

Activities of Daily Living in Behavioral Variant Frontotemporal Dementia

Differences in Caregiver and Performance-based Assessments

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Abstract: Patients with the behavioral variant of frontotemporal dementia have marked impairment in everyday life, yet little is known about factors underlying this impairment. Moreover, a recently identified subgroup with normal brain imaging has an excellent prognosis (phenocopy cases) and their performance on activities of daily living (ADL) tasks is unknown. Eighteen behavioral variant frontotemporal dementia patients were assessed on 2 ADL measures, the Disability Assessment for Dementia, a caregiver-based interview, and the Assessment of Motor and Process Skills, a performance-based instrument. Behavior change, global cognition, executive function, and magnetic resonance imaging brain atrophy were also evaluated. There was no association between the 2 ADL measures. A model combining the Addenbrooke's Cognitive Examination Revised (global cognition) and Frontal Systems Behavior Scale (frontal dysfunction) explained the variance on ADL performance. A qualitative rating distinguished between pathologic and phenocopy patients better than the performance-based assessment. Degree of frontal dysfunction and overall dementia determined the level of ADL impairment. The phenocopy patients were clearly distinguishable when evaluated using a performance-based, and even better with a qualitative rating assessment.

Key Words: activities of daily living, functional impairment, frontotemporal dementia

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Frontotemporal dementia (FTD) is characterized by focal atrophy of the frontal and temporal lobes. It encompasses 3 clinical variants: a behavioral variant, where changes in social conduct and personality prevail [behavioral variant of frontotemporal dementia (bv-FTD)], and 2 language variants: semantic dementia and progressive nonfluent aphasia.^{1,2}

The practical impact of FTD on everyday life has been addressed only recently. Patients with the language variants tend to present with mild impairment in activities of daily living (ADL) which remain relatively stable.^{3,4} Those with bv-FTD, by contrast, typically present with moderate to

severe everyday disability even when first diagnosed. Their level of impairment is greater than in Alzheimer disease (AD), even after controlling for age and length of disease.³ Moreover, their rate of deterioration seems to be faster than AD.⁵

It remains unclear why the bv-FTD group is so markedly impaired. There are suggestions that frontal executive dysfunction could explain their functional ADL impairment. Studies in AD have shown that apathy, in combination with executive dysfunction, leads to more impairment in ADLs.^{6–9} For FTD, however, this relationship has not been confirmed. In one study involving a combination of FTD and AD patients, no association between frontal tasks, such as the Behavioral Assessment of the Dysexecutive Syndrome and the Tower of London, and ADL scales was found.¹⁰

We decided to investigate this group further, introducing the use of a performance-based ADL assessment rather than relying on caregiver reports only. We also wanted to investigate the factors that might contribute to their everyday impairment.

A further complication is the recent finding of a distinct subgroup of bv-FTD patients, who lack atrophy on magnetic resonance imaging (MRI) scans and show very little change over a number of years, but whose caregivers report equivalent symptoms to those with brain atrophy. In a large clinical study of the 3 variants, all semantic dementia and progressive nonfluent aphasia patients demonstrated abnormal MRI scans, whereas half of the bv-FTD did not.¹¹ Moreover, the scan-normal bv-FTD patients were universally male and had a remarkable better prognosis.¹¹ Clinically, the 2 subsets of bv-FTD patients had similar cognitive and behavioral scores. It seems that despite presenting with identical complaints, the subset with imaging changes deteriorate (and eventually have pathologically FTD¹²), whereas the better prognosis group continue to attend the hospital appointments, remaining clinically stable over a number of years. This subgroup has been termed the “phenocopy” group, as opposed to the truly pathologic in recent studies.¹¹ A number of possible etiologies have been proposed: some patients may fall within the Asperger's spectrum with midlife decompensation whereas others possibly have a functional disruption of frontal systems secondary to a low-grade neuropsychiatric syndrome.^{11,13}

We investigated how these 2 subsets of bv-FTD patients, phenocopy and pathologic, would perform ADLs when assessed in real life.

We hypothesized that there would be a dissociation of functional scores, according to the type of assessment used: informant-based or performance-based. We expected to

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find greater discrepancy of ADL scores in the phenocopy subgroup, that is, more impairment on the caregiver-based assessment.

METHODS

Participants

Participants were recruited from the Early Dementia Onset clinic at Addenbrooke's Hospital, Cambridge, UK. They were included if they: (1) had a family member or caregiver, who could reliably give answers regarding the patient's routine and behavior; (2) had undergone a structural MRI scan within 12 months of the ADL assessment; (3) had undergone an Addenbrooke's Cognitive Examination Revised (ACE-R) and tests of executive function (see below) within 90 days of ADL assessments. Eight patients were not included in the study because of either (1) a physical impairment that could potentially confound assessment of ADLs; (2) evidence of major depression; or (3) evidence of significant cerebrovascular disease (infarcts or confluent white matter changes).

Eighteen patients fulfilled criteria, 10 phenocopy and 8 pathologic patients. Both groups met clinical criteria for bv-FTD,² but the phenocopy subgroup had no evidence of atrophy on their MRI at presentation as evaluated by a validated semiquantitative visual rating scale¹⁴ and showed no progression (no change on ACE-R scores, nor evidence of clinical deterioration) over at least 2 years of follow-up.¹¹ These MRI ratings were used in combination with clinical review of both neurologists (C.M.K. and J.R.H.) and were used as a gold standard to separate phenocopy and pathologic cases. The 2 raters were unanimous in their classification of cases. The occupational therapist (E.M.) who visited and performed both caregiver and patient-based assessments was blind to their status as pathologic or phenocopy cases during the home visits.

Instruments

Brief Cognitive Assessment (ACE-R) and Neuropsychologic Executive Tests

The ACE-R is designed to assess 5 cognitive domains, and has been shown to be sensitive to early stages of dementia. Recommended cut-offs are 88 and 82, with variable sensitivity and specificity for dementia.¹⁵ One patient was unable to complete the ACE-R ($n = 17$).

Patients were given the following tests of executive function: the Trail Making Test B,¹⁶ the Key Search and the Zoo Map from the Behavioral Assessment of the Dysexecutive Syndrome.¹⁷ Two patients could not perform the executive tasks ($n = 16$).

Behavioral Change

Patients were assessed on the Cambridge Behavioral Inventory (CBI),^{18,19} a caregiver-based questionnaire. Items are scored according to frequency (0 to 4), with higher scores representing higher frequency of abnormal behavior. The CBI has been validated against the neuropsychiatry inventory and shown to discriminate between dementia syndromes.

Frontal Assessment

The Frontal Systems Behavior Scale (FrSBe),²⁰ assesses frontal dysfunction (disinhibition, apathy, and executive dysfunction) and it compares the patient's status

before and after diagnosis. Scores above cut-off denote impairment. There is a caregiver and a self-reported version of the test. For the data analyses, we concentrated on scores from the "after illness" subtotal.

Visual MRI Rating Scale

The MRI rating scale is a visually based semiquantitative schedule that assesses atrophy in the frontal, anterior temporal, and posterior temporal brain regions. Each region receives a score from 0 to 4; scores of 0 and 1 are considered within the normal range; 2, 3, and 4 correspond to mild, moderate, and severe atrophy.¹⁴ We also generated a total score of atrophy by adding up all regions together, where greater scores denote greater atrophy in the frontal and temporal lobes (max score 16). Not all patients had MRI scans at the time of the home visit ($n = 14$); 2 refused to be scanned so their classification as phenocopy or pathologic was based on MRI scanning before the time of the study. We did not include their ratings into the analyses.

ADL

ADL ability was assessed with 2 different scales, a caregiver-based scale, the Disability Assessment of Dementia (DAD) and a patient-based scale, the Assessment of Motor and Process Skills (AMPS).

The DAD is an informant-based scale.²¹ It includes 40 items—17 related to basic self-care (basic ADLs: "hygiene," "dressing," "continence," and "eating") and 23 related to instrumental activities of daily living ("meal preparation," "telephoning," "going on an outing," "finance and correspondence," "medications," and "leisure and housework"). Lower scores on the DAD denote greater impairment. The scale is designed to have its total score corrected to 100, that is, nonapplicable questions are excluded from the total score to avoid sex bias toward activities (eg, cooking, house chores, finances).

Patients were also assessed with the AMPS. The AMPS is a performance-based scale that has been used extensively.^{22–25} The patient performs 2 everyday tasks from a set of 83 standardized tasks. The assessment simultaneously measures 16 motor (eg, coordination, grip, transportation, etc.) and 20 mental process skills (eg, searching, choosing, organizing, sequencing, etc.), and their effect on the ability of the person to perform familiar ADL tasks. Both tasks' scores are used in conjunction for the AMPS score. Raw scores from each motor and process skill are converted into logits, using a Rasch model approach. A software program compares a patient score against age and sex-matched controls; scores lower than cut-offs denote impairment. For the analyses, we concentrated on the process component scores, as we expected normal scores on the motor component of the assessment.

Qualitative Rating

Once the occupational therapy (OT) started doing the home visits, it became clear that the AMPS as a factor was unlikely to capture nuances of behavior demonstrated during an extensive home assessment. Some patients were very good hosts during the visit (organized their own appointments over the phone; made conversation during the visit; offered to make a cup of tea or coffee; were keen to demonstrate their ADL abilities, etc.)—this appropriate behavior would not be captured by the ADL assessment.

TABLE 1. Mean Scores of bv-FTD Patients on ACE-R and Executive Tests (SD in Brackets)

Cognitive Tests (Max Score)	bv-FTD, n = 18	bv-FTD Pathologic, n = 8	bv-FTD Phenocopy, n = 10	Phenocopy vs. Pathologic
ACE-R (100)	77.9 (16.9)	65.4 (19.8)	86.6 (6.4)	*
Trails B, sec	212 (142.9)	305 (173)	143 (58)	n.s.
Zoo Map (4)	1.71 (1.3)	0.4 (0.5)	2.4 (1)	*
Key Search (4)	2.9 (1.1)	2.7 (0.8)	3 (1.3)	n.s.
CBI total (324)	103 (57.9)	104 (51.7)	102.3 (64.6)	n.s.
CBI apathy (32)	57.5 (24.4)	57.6 (15.9)	57.5 (29.9)	n.s.

* $P < 0.05$.

ACE-R indicates Addenbrooke's Cognitive Examination Revised; bv-FTD, behavioral variant frontotemporal dementia; CBI, Cambridge Behavioral Inventory; max, maximum; n.s., not significant.

Other patients, however, produced stereotypical and even bizarre behaviors while the therapist was there, and this type of behavior is not traditionally rated into performance-based assessments (eg, telling the OT he was going to show something, then getting 2 spoons and banging them onto the door very loudly while giggling; counting numbers aloud while preparing a sandwich; swearing at the therapist).

We decided, therefore, to introduce a qualitative analysis of the whole home visit, which was based on grounded theory.²⁶ The main principal of this approach is the generation of a theory which is grounded on the data, especially actions, interactions, and social processes.²⁷ To achieve this, the entire home visit was recorded in notes (*note-taking*); different types of behaviors were identified (*coding*) in all 18 visits, and the visit notes were reviewed several times (*constant comparison*) to create core behavior categories (*core categories*) using a reiterative method until *saturation* was reached. From these behavior categories, it became clear that some core behaviors could be grouped into positive and others into negative behaviors. The number of negative behaviors clearly surpassed the number of positive ones. Each patient was then rated in the whole list of behaviors, having been assigned a score of 1

(presence) or 0 (absence) for each. We then created a score, subtracting the positive score from the negative score for each patient: this score was named qualitative rating. In this way, a patient who did not have many negative behaviors and had socially adequate behaviors while the therapist was present received a positive score (number of positive behaviors – negative ones). On the other hand, patients who had a few socially adequate behaviors but also many unusual behaviors (counting numbers aloud to himself while preparing a sandwich, for instance) received a negative score.

Data Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences 12.0 (SPSS) for Windows. The value of α was set at 0.05.

Spearman correlations were used to investigate association between variables. Multiple regression analysis, enter method, was used to identify which cognitive tests could explain the variance on the AMPS scores. Discriminant analysis was used to verify accuracy of group classification with the performance-based assessment.

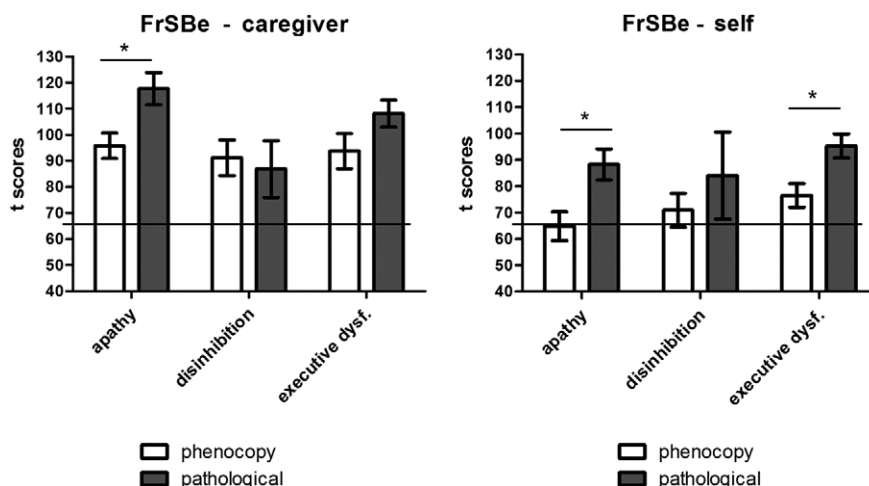


FIGURE 1. FrSBe "after illness," caregiver and patient self-ratings for apathy, disinhibition, and executive dysfunction (Cut-off is at 65). * t test, $P < 0.05$. FrSBe indicates Frontal Systems Behavior Scale.

TABLE 2. Activities of Daily Living Mean Scores, Caregiver and Performance-based (SD in Brackets)

ADL Assessments	bv-FTD, n = 18	bv-FTD Pathology, n = 8	bv-FTD Phenocopy, n = 10	Phenocopy vs. Pathology
DAD (%) (0-100)	61 (27)	55 (30)	66 (24)	n.s.
AMPS process (cut-off 0.78)	1.05 (0.69)	0.7 (0.5)	1.4 (0.7)	*
AMPS motor (cut-off 1.39)	2.12 (0.62)	1.94 (0.68)	2.26 (0.56)	n.s.

Cut-offs for AMPS process and AMPS motor are presented as a group mean.

* $P < 0.05$.

ADL indicates activities of daily living; AMPS, Assessment of Motor and Process Skills. Scores below cut-off denote impairment; bv-FTD, behavioral variant frontotemporal dementia; DAD, Disability Assessment for Dementia; n.s., not significant.

In addition, a combination of both quantitative and qualitative methods was used, when we applied discriminant analysis to verify accuracy of group classification for the qualitative rating.

RESULTS

Demographics

Participants were mostly male (17:1). Average age was 62.4 (SD = 6.8) and mean years of education was 12.6 (SD = 2.3). Disease duration was calculated by onset of symptoms, as reported by caregivers, and mean group was 7.3 years (SD = 4.4).

The pathologic and phenocopy subgroups were matched for age and education, but duration of disease was significantly longer in the phenocopy subgroup ($M = 9.4$, $SD = 4.2$) than in the pathologic group ($M = 4.8$, $SD = 3.1$; $F = 1.639$, $P = 0.019$).

Cognitive Tests

On cognitive assessment, the bv-FTD group scored below cut-off on the ACE-R and the Zoo Map; they were borderline on the Key Search (Table 1). Significant subgroup differences were seen on the ACE-R and the Zoo Map test, with phenocopy scoring significantly better than pathologic patients.

Behavioral Measures

All patients had moderate to high CBI scores; the highest endorsement was found on the apathy subsection. There were no differences between the 2 FTD subgroups.

Frontal Tests

On the FrSBe rating, which measures frontal dysfunction, scores were analyzed (from the “after illness”

subsection) separately for apathy, disinhibition, and executive dysfunction, as shown on Figure 1. Patients were rated above cut-off on all 3 frontal measures by their caregivers and interestingly also by themselves, but with a significant difference between their ratings for all 3 components. For caregivers, “apathy” received the most endorsement, whereas for patients it was “executive dysfunction.” Once subdivided in phenocopy and pathologic cases, significant differences were found on apathy (caregiver and self-rating) and executive dysfunction (self-rating), with pathologic patients having worse scores.

MRI Rating

The MRI ratings were used as part of the criteria for identifying phenocopy from pathologic patients. Not surprisingly, the phenocopy subgroup showed no abnormality in their brain scans, with composite scores ranging from 0 to 1. All pathologic patients had abnormal MRI scans, with scores ranging from 4 to 12 (maximum 16).

ADL Assessment (Table 2)

On ADLs, results for caregiver and performance-based assessments were not consistent. Taken as a whole, bv-FTD patients had moderate to severe impairment on the DAD (61% of ability remained). The 2 subgroups, phenocopy and pathologic, did not differ on this caregiver-based ADL measure (respondents on the DAD were 17 wives and 1 daughter).

On the process component of the AMPS, however, the combined group scored just above the recommended cut-off, which corresponded to normal functioning. Unlike on the DAD, there was a significant difference between the subgroups, with pathologic patients scoring significantly lower than phenocopy. On the motor component of the AMPS the groups scored above cut-off, as expected. Not surprisingly, the DAD and the process component of the AMPS did not correlate with each other.

Factors Explaining the Variance on AMPS Scores

With a priori expectation of some degree of relationship between frontal dysfunction and ADLs, we performed a multiple logistic regression (enter method), with the AMPS process score as the dependent variable, experimenting with 2 independent variables at a time, due to our small sample size. The most significant model to explain the variance of AMPS process scores combined the ACE-R and the total FrSBe “after illness” (caregiver version). This

TABLE 3. Independent Variables Identified on the Multiple Logistic Regression Analysis; Dependent Variable was the Process Component of the AMPS (Enter Method)

Predictor	β	P
ACE-R	0.037	0.003
FrSBe “after illness” (caregiver)	0.022	0.032

ACE-R indicates Addenbrooke’s Cognitive Examination Revised; AMPS, Assessment of Motor and Process Skills; FrSBe, Frontal Systems Behavior Scale.

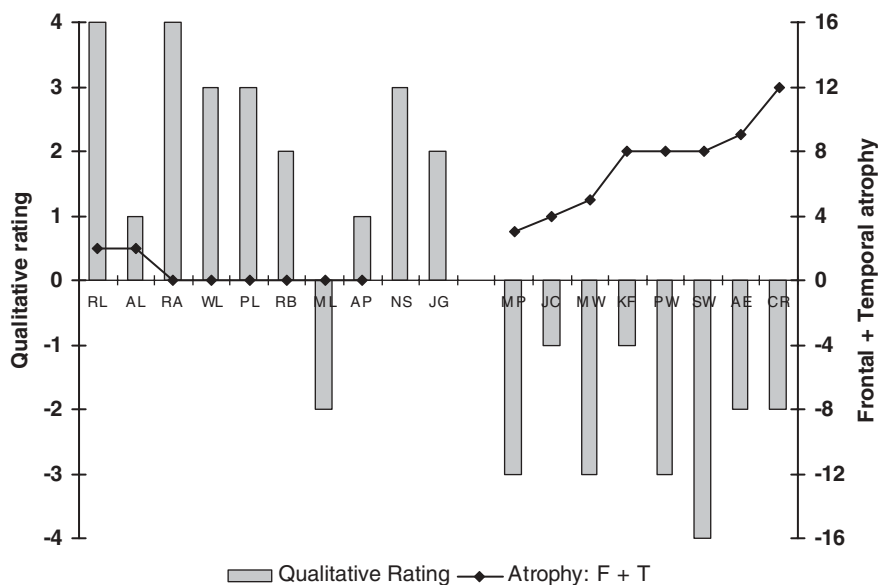


FIGURE 2. Qualitative rating and magnetic resonance imaging ratings on phenocopy (left on x axis) and pathologic cases (right on x axis). Left y axis represents qualitative ratings (minimum -4 , maximum $+4$), and right y axis represents brain atrophy (minimum 0 , maximum 16).

model accounted for 60.4% of the variance of AMPS process scores ($F_{2,9} = 9.41$, $P = 0.006$). Tolerance between variables was within acceptable limits (Table 3).

We also expected the process component of the AMPS to be able to discriminate well phenocopy from pathologic patients. On the discriminant analysis, the process component of the AMPS was very good at detecting group classification, with 77.8% of group accuracy.

Qualitative Rating

As explained in the method section, a qualitative rating derived from the grounded theory analysis was generated. This qualitative rating was applied in a discriminant analysis, revealing that it was excellent at distinguishing between phenocopy and pathologic cases (94.4%).

Qualitative Rating and MRI Rating

As shown on Figure 2, we explored the relationship between brain atrophy and degree of qualitative behavioral change on a case-by-case basis by rank-ordering patients according to their composite MRI rating. All but one of the phenocopy patients had a qualitative rating above zero, denoting more positive behaviors than negative ones. By contrast, all pathologic patients had qualitative ratings below zero, denoting the presence of more negative behaviors. A strong inverse correlation between qualitative scores and MRI ratings was found ($r = -0.68$, $n = 18$, $P < 0.005$), as shown on Figure 2.

DISCUSSION

We hypothesized that the 2 subsets of bv-FTD patients, phenocopy and pathologic, would have different levels of performance in ADL. In addition, we expected to identify a dissociation of functional scores depending on the format (caregiver vs. performance-based) of instrument used. Interestingly, we found no differences between phenocopy and pathologic patients in the caregiver-based

ADL assessment, whereas a clear distinction was identified on the performance-based measure, with pathologic patients scoring significantly lower.

On the performance-based assessment, the AMPS, the majority of bv-FTD patients were correctly classified into phenocopy and pathologic (78% accuracy). By contrast, the profile on the DAD did not differentiate between the groups. In AD, there is evidence that caregiver and performance-based assessments may not correlate significantly,²² or only modestly,²³ although both measures revealed ADL impairment. Curiously, in the AD studies, caregivers tended to overestimate patients' abilities, whereas the opposite was true in our study. Our results reveal that caregivers of phenocopy patients notice changes in their level of everyday activities, as seen on the DAD, but this does not necessarily reflect underlying lack of ability, as seen on the AMPS.

So which factors do explain the variance on AMPS process scores for bv-FTD patients? We identified a model combining scores on the ACE-R (global cognition) and the FrSBe (frontal dysfunction). This model shows that ADL impairment is dependent on frontal and global cognitive dysfunction. A previous study found no association between executive tests and ADLs in FTD,¹⁰ but this could be due to methodologic differences, as they collapsed the 3 FTD variants and did not use a performance-based assessment. On the other hand, AD studies have shown that frontal dysfunction, as measured by apathy and executive dysfunction, explains the variance in ADL performance.⁶⁻⁸

Although the AMPS did discriminate well between phenocopy and pathologic patients, the qualitative rating, developed to evaluate the whole home assessment, produced even better discrimination (94%), and correlated extremely well with the MRI ratings. This result is probably explained by the multifaceted approach of the qualitative rating: categories identified in this method combined aspects of behavioral impairment during the

ADL task and in the social interaction with the OT. It is also interesting to note that the number of more prominent negative behaviors in the pathologic patients might have a direct impact on their performance of ADLs.

It is not completely clear why there was a discrepancy between caregiver and performance-based assessments. Apathy could be one of the keys to the discrepancy between the 2 ADL measures, as pathologic patients showed prominent impairment on the AMPS and also on the FrSBe apathy, both caregiver and self-rating. Additional reasons could be that caregivers of phenocopy patients overestimate the degree of impairment. Patients may have adopted a “sick role,” which is then self-perpetuating; even though they are capable of performing the activities, they no longer undertake them at home. Alternatively, they manage to demonstrate intact abilities in the constraints of a formal evaluation but not on an everyday basis. If the latter, then our results suggest a different substrate underlying functional impairment in phenocopy patients.

Our results corroborate previous findings^{11,13} of a distinct benign subgroup of bv-FTD patients, which is characterized by normal MRI scans, marked changes in behavior, and carer-reported changes in ADL functioning (as seen in the pathologic subgroup), but better neuropsychologic test results and normal ADL abilities when evaluated on performance-based assessments. The phenocopy patients are clearly distinct from the pathologic group in the qualitative rating, and do not deteriorate with time.

A full discussion of the etiology of the phenocopy cases is beyond the scope of this article. A proportion of patients probably have long-standing personality disorders within the Asperger spectrum, which has decompensated in midlife whereas others may have a neuropsychiatric disorder (for fuller discussion see Davies et al¹³ and Kipps et al^{11,28}). Justification for regarding the pathologic cases as having true FTD is strong. Although none of the participants in the current study have died, we have followed similar patients who presented to the Cambridge clinic in the 1990s for many years and achieved a very high rate of consent to postmortem study. Of those patients with the clinical syndrome of bv-FTD, brain atrophy on MRI and clear progression to full-blown dementia, all had neurodegenerative disease with most falling within the FTD spectrum: in the recent series of 100 patients with a focal cortical dementia, 28 met criteria for bv-FTD of whom 26 had 1 of the forms of FTD (tau-positive or ubiquitin-positive tau-negative inclusion pathology) and 2 had AD.²⁹

The ratio of patients in the current study should not be taken to represent their incidence. Phenocopy patients, by the nature of their benign prognosis, continue to attend clinics and may become, therefore, over represented in studies.

To the best of our knowledge, this is the first study that evaluates bv-FTD patients in everyday life using a performance-based measure and that attempts to compare caregiver-based with performance-based measures. In addition, it is the first study to address underlying cognitive and behavior factors that might explain the severe impairment bv-FTD patients suffer in everyday life. It would have been even better to have longitudinal ADL performance-based assessment on these patients. Studies

involving a larger number of patients are clearly important to replicate our findings.

The existence of a phenocopy subgroup in bv-FTD deserves clinical and research attention, and should be investigated further. A clear diagnosis of bv-FTD has strong associations with prognosis and intervention, for both patients and caregivers. It is extremely difficult for families to accept a diagnosis of dementia and to manage its implications, but having to deal with the removal of this label due to absence of deterioration is equally or even more challenging.

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