients.

Some studies have shown that bv-FTD perform poorly on tests of executive function such as the Trails<sup>9</sup>; the Brixton task of spatial anticipation; the Hayling Test, which requires inhibition of

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prepotent responses<sup>10</sup>; and verbal fluency,<sup>9,11</sup> but AD patients show a similar performance profile on these tests.<sup>12</sup> By contrast, other executive tests yield inconsistent impairment, in particular the Wisconsin Card Sorting Test,<sup>13</sup> the Tower of London,<sup>14</sup> and the Digit Span task.<sup>4,15</sup> Thus, discriminating bv-FTD from other dementias on the basis of executive test performance remains difficult. Diagnosis often depends on the interpretation of clinical signs (e.g., perseveration, confabulation, poor organization<sup>16</sup>), which are difficult to quantify.

To further complicate the picture, recent studies have shown that bv-FTD patients vary widely in their prognosis,<sup>7,17,18</sup> with some patients showing a rapid disease progression over a few years and others showing little or no progression over a decade. Patients with long disease duration may be identifiable at presentation by the lack of atrophy on MRI and absence of hypometabolism on PET despite equivalent degrees of behavioral disturbance.<sup>7,17</sup> These findings raise the question of whether bv-FTD patients should be split into progressive and nonprogressive groups.

This heterogeneity in the syndrome of bv-FTD may explain the variable findings on executive tests: only the progressive group shows frontal brain atrophy and thus should exhibit executive deficits, whereas the nonprogressive group should present little or no executive dysfunction.

We tested this hypothesis by allocating bv-FTD patients into progressive and nonprogressive groups based on MRI appearance at presentation and contrasting their results on a range of executive neuropsychological tests. In addition, we explored which executive tests are useful diagnostic markers for discriminating between the groups at first presentation.

**METHODS Case selection.** Patients were selected from the Cambridge Dementia Clinic database. Eighty-nine patients with a diagnosis of bv-FTD and follow-up for at least 3 years were identified. Two senior neurologists (J.R.H. and C.K.), blind to the subgroups, classified the cases retrospectively into progressive vs nonprogressive based on 1) atrophy on MRI at presentation; nonprogressors scored 0 or 1 across all brain regions on a visual MRI rating scale (for details of the rating scale, see references 7 and 17); and 2) progression, defined as a decline on a general cognitive test (i.e., Addenbrooke Cognitive Examination [ACE]–Revised, see reference 19), over a 3-year period. All pa-

tients met current consensus criteria for FTD<sup>3</sup> with insidious onset, decline in social behavior and personal conduct, emotional blunting, and loss of insight. Thirty-nine patients were excluded from the study for being assessed before 1997 when neuropsychological protocols were still established (n = 12), having combined FTD with motor neuron disease (n = 3), or having less than six of the selected neuropsychological tests (see below) (n = 24). Of these excluded, 32 were progressors and 7 were nonprogressors; hence, of the total cohort (59 progressors and 30 nonprogressors), 27 progressors (45%) and 23 nonprogressors (76%) were able to be included in the study (see table 1 for demographic details). All patients were comprehensively assessed by a multidisciplinary team to ensure the absence of other neurologic or psychiatric (e.g., schizophrenia, depression, mania) symptoms. All caregivers completed the Cambridge Behavioral Inventory (CBI)<sup>20–22</sup> to assess the behavioral symptoms. The CBI has been validated against the Neuropsychiatric Inventory (NPI)<sup>23</sup> and shows good categorization of different dementias.

Controls were selected from a healthy volunteer panel or were patients' spouses or carers.

**Test selection.** The following executive tests were administered: Behavioral Assessment of the Dysexecutive Syndrome (BADS) Key Search and Zoo Map,<sup>24</sup> Brixton Spatial Anticipation Test and Hayling Test,<sup>25</sup> Digit Span,<sup>26</sup> FAS Verbal Fluency,<sup>27</sup> and Trail Making Test.<sup>28</sup> In the BADS Key Search, subjects are asked to imagine they have lost their keys in a field represented by a piece of paper and then to draw a line to show how they would search a field for the lost keys. In the BADS Zoo Map, patients are told to visit a series of designated locations on a map of a zoo, following certain rules. BADS scores are indicated by a Total Profile Score combining the time taken and the efficiency of the solution. The Brixton Spatial Anticipation Task is a rule attainment task, similar to the Wisconsin Card Sorting Test, for which we used the Total and Scaled Error of the tests. In this task, patients see several pages of an array of 10 circles, with one blue circle filled in blue. The position of the filled circle changes from one page to another by simple rules, and the patient has to predict where the next filled position will be. The Hayling Test evaluates inhibition of a prepotent response by using a sentence completion task in which patients have in a first section to complete the sentence as quickly as possible. The second section of the test requires the patient to complete a sentence with a word that is unconnected to the sentence, which requires inhibiting an automatic response. The Hayling Test is represented by the Error Scaled Score and the Overall Scaled Score. The Digit Span is a working memory test allowing the assessment of short-term memory for digits. For the FAS Verbal Fluency Test, we recorded the Total Response and Correct. Finally, for the Trail Making Test, we included the Time and Error measures of parts A and B.

Patients underwent general cognitive screening using the ACE.<sup>29,30</sup> Only data from the first assessment were included in all analyses.

**Statistics.** Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL). Parametric demographic (age, education), neuropsychological (executive and general cognitive tests), and behavioral (CBI, NPI) data were compared across the three groups (progressors, nonprogressor, and controls) via one-way analyses of variance followed by Tukey post hoc tests. A priori, variables were plotted and checked for normality of distribution by Kolmogorov–Smirnov tests. Variables revealing nonnormal distributions were log transformed, and the appropriate log values were used in the analyses.

**Table 1** Mean (SD) scores for bv-FTD patients and controls on demographics and general cognitive tests

Demographics, cognitive and behavioral tests	Controls	Progressors	Nonprogressors	F value	Progressors vs controls	Nonprogressors vs controls	Progressors vs nonprogressors
n	40	27	23	—	—	—	—
Age, y	65.1 (6.2)	64.4 (7.5)	66.2 (7.1)	NS	NS	NS	NS
Education, y	13.9 (2.3)	11.6 (2.1)	12.2 (2.5)	*	*	‡	NS
Age at onset, y	—	57.2 (7.8)	55.6 (6.8)	NS	—	—	—
Handedness, R/L	—	25/1	18/2	—	—	—	—
Sex, M/F	—	17/10	21/2	—	—	—	—
ACE [100]	94.3 (3.6)	73.7 (13.3)	85.7 (14.8)	*	*	†	*
Attention/Orientation	9.8 (1.5)	10.9 (3.2)	11.8 (2.9)	‡	NS	‡	NS
Memory	29.8 (1.7)	18.5 (7.8)	22.7 (6.4)	*	*	*	‡
Verbal Fluency	11.8 (1.7)	6.4 (3.3)	9.5 (3.1)	*	*	NS	*
Language	23.2 (5.5)	22.2 (5.9)	24.9 (4.5)	NS	NS	NS	NS
Visuospatial	8.9 (5.7)	8.5 (4.1)	9.5 (3.4)	NS	NS	NS	NS
MMSE [30]	29.1 (.85)	26.1 (3.5)	28.3 (1.5)	*	*	NS	†
CBI [316]	9.5 (11.5)	112.4 (47.1)	89.1 (48.5)	*	*	*	NS

F values indicate significant differences across groups; Tukey post hoc tests compare differences between group pairs.

\* $p < 0.000$ .

† $p < 0.01$ .

‡ $p < 0.05$ .

bv-FTD = behavioral variant frontotemporal dementia; NS = not significant; ACE = Addenbrooke Cognitive Examination; MMSE = Mini-Mental State Examination; CBI = Cambridge Behavioral Inventory.

Comparisons of progressors vs nonprogressors revealed no significant difference for any of the demographic variables. There was, however, a much higher percentage of men in the nonprogressor group ( $p < 0.025$ ; table 1). Controls were not significantly different from the two patient groups for age but had significantly more years of education than progressors ( $p < 0.001$ ) and nonprogressors ( $p < 0.025$ ) did.

**RESULTS Sensitivity of task measures to differentiate mean group performances. Global cognitive function.** As shown in table 1, the performance of progressors and nonprogressors was generally worse in comparison with controls, with the exception of language and visuospatial subscores of the ACE. Post hoc tests showed that neither patient group differed from controls for language and visuospatial skills. For all other scores, progressors and nonprogressors were significantly impaired. Interestingly, progressors and nonprogressors differed in their performance on the Mini-Mental State Examination, with nonprogressors performing in the control range, while progressors were significantly impaired.

**Behavioral disturbance.** On the CBI (table 1 and figure 1), significant group effects were present for all subscores (Memory, Attention/Orientation, Everyday Skills, Self Care, Mood, Beliefs, Disinhibition, Eating, Sleep, Stereotypic Behavior, Motivation). Follow-up post hoc comparisons confirmed that progressors and nonprogressors differed from controls on all scores (all  $p$  values  $< 0.025$ ), with the exception of Self Care, which was equivalent in nonprogressors and controls.

Progressors and nonprogressors differed on the Sleep subscore ( $p < 0.000$ ).

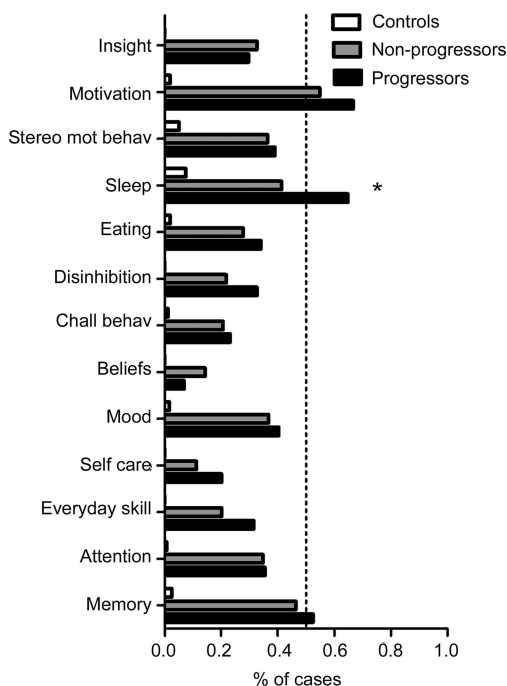
As indicated in figure 1, the profiles of impaired scores on the CBI showed a very similar level of behavioral deficit in progressors and nonprogressors. Both patient groups had more than 30% endorsement in the Memory, Attention, Mood, Disinhibition, Eating, Sleep, Stereotypic Motor Behavior, Motivation, and Insight subcategories.

**Executive function.** The results of the executive test for all three groups (progressors, nonprogressor, and controls) are shown in table 2. Scores of the BADS Key Search were not significant different across groups, whereas the BAD Zoo Map showed a significant group main effect. Follow-up  $t$  tests showed no difference between controls and nonprogressors but significant impairment in progressors. More importantly, the two FTD subgroups differed significantly.

The Brixton Total Scores showed no significant group main effects. For the Hayling Test, analyses showed significant main effects, with follow-up  $t$  tests showing nonsignificant differences between nonprogressors and controls but significant differences for progressors vs controls and progressors vs nonprogressors.

For the Digit Span, good differentiation between the progressors and the other groups was observed for the Backward Score only (see also figure 2). On FAS Letter Fluency, progressors and

**Figure 1** Percentages of cases impaired on the subscores of the Cambridge Behavioral Inventory



Dotted line indicates 50% of all cases. \*Progressors and nonprogressors differed on the Sleep subscore ( $p < 0.000$ ).

nonprogressors could also be distinguished by both Total Response and Correct scores. The Trails scores showed a similar pattern, with Trails A and B Time and Errors showing significant group main effects. Post hoc tests showed that, except for the Trails A Errors, nonprogressors were not significantly different from control participants, whereas progressors differed from the other two groups.

In summary, progressors and nonprogressors showed similar behavioral profiles, with the exception of the sleep component. Executive test results were inconsistent across tests: some tests did not discriminate the groups well (BADs Key Search, BADs Zoo Map, and Brixton), whereas others (Digit Span, Hayling, Letter Fluency, and Trails) had better diagnostic potential because nonprogressors also performed normally.

#### Efficacy of test measures for patient classification.

Classification of patients was explored first 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 SDs of the controls' mean. Second, we conducted a logistic stepwise regression with the forward stepwise likelihood ratio method. The regression analysis allows determination of which executive and clinical

variables indicate a classification into progressing and nonprogressing cases.

**Measure of overlap between groups.** Table 3 shows the overlap among the three groups (progressors, non-progressors, and controls) for each executive task measure. Lower percentages indicate a smaller overlap of each patient group with the normal control range and vice versa.

The overlap between nonprogressors and control ranged from 100% (Trails A Errors) to 33% (BADs Zoo Map), with the majority showing considerable overlap.

In contrast, the overlap of scores between the progressors and controls was overall much lower; except for the Trails A (69%), all other subscores had an overlap of 50% or lower, indicating considerable executive impairment in the majority of this patient group.

We also investigated overlap between the bv-FTD subgroups. A large difference score indicated good discrimination, and a low score indicated poor discrimination. Digit Span Total (44%), FAS Correct (38%), and Trails B Error (36%) showed the best discrimination between patient groups.

The percentages of cases impaired on selected subscores for the progressors were as follows: FAS Letter Fluency (Correct: 90%, Response: 84%), Digit Span Backward Score (80%), Trails (A Time: 77%, B Time: 74%), and Hayling (Overall: 72%); and those for the nonprogressor were as follows: FAS Letter Fluency (Correct: 52%, Response: 58%), Digit Span Backward Score (65%), Trails (A Time: 43%, B Time: 45%), and Hayling (Overall: 44%). More importantly, in different combinations these tests were able to detect approximately 80% of progressive bv-FTD cases, although between 10% and 25% of progressors performed normally regardless of the combination considered.

In summary, there was considerable overlap between the groups across executive test variables. Difference scores for Digit Span, Letter Fluency, and Trails showed the best differentiation between progressors and nonprogressors.

**Logistic regression analysis.** A logistic regression analysis was performed using task measures that showed a significant distinction between groups (Zoo Map Total Score, Digit Span Backward Score, Hayling Error Score, Hayling Overall Score, FAS Response, FAS Correct, Trails A Time, Trails B Time and Errors). Controls were excluded from the analysis, resulting in a dependent factor of group (progressors vs nonprogressors). This showed that 86.4% of the patients could be correctly classified based on the Digit Span Backward (accounting for 81.8%) and the

**Table 2** Mean (SD) scores for bv-FTD patients and controls on executive and behavioral tests

Executive test	Controls	Progressors	Nonprogressors	F value	Progressors vs controls	Nonprogressors vs controls	Progressors vs nonprogressors
BADS Key Search	2.6	2.72 (3.2)	2.72 (1.3)	NS	—	—	—
BADS Zoo Map	2.1 (1.3)	1.1 (1.3)	2.3 (0.95)	†	‡	NS	†
<b>Brixton</b>							
Total Errors	18.2 (7.7)	21.8 (9.1)	19.1 (11.1)	NS	NS	NS	NS
Scaled Score	5.3 (2)	4.3 (1.9)	5.3 (2.6)	NS	NS	NS	NS
<b>Digit Span</b>							
Total Score	16.8 (2.7)	11.8 (3.9)	14.6 (4.1)	‡	‡	NS	NS
Forward Score	9.2 (1.9)	7.3 (2.2)	7.9 (2.5)	‡	†	NS	NS
Backward Score	7.8 (2.1)	4.7 (2.2)	6.6 (2)	‡	*	NS	†
<b>Hayling</b>							
Error Score	6.2 (1.8)	3.7 (2.4)	5.7 (1.9)	†	†	NS	†
Overall Score	5.7 (1.2)	3.1 (1.7)	4.4 (1.7)	*	*	NS	‡
<b>Letter Fluency</b>							
FAS Response	13.2 (3.9)	7.7 (4.9)	12.3 (6.1)	*	*	NS	†
FAS Correct	12.7 (3.7)	6.8 (4.4)	11.5 (5.3)	*	*	NS	†
<b>Trails</b>							
A Time, s	37.9 (9.5)	62.9 (28.4)	45.8 (17.9)	*	*	NS	†
A Errors	0.2 (0.5)	0.58 (1.3)	0 (0)	‡	NS	NS	‡
B Time, s	87.2 (46.7)	217.6 (167)	112.5 (61.6)	*	*	NS	†
B Errors	0.48 (1)	3.7 (5.1)	0.95 (2.1)	*	*	NS	†

F values indicate significant differences across groups; Tukey post hoc tests compare differences between group pairs.

\* $p < 0.000$ .

† $p < 0.01$ .

‡ $p < 0.05$ .

bv-FTD = behavioral variant frontotemporal dementia; BADS = Behavioral Assessment of the Dysexecutive Syndrome; NS = not significant.

Hayling Overall Score (4.6% of the total group classification). No other covariate improved classification of patients into progressing and nonprogressing cases. Logistic regression showed that no covariates usefully discriminated nonprogressive cases from healthy controls.

**DISCUSSION** Our study uses a novel approach to corroborate the existence of progressive and nonprogressive bv-FTD subgroups by using neuropsychological means. This is clinically relevant in that it aides the clinician by providing a clearer prognosis for patients and their families.

The results of our study show that 1) progressive and nonprogressive bv-FTD cases can be discriminated on the basis of their performance on executive tests; 2) by using a combination of the FAS Letter Fluency, Digit Span, Trails, and Hayling executive tests, clinicians can discriminate progressive bv-FTD cases from healthy or nonprogressive cases at first presentation; 3) nonprogressors perform in the normal range across most executive scores, although carers report on equivalent degree of behavioral disturbances in progressive cases; and 4) a small but important minority of around 20% of pro-

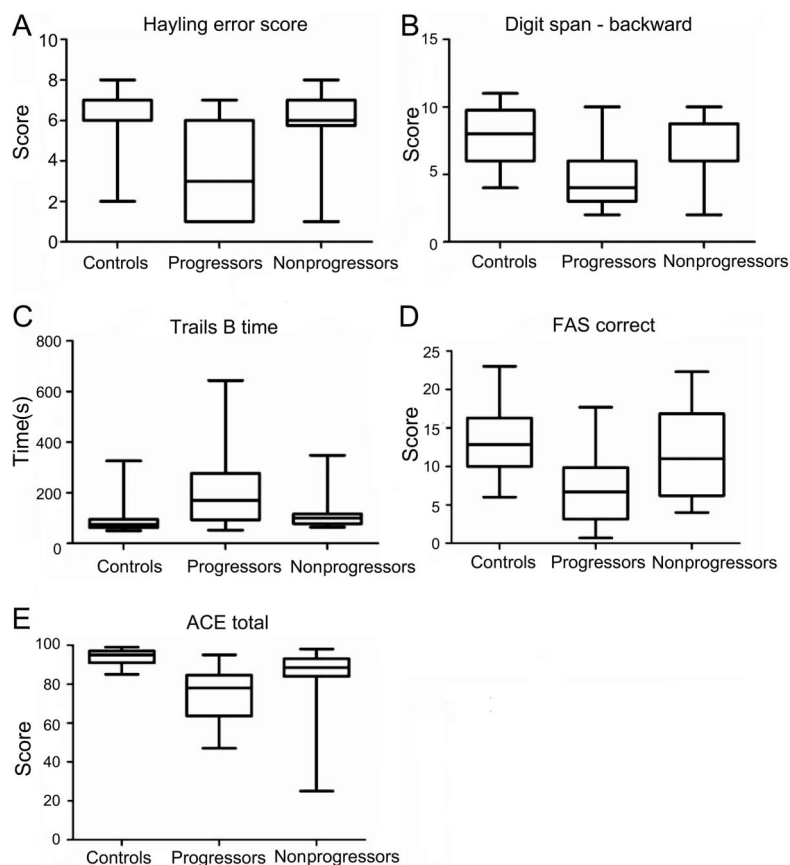
gressive cases perform normally on all tests when first assessed in the clinic.

All of the executive tests used, with exception of the Brixton and BADS Key Search, yielded at least one score that distinguished progressors from nonprogressors.

More interesting, though, Digit Span Backwards emerged as efficient indicator of group membership. This was further confirmed by the logistic regression analysis, which showed that this score correctly classified approximately 82% of bv-FTD patients. The Hayling Test also contributed to the regression model. Deficits were also consistently observed in the Trails planning times (in particular Trails B), as well as the FAS Letter Fluency scores. These results suggest that tests of working memory and failure to inhibit prepotent response are likely to contribute to early diagnosis.

What are the clinical implications of our findings? All suspected bv-FTD patients present with disturbed behavior, and those with progression over 3 years are similar to those who remain static. The subgroups can, however, be distinguished to a high degree

**Figure 2** Box plots of selected variables for the (A) Hayling, (B) Digit Span, (C) Trails, (D) FAS Correct executive tests, and (E) ACE Total across the two groups



Whiskers indicate minimum and maximum scores. ACE = Addenbrooke Cognitive Examination.

based on their executive test scores even at first presentation. If a patient shows abnormal scores on executive tests, it is almost certain that the patient has true bv-FTD, which can be then confirmed by structural MRI volume measurements or functional imaging (SPECT or fluorodeoxyglucose PET) if available.<sup>31</sup> If a patient presents with normal scores on the executive tests, it is likely that the patient is a nonprogressor or phenocopy patient. Still, the clinician has to keep in mind that 10% to 25% of our sample of the progressive FTD cases showed normal scores across some of the executive tests. Thus, normal scores should not be used as true exclusion criteria for bv-FTD.

At a theoretical level, the most discriminatory tests tap into prefrontal functions that are seemingly impaired in progressors. In particular, tasks that are reliant on processes that recruit dorsolateral and ventrolateral prefrontal cortex areas, such as the Digit Span (working memory),<sup>32</sup> Trails (task switching),<sup>33</sup> and FAS Letter Fluency (selection),<sup>34</sup> were good predictors for group membership. Moreover, the Hayling task, which is reliant on orbitofrontal cortex function,<sup>35</sup> for inhibiting pre-

potent responses was an important measure to distinguish progressors from nonprogressors. The results of our study should be not surprising in that progressive bv-FTD patients show cortical atrophy in mesial, ventral, and orbitofrontal cortical areas. In contrast, nonprogressive or phenocopy patients do not show macroscopic atrophy in any of the above prefrontal brain areas.<sup>7</sup>

We have used the term nonprogressors for patients who showed very slow or no progression over several years without apparent brain atrophy. The nosology of these patients is a matter of ongoing debate. It seems increasingly unlikely that they have true FTD but rather a phenocopy, which “mimics” the behavioral symptoms of bv-FTD. A proportion probably have long-standing personality disorders within the Asperger spectrum, which has decompensated in midlife, whereas others may have a neuropsychiatric disorder (for a fuller discussion, see references 7 and 17). Phenocopy patients, by the nature of their benign prognosis, continue to attend clinics and may, therefore, become overrepresented in studies. After classification of our total sample, we identified 30 nonprogressors and 59 progressors but had to exclude 39 because patients were seen before neuropsychological protocols were established, had very few neuropsychological assessments, or had a diagnosis of FTD and motor neuron disease (see Methods). It is interesting to note that in our sample of nonprogressing patients, a large proportion of cases were male, whereas for progressive cases, sex was equally distributed, which was significant across groups ( $p < 0.025$ ). This factor hints toward an Asperger spectrum disorder, which is three to four times higher in males than in females.<sup>36</sup>

Previous inconsistent performance on executive function tests in bv-FTD<sup>31</sup> is probably explained by the admixture of cases in prior studies, because nonprogressive phenocopy cases do not show neuropsychological deficits. Studies containing a significant number of such patients would, therefore, yield non-significant results.

Nevertheless, it is important to note that, even though the sensitivity of tests for detecting true FTD was high, the specificity was not explored. In particular, it might be of interest to compare bv-FTD patients with other patient groups, notably Alzheimer, depressed, and schizophrenia patients. The specificity could be improved by tapping more precise prefrontal processes, especially social, emotion, and mentalizing abilities, which have been shown to be heavily reliant on orbitofrontal and ventral prefrontal cortex structures.<sup>37,38</sup>

**Table 3** Overlap percentage of bv-FTD patients with the control range scores

Executive test	Progressors	Nonprogressors	Difference score, nonprogressors – progressors
BADS Key Search	32	56	24
BADS Zoo Map	32	33	1
<b>Brixton</b>			
Total Errors	43	36	-7
Scaled Score	48	36	-11
<b>Digit Span</b>			
Total Score	21	65	44
Forward Score	48	70	22
Backward Score	20	35	15
<b>Hayling</b>			
Error Score	48	83	35
Overall Score	28	56	28
<b>Letter Fluency</b>			
FAS Response	16	42	26
FAS Correct	10	48	38
<b>Trails</b>			
A Time, s	23	57	34
A Errors	69	100	31
B Time, s	26	55	28
B Errors	50	86	36

bv-FTD = behavioral variant frontotemporal dementia; BADS = Behavioral Assessment of the Dysexecutive Syndrome.

Finally, our study classified cases retrospectively into progressors and nonprogressors, whereas for future studies it will be important to ascertain group membership prospectively by using consistent neuropsychological batteries with structural and metabolic imaging protocols.

### AUTHOR CONTRIBUTIONS

The statistical analyses were conducted by M.H.

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