

# Rate of Change of Functional Abilities in Frontotemporal Dementia

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## Key Words

Frontotemporal dementia · Activities of daily living · Behavioural variant FTD · Semantic dementia · Progressive non-fluent aphasia

## Abstract

**Background:** Frontotemporal dementia (FTD) causes progressive change in activities of daily living (ADLs) and little is known about their rate of decline. This study aimed to examine changes in ADLs, including subcomponents of initiation, planning or execution. **Methods:** A total of 72 ADL and general cognitive assessments were analysed. The patients were subdivided into behavioural variant FTD (bvFTD) pathological and phenocopy subgroups, semantic dementia (SemDem) and progressive non-fluent aphasia (PNFA). **Results:** Pathological bvFTD, SemDem and PNFA groups showed significant decline on ADLs after 12 months, while the phenocopy subgroup did not. In terms of subcomponents of ADLs, each variant showed different profiles of decline. The decline in ADL and cognitive scores were significantly correlated. **Conclusions:** FTD variants show differential annual rates of functional decline. The rate of decline should be taken into consideration when discussing prognosis.

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## Introduction

Frontotemporal dementia (FTD) is the umbrella term that encompasses 3 distinctive clinical syndromes with heterogeneous neuropathology: behavioural variant FTD (bvFTD), and 2 language variants, semantic dementia (SemDem) and progressive non-fluent aphasia (PNFA) [1]. Patients with bvFTD present with marked change in personality and social conduct [2], whereas symptoms in semantic dementia (SemDem) and progressive non-fluent aphasia (PNFA) remain language related [3]. Recent studies have established that FTD impacts considerably on everyday activities even at the early stages, which cannot be attributed to language deficits only in those with SemDem and PNFA [4]. Moreover, in bvFTD, the impact is of a greater extent than in Alzheimer's disease (AD) [4–7]. However, little is known about the rate of deterioration of activities of daily living in FTD patients over a 12-month period and if this deterioration is associated with changes in general tests of cognitive function.

A further complication is the recent finding of a distinct subgroup of bvFTD patients who lack atrophy on 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 SemDem and PNFA patients demonstrated

abnormal MRI scans, whereas half of the bvFTD did not [8]. Moreover, the scan-normal bvFTD patients were universally male and had a remarkable better prognosis [8]. Clinically, the 2 subsets of bvFTD patients had similar behavioural scores, but further analyses of their cognitive profiles at presentation had revealed important differences in executive function [9], performance-based activities of daily living (ADLs) [10], and on tests of emotion detection [11]. Despite presenting with identical complaints, the subset with imaging changes deteriorate (and eventually have pathologically FTD [12]), while 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' (or non-progressor) group, as opposed to the truly pathological in recent studies [8]. A number of possible aetiologies have been proposed: some patients may fall within the Asperger's spectrum with mid-life decompensation while others possibly have a functional disruption of frontal systems secondary to a low-grade neuropsychiatric syndrome [8, 13].

Even in the AD literature, the published findings on functional decline are inconsistent. Interpretation is problematic as different ADL scales have been used, which makes direct comparison difficult [14, 15]. In general, decline in ADL functioning is dependent on the level of disease severity, e.g. as measured by a cognitive test such as the Mini Mental State Examination (MMSE), with patients in the moderate and severe stages declining more rapidly than those with mild dementia [16], especially in basic ADLs (BADLs) [17]. On the Disability Assessment for Dementia (DAD), an assessment that has been increasingly used in drug trials for its sensitivity to change, average annual decline in AD patients is about 15 points for total score, 16 points for BADLs and 11 points for instrumental ADLs (IADLs) related questions [16, 17]. Moreover, studies using the DAD have identified the degree of change according to the subscale of the activity, i.e. the DAD enables interpretation in terms of sub-scores in initiation, planning and execution. AD patients lose annually, on average, 8.5 points on initiation, 18.3 on planning and 14 points on execution [16, 17].

Longitudinal studies of the interrelationship between cognition and everyday life have shown a linear relationship in the decline of DAD and various measures of cognition, including the MMSE [15, 17] and the Dementia Rating Scale [18], as well as between the MMSE and other ADL scales [19].

Studies in FTD are scarce. The only published study of functional decline in FTD used a simple BADL scale not

specifically designed for dementia patients, and identified a much faster progression in FTD patients than in AD, which was associated with a decline in MMSE scores [6].

The objectives of this study were: (1) to compare scores of the 3 FTD variants on the DAD, as well as sub-scores of BADLs and IADLs after a 12-month follow-up period; (2) to identify if deterioration of ADL abilities would be more prominent in initiation, planning or execution components and (3) to see if those with bvFTD phenocopy syndrome can be identified by these measures and (4) to verify if changes in DAD and Addenbrooke's Cognitive Examination Revised (ACE-R) scores are associated. We hypothesised there would be a significant deterioration for both measures, DAD and ACE-R, and that this change would be correlated. We also expected to see a higher rate of deterioration in the planning subscale rather than in the other 2 performance subscales (initiation and execution), based on prior cross-sectional findings [4].

## Methods

### *Participants*

Thirty-six patients and caregivers participated in the study (bvFTD = 16; SemDem = 11; PNFA = 9). These patients were seen either in the clinic, care facility or at home on 2 occasions approximately 12 months apart ( $M = 12.9 \pm 3.1$ ). At baseline, patients were included if they (1) fulfilled criteria for FTD [1]; (2) had an accompanying person who could give a reliable account of the patient's routine; (3) did not have a physical disability that could confound assessment of ability to perform activities of daily living; (4) did not have major depression; (5) had undergone an ACE-R [20] and MMSE [21] within 90 days of the functional assessment.

All patients underwent a MRI scan and were excluded if they had evidence of significant cerebrovascular disease (infarcts or confluent white matter changes). Patients with bvFTD were classified as phenocopy cases on the basis of a lack of atrophy in their initial MRI scans as well as on follow-up scans after 12 months [10]. Diagnoses were made by a multidisciplinary consensus (neurologist, neuropsychiatrist and neuropsychologist), and ADL measures described in this study were not included in the diagnostic process. Duration of disease was estimated by onset of symptoms as reported by the informant at the time of diagnosis. The study was approved by the Addenbrooke's Hospital Ethics Committee, and patient and/or family consent was obtained from each participant.

### *Instruments*

#### General Cognitive Assessment

The ACE-R is the updated version of the ACE [20] designed to assess 5 cognitive domains: attention/orientation, memory, verbal fluency, language and visuospatial abilities. The total score is 100;

**Table 1.** Patient demographics: sex, age, education and duration of illness

	bvFTD <i>phen</i> (n = 10)	bvFTD <i>path</i> (n = 6)	SemDem (n = 11)	PNFA (n = 9)
Sex, male patients	100%	83%	82%	78%
Age, years	61.9 (8.4)	62.2 (5.3)	63.8 (7.2)	64.9 (6.2)
Education, years	11.4 (2)	13.2 (2.5)	13 (2.5)	12 (2.7)
Duration of illness, years	7.7 (4.1)	3.6 (2.7)	5.1 (2.2)	5.5 (2.2)

Mean with standard deviation in parentheses.

bvFTD *phen* = bvFTD phenocopy; bvFTD *path* = bvFTD pathological.

higher scores reflect better ability. The ACE-R was designed to be sensitive to early stages of dementia, and incorporates the MMSE. Not all patients were able to perform the test after 12 months, the majority of them because of language difficulties, and one because of global cognitive decline (at 12 months the number of patients able to complete the ACE-R were: bvFTD phenocopy = 10/10; bvFTD pathological = 5/6; SemDem = 8/11; PNFA = 3/9).

#### Functional Assessment

Activities of daily living were assessed by using the DAD [22]. The DAD is an informant-based scale, which includes 40 items – 17 related to basic self-care (BADLs: ‘hygiene’, ‘dressing’, ‘continence’, ‘eating’) and 23 related to instrumental activities of daily living (IADLs: ‘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 has a total score corrected to 100, i.e. non-applicable questions are excluded to avoid gender bias towards activities (e.g. cooking, house chores, finances). In addition, 3 other sub-scores regarding components of activity performance can also be derived, namely initiation, planning and execution. These different sub-scores can reveal impairment in different aspects of performing an activity, i.e. if they are motivation related, or if difficulties relate to planning skills, or to the actual execution of the activity.

We used the DAD total, BADLs, IADLs, initiation, planning and execution scores for the analyses. All caregivers were interviewed by an experienced research occupational therapist (E.M.) at baseline and again after 12 months.

#### Statistics

Data were analysed using SPSS 15.0 (SPSS Inc., Chicago, Ill., USA). Parametric demographic data (age, education), as well as DAD, IADLs, initiation, planning, execution were compared across the 4 groups (bvFTD phenocopy, bvFTD pathological, SemDem and PNFA) via repeated measures ANOVAs, followed by Tukey HSD post-hoc tests. A priori, variables were plotted and checked for normal distribution by Kolmogorov-Smirnov tests. Two variables (BADL baseline and follow-up) were non-normally distributed and were log transformed for the analyses. Correlation between total DAD and ACE-R score change was analysed using Pearson correlation.

## Results

### Group Demographics

Age and education were matched for the 3 variants and phenocopy patients. Duration of illness was not similar; pathological bvFTD patients had a significantly shorter duration of illness than the phenocopy group (table 1).

### General Cognitive Assessment: ACE-R

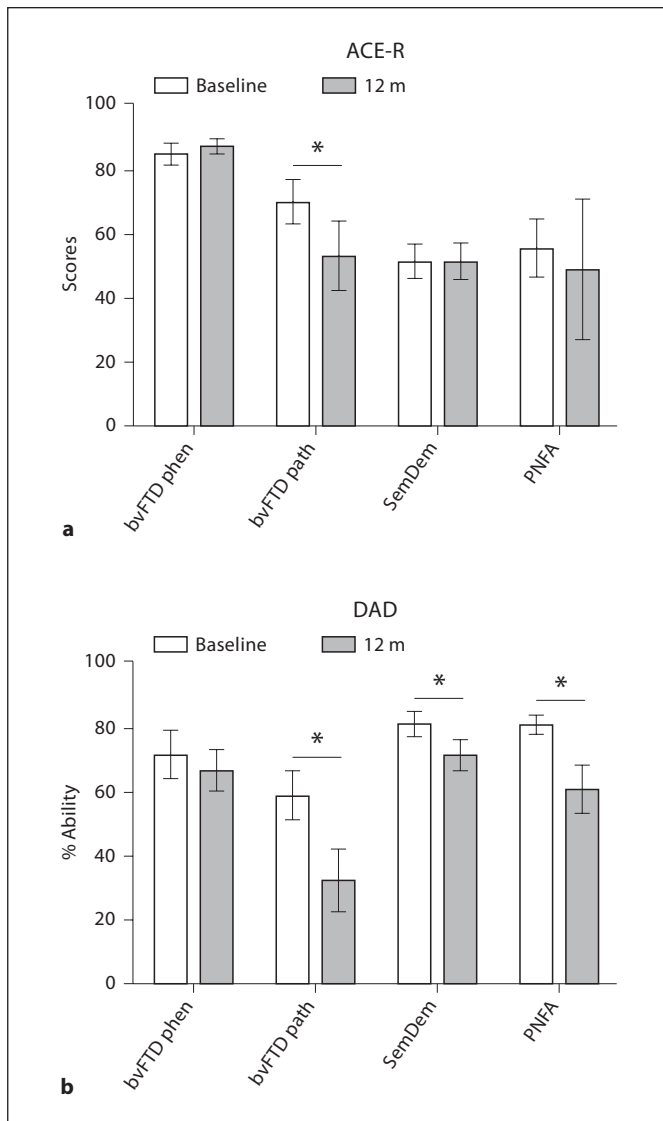
A repeated measures ANOVA disclosed a main effect of time ( $F_{(1, 21)} = 24.902, p < 0.0005$ ), group ( $F_{(3, 21)} = 7.638, p < 0.005$ ), and also an interaction between time and group ( $F_{(3, 21)} = 11.352, p < 0.0005$ ). Post hoc analysis revealed that changes in SemDem ( $p < 0.005$ ) and bvFTD pathological ( $p < 0.05$ ) were significantly different from bvFTD phenocopy.

Within group comparisons showed that only bvFTD pathological patients had a significant decline in ACE-R scores over a 12-month period (fig. 1a). Of note, not all PNFA patients were able to be assessed on the ACE-R after 1 year due to marked deterioration in language abilities ( $n = 3$ ).

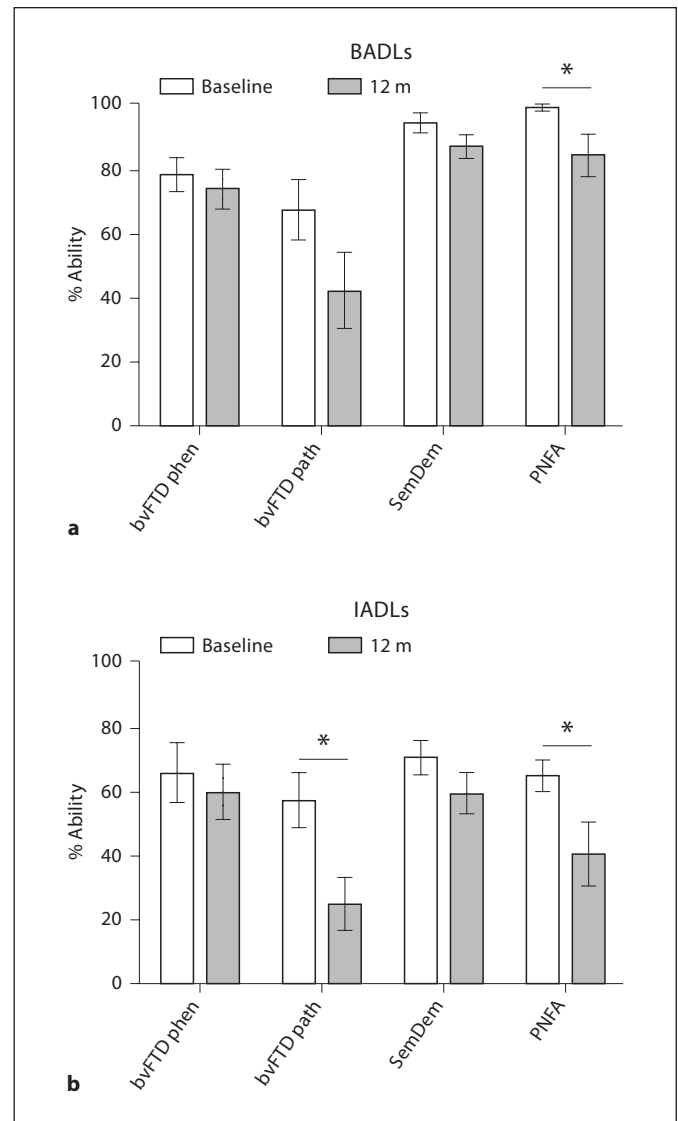
### Activities of Daily Living

A repeated measures ANOVA for DAD total score disclosed a main effect of time ( $F_{(1, 32)} = 36.624, p < 0.0005$ ), group ( $F_{(1, 32)} = 36.624, p < 0.0005$ ), and a significant interaction of group  $\times$  time ( $F_{(3, 32)} = 3.451, p < 0.05$ ). Post hoc revealed that the decline for DAD bvFTD pathological was significantly differently from SemDem ( $p < 0.05$ ).

DAD total scores were significantly lower after a 12-month period for all patient groups except for the bvFTD phenocopy group (fig. 1b). Of note is the fact that phenocopy and pathological bvFTD patients had similar levels of impairment at baseline (moderate impairment;  $t = -1.074$ ; d.f. = 14;  $p = 0.301$ ) but deterioration was signifi-



**Fig. 1. a** ACE-R scores for bvFTD phenocopy (n = 10), bvFTD pathological (n = 6), SemDem (n = 8) and PNFA (n = 3). **b** Percentage of ability on DAD scores for bvFTD phenocopy (n = 10), bvFTD pathological (n = 6), SemDem (n = 11) and PNFA (n = 9). Error bars represent SEM. \* p < 0.05.



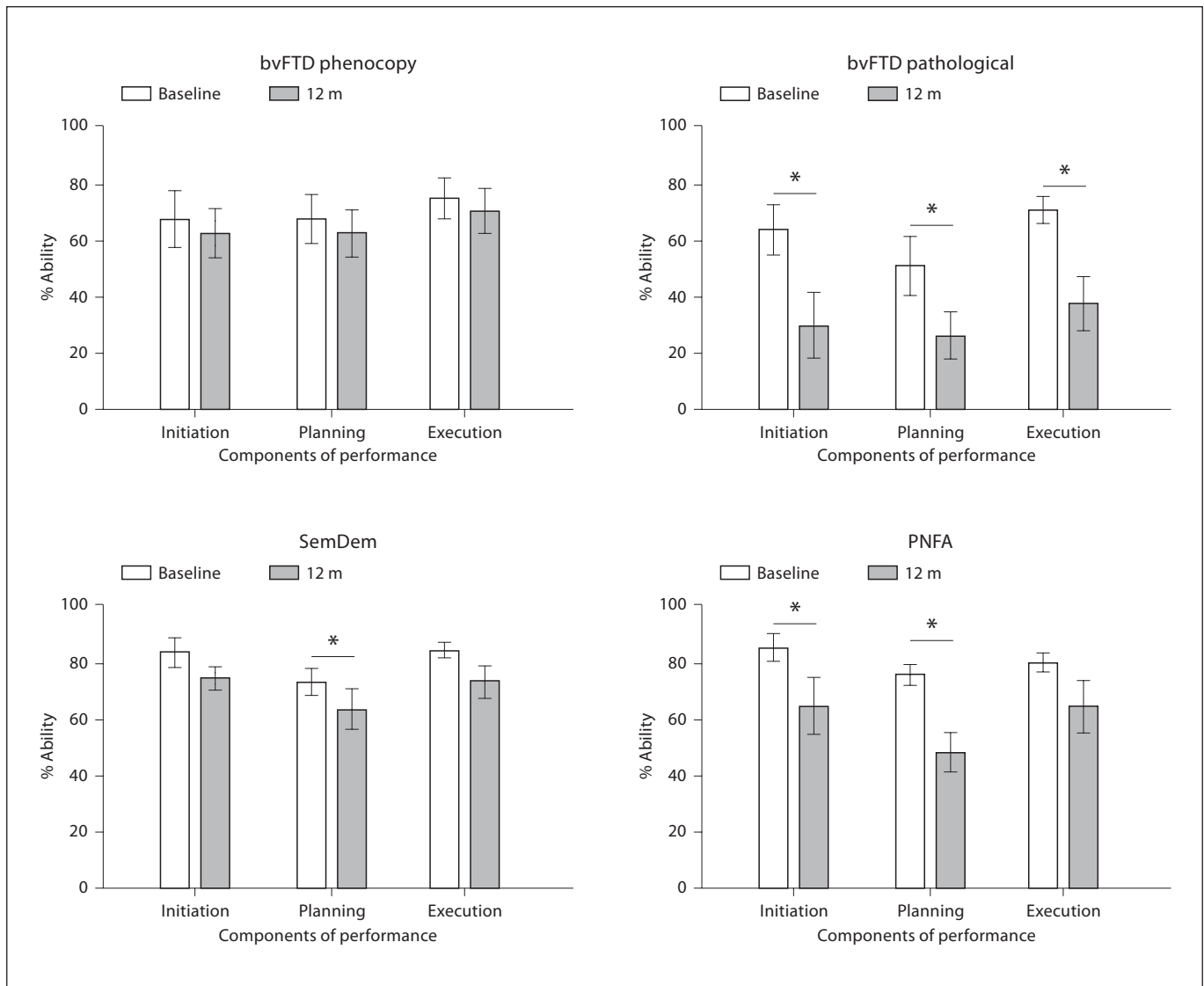
**Fig. 2. Percentage of ability on BADL (a) and IADL (b) scores for bvFTD phenocopy (n = 10), bvFTD pathological (n = 6), SemDem (n = 11) and PNFA (n = 9). Error bars represent SEM. \* p < 0.05.**

cant only for pathological patients. On average, the bvFTD phenocopy group lost 5 points, the bvFTD pathological lost 27 points, SemDem lost 12 and PNFA lost 21 points annually.

Changes in BADLs and IADLs were explored. For BADLs, a repeated measures ANOVA revealed an effect of time ( $F_{(1, 31)} = 14.455$ ,  $p < 0.0005$ ), no group effect and no interaction of group  $\times$  time (fig. 2a). When comparing changes on BADLs within patient groups, significant

decline was detected only for PNFA patients (fig. 2a). On average, bvFTD phenocopy patients lost 5 points on their BADL scores, bvFTD pathological lost 25 points, SemDem lost 10 and PNFA lost 16 points.

On IADLs, a repeated measures ANOVA revealed an effect of time ( $F_{(1, 32)} = 36.413$ ,  $p < 0.0005$ ), no group effect but an interaction of group  $\times$  time ( $F_{(3, 32)} = 3.615$ ,  $p < 0.05$ ). When comparing changes on IADLs within patient groups, significant decline was detected for bvFTD path-



**Fig. 3.** Rate of change on initiation, planning and execution after 12 months for bv-FTD phenocopy (n = 10), bvFTD pathological (n = 6), SemDem (n = 11) and PNFA (n = 9). Error bars represent SEM. \* p < 0.05.

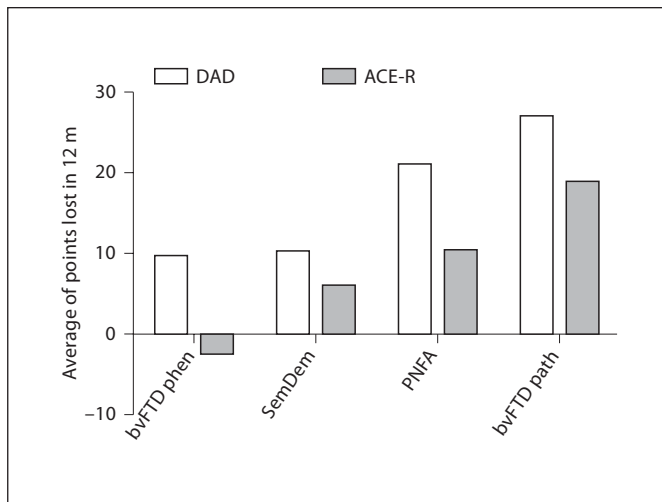
ological and also PNFA patients, in keeping with the deterioration seen on their DAD scores (fig. 2b). In terms of their IADL score decline, the bvFTD phenocopy group lost 6 points, the bvFTD pathological 31 points, SemDem 11 points and PNFA 21 points on average.

*Components of ADL Performance: Initiation, Planning and Execution*

Changes on ADL performance over a 12-month period can be also evaluated via the components of performance on the DAD. A repeated measures ANOVA dis-

closed a main effect of time and component. An interaction between time and group was identified, but no interaction between component and patient group.

Subsequent ANOVAs revealed (fig. 3) that for bvFTD phenocopy patients, there was no main effect of time or component, i.e. patients did not have significant changes over the 12-month period for any component. For bvFTD pathological patients, however, there was a main effect of time, but no main effect of subscale; all subscales declined similarly. SemDem patients showed a main effect of time and component – planning declined while the



**Fig. 4.** Annual loss in DAD and ACE-R scores for bvFTD phenocopy (n = 10), bvFTD pathological (n = 6), SemDem (n = 11) and PNFA (n = 9).

other 2 components were stable, and no interaction between time and component. For PNFA patients, a main effect of time and component were identified, with initiation and planning declining significantly; no interaction between time and component was found.

#### Comparison of Changes on ACE-R and DAD

To compare the rate of change on ACE-R and DAD scores (fig. 4) we obtained a single value of each measure that was calculated by subtracting the score of the follow-up visit from the score of the baseline assessment. Since not all PNFA patients could be reassessed after 12 months, we combined all 4 groups for a correlation between ACE-R and DAD. There was a significant association between scores on the DAD and ACE-R ( $r = 0.550$ ;  $p < 0.005$ ).

## Discussion

This is the first study to have examined longitudinal functional changes in variants of FTD using an appropriate instrument. We have shown significant decline in ADLs in those with bvFTD pathological, SemDem and PNFA, but not in those designated bvFTD phenocopy patients. Moreover, the hypothesised association between decline in ACE-R and DAD scores was confirmed.

Despite the relatively short period of 12 months between baseline and follow-up assessments, our study revealed significant change in all FTD variants' functional

scores. More importantly, the rate of deterioration for bvFTD pathological and PNFA patients were more marked than those reported in studies of AD patients, whereas SemDem patients declined in a similar rate to AD [16, 17]. This differential rate of decline across variants of FTD goes some way to explaining prior inconsistencies in the literature [6, 23, 24]. In our study, we separated FTD in 3 variants and phenocopy cases, while prior studies have combined them all in one single group. SemDem patients start at similar levels of ability in comparison to PNFA, but show a much milder decline after 12 months. The accentuated deterioration in PNFA is somewhat surprising, given that it is defined primarily as a language disorder. Executive dysfunction and early stages of apraxia, combined with their language output disorder, are likely to significantly affect their functional ability. This may relate to the heterogeneous underlying pathology in PNFA, which includes frontotemporal lobar degeneration (FTLD) with tau-positive inclusions, AD pathology [25] and corticobasal degeneration [26, 27]. Further investigation should determine the basis of the marked functional change in this subgroup.

The lack of progression in the bvFTD phenocopy group is, of course, entirely predictable but it should be noted that their designation as phenocopy (or non-progressors) was made on the basis of their MRI at presentation which demonstrated, in contrast to the bvFTD pathological group, a lack of visual brain atrophy. The ADL profile in the 2 bvFTD groups was not significantly different at baseline on the DAD as previously reported [10]. Recent studies have shown that despite presenting similar behavioural profiles, they are distinguishable on the basis of executive tests performance [9], performance-based ADLs [10] and on tests of emotion detection [11]. The present study suggests that patients with bvFTD phenocopy syndrome can be clearly separated within 12 months by their lack of change on the DAD.

The use of the DAD enabled components of performance, i.e. initiation, planning and execution, to be explored. The bvFTD pathological group showed a decline in all components. SemDem patients, by contrast, showed significant decline in planning only, i.e. their ability to initiate and complete most everyday tasks was well maintained. PNFA patients showed decline in all 3 components, which reached significance for initiation and planning.

The relationship between DAD and ACE-R scores, not surprisingly, paralleled each other, although the rate of decline in the DAD was much more marked than on the ACE-R for bvFTD pathological and PNFA groups. Previ-

ous studies have shown no such correlation between ADL and cognitive decline in FTD [4, 28], but these were cross-sectional studies. In AD, findings are inconsistent. Three longitudinal studies have compared the DAD with cognitive testing: one showed that patients with lower scores in cognitive tests, such as the MMSE, had greater decline in their ADL scores [16], whereas the second demonstrated that this was related to BADL scores only, not for the total DAD score [17]. In the third study using the DAD, the relationship between DAD and cognitive tests was not significant. Other studies have not found a direct association between MMSE and ADL measures [19, 29, 30], whereas another found a strong association between a performance-based ADL scale and neuropsychological assessments [31]. The lack of a gold standard in evaluating ADLs [14] makes comparisons between studies rather difficult.

This study presents limitations. Our samples were quite small, especially for PNFA, suggesting caution in making generalisations. In addition, the follow-up time

ideally should be longer. Finally, we have had pathological confirmation for only 3 patients.

This study shows that deterioration in ADLs is marked for all FTD variants after 12 months except for those designated bvFTD phenocopy. It highlights that phenocopy patients can be differentiated from those with true pathological bvFTD on the basis of their ADL scores after 12 months. More importantly, this study emphasizes the devastating impact of FTD on patient's everyday life abilities that varies across the FTD subtypes. These functional changes should be taken into consideration when discussing likely disease progression.

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