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Comparing longitudinal behavior changes in the primary progressive aphasias

Tim Van Langenhove ^{a,b,c,d}, Cristian E. Leyton ^{a,b,e}, Olivier Piguet ^{a,b,c}, John R. Hodges ^{a,b,c}

Running title

Behavior changes in the PPA subtypes

Affiliations

^a Neuroscience Research Australia, Sydney, Australia

^b ARC Centre of Excellence in Cognition and its Disorders, Sydney, Australia

^c School of Medical Sciences, The University of New South Wales, Sydney, Australia

^d Institute Born-Bunge, University of Antwerp, Antwerp, Belgium

^e Faculty of Health Sciences, The University of Sydney, Sydney, Australia

Contact details of corresponding author

Dr. Tim Van Langenhove

Neuroscience Research Australia

Margarete Ainsworth Building

Barker Street (PO Box 1165)

Randwick NSW 2031

Australia

Email: tim.vanlangenhove@gmail.com

Tel: +61 2 9399 1134 Fax: +61 2 9399 1047

ABSTRACT

Background: Differentiating between primary progressive aphasia (PPA) variants based on the profile of language deficits can be difficult in a proportion of patients. Further, little is presently known about the pattern of longitudinal changes in behavior in PPA variants.

Objective: To determine the presence of behavioral changes in the main variants of PPA: semantic (sv-PPA), nonfluent/agrammatic (nfv-PPA) and logopenic (lv-PPA), and establish the course of these changes over time.

Methods: We measured behavioral changes in 73 prospectively recruited PPA (30 sv-PPA, 22 nfv-PPA and 21 lv-PPA), as well as 33 behavioral variant frontotemporal dementia (bv-FTD) and 31 Alzheimer disease (AD) patients, at baseline and after 1 year, using the Cambridge Behavioural Inventory Revised. All included patients had mild dementia severity at baseline.

Results: Both at baseline and follow-up, sv-PPA exhibited significantly more behavioral disturbances of the type characteristic of bv-FTD compared with other PPA variants. 74% of sv-PPA patients with mild dementia severity exhibited at least one behavior disturbance at baseline, which increased to 84% during follow-up. Behavioral symptoms did not differ between nfv-PPA and lv-PPA groups at baseline. At follow-up, however, empathy loss was significantly more pronounced in nfv-PPA. The prevalence and course of behavioral symptoms in lv-PPA was similar to that found in AD.

Conclusions: sv-PPA show more prominent FTD-like behavioral disturbances compared with other PPA variants which typically emerge already early in the disease course. Empathy loss may be an important factor that helps differentiating nvf-PPA from lv-PPA. Our results may allow improved prediction of likely progression in behavioral symptoms across the PPA variants.

Keywords

Aphasia, Primary Progressive; Frontotemporal Dementia; Behavioral Symptoms; Empathy; Longitudinal Studies

INTRODUCTION

Primary progressive aphasia (PPA) are clinically and pathologically heterogeneous disorders [1, 2]. In 2011, consensus criteria were published for the diagnosis of three clinical variants, semantic (sv-PPA), nonfluent/agrammatic (nfv-PPA) and logopenic (lv-PPA), based on the type of language and speech deficits [3]. Clinicopathological correlation studies have shown that the most common underlying pathology in sv-PPA and nfv-PPA is frontotemporal lobar degeneration, whereas most patients with lv-PPA have Alzheimer disease (AD) pathology [4-6]. Although the majority of individuals presenting with PPA fit these criteria, a significant proportion remains unclassifiable due to the presence of either mild or overlapping linguistic deficits [7-9]. Further, many of the features towards a PPA diagnosis rely on the evaluation of connected speech and some of these key distinguishing features (e.g., motor speech disorder of nfv-PPA and phonological errors of lv-PPA) can be difficult to assess or to distinguish, particularly for clinicians who are not language experts [1]. Yet, making an accurate diagnosis and correct prediction of the pathology in life in PPA has important implications for management and the prognosis [10], and will be crucial as effective therapies are being developed.

While language disturbance is by definition the most prominent feature of PPA, increasing evidence has also demonstrated the presence of impairments in other aspects of cognition, which can help differentiate between the PPA subtypes [11]. Given the overlap in distribution of atrophy and pathology between sv-PPA, nfv-PPA and behavioral variant frontotemporal dementia (bv-FTD), a form of dementia characterized by early and progressive changes in behavior and personality [12, 13], one would predict more frequent and more severe behavioral changes in these two PPA subtypes compared with lv-PPA. Few studies, however, have directly compared behavior changes across the different subtypes of

PPA, of which only one has used the current diagnostic criteria [[14-16](#)]. Moreover, longitudinal studies that formally investigated the emergence of behavioral disturbances over time in the different PPA subtypes are currently lacking. Understanding the prevalence and course of behavioral changes in PPA is also important for the management of PPA patients as these symptoms are reported to increase caregiver burden and contribute to institutionalization [[17, 18](#)].

In this study, we set to investigate the prevalence and course of behavior changes, in a well-characterized cohort of PPA patients, using the Cambridge Behavioural Inventory Revised (CBI-R) questionnaire to assess the typical FTD-like behavior changes [[19](#)]. We hypothesized that the PPA syndromes would exhibit different profiles of behavioral change, given the respective locus of predominant brain atrophy in these groups. In addition, given the different underlying neuropathological processes associated with the PPA syndromes, we also anticipated divergent course and profile of behavioral disturbances over time. To improve the comparability across subgroups and the clinical applicability of the findings to establish the prognosis of behavioral symptoms, all patients had mild dementia severity at baseline.

MATERIALS AND METHODS

Participants

All PPA patients (n = 73) were prospectively recruited between 2007 and 2014 and longitudinally followed at FRONTIER, the specialist Frontotemporal Dementia Clinic at Neuroscience Research Australia in Sydney (www.ftdrg.org). At each time point, all participants underwent a comprehensive assessment, which included a neurological examination, language assessment, neuropsychological evaluation, and structural brain imaging [20, 21]. A corroborating and behavioral history was obtained from a close relative or carer of each patient. All patients met the relevant clinical diagnostic criteria for PPA (sv-PPA, nfv-PPA or lv-PPA) [3]. All included patients had two assessments separated by approximately one year and mild dementia (i.e., clinical dementia rating, (CDR) ≤ 1) at baseline evaluation [22]. Thirty-five PPA patients underwent amyloid PET imaging using the ligand 11C-Pittsburgh compound B (PiB). Patients were considered to have a positive PiB-PET scan if the neocortical PiB standardized uptake value was 1.5 or more [23]. The results were mostly in accordance with the suspected pathology except for one sv-PPA and one nfv-PPA patient who had positive and one lv-PPA patient who had negative PiB-PET scans. We excluded these three patients to improve the nosological homogeneity of PPA subgroups and to ensure coherent neuropathological relationships across groups. To compare with the PPA cohorts, we included a group of probable bv-FTD (n = 33) [13] and probable AD patients (n = 31) [24], matched for disease severity.

Standard protocol approvals, registrations, and patient consents

This study was approved by the South Eastern Sydney Local Health District and the University of New South Wales human ethics committees. Written informed consent was obtained from the participant and/or primary caregiver.

Behavior evaluation

Behavioral changes were assessed using the CBI-R, an informant-based questionnaire comprising 45 items that cover aspects of behavior, cognition and activities of daily living [19] and which was specifically designed to capture the changes that are typical of FTD. The CBI-R measures the level of functioning over the previous month, allowing to track changes over time. A review of the individual items of the questionnaire showed that two questions which are part of the motivation subscale measure empathy loss ('appears indifferent to the worries and concerns of family members' and 'shows reduced affection'), whereas the remaining questions measure apathy ('shows less enthusiasm for his or her usual interests', 'shows little interest in doing new things' and 'fails to maintain motivation to keep in contact with friends or family'). We analyzed empathy loss and apathy separately because they encompass different behavioral symptoms that are both characteristic of bv-FTD. This modified version of the CBI-R evaluates 11 domains: memory and orientation, everyday skills, self care, disinhibition, mood, hallucinations and delusions, eating habit changes, sleep, stereotypical and motor behavior, apathy and empathy loss. Caregivers were asked to score the frequency of each item on a 5-point scale, where 0 denotes never, 1 a few times per month, 2 a few times per week, 3 daily occurrence and 4 constant occurrence. For each domain a score was calculated, which represents the percentage of the maximum achievable score. A score of ≥ 25 was considered as a clinically relevant change (which corresponds with a frequency of at least a few times per week, while a score of less than 25 corresponds with none or a few times per month). In a group of non-

demented control individuals judged by their spouse ($n = 35$), endorsements on the CBI-R were rare and, except for the domain sleep, almost none exceeded a score of ≥ 25 (Supplementary Table 1).

Statistical analysis

Data were analyzed using IBM SPSS Statistics (version 22.0, IBM). Kolmogorov-Smirnov tests were applied to determine suitability of variables for parametric analyses. We examined differences in baseline characteristics across groups using analysis of variance followed by Tukey post hoc tests, Chi-square tests or Mann-Whitney tests when appropriate. CBI-R scores were analyzed using Mann-Whitney tests because the distributions of these scores were negatively skewed. Correlations were examined between behavioral disturbances (domain disinhibition of the CBI-R) and CDR sum of boxes scores, Addenbrooke's Cognitive Examination III (ACE-III, [\[25\]](#)) scores, age and disease duration using the Spearman's rho test. Sex differences in behavioral changes (disinhibition) were assessed using Mann-Whitney tests. The p-value for statistical significance was set at 0.05, or otherwise stated.

RESULTS

Patients characteristics

The demographic and clinical characteristics of the patient groups are shown in Table 1. Patient groups did not differ for disease severity (CDR scores) at baseline and for time elapsed between baseline and follow-up. Behavioral variant FTD patients included a larger proportion of males compared with all other groups and estimated length of symptom duration at baseline was longer in sv-PPA patients compared with nvf-PPA and AD patients. Whilst baseline ACE-III scores also differed across groups, the decline over time on this measure did not. The increase in CDR scores was greater for bv-FTD compared with AD, but was similar between PPA groups.

Evaluation for associations between behavioral symptoms and baseline clinical characteristics revealed a moderate correlation with CDR sum of boxes scores ($\rho = 0.44$, $p < 0.01$) and a mild correlation with disease duration ($\rho = 0.26$, $p < 0.01$). Sex, age and ACE-III scores were not associated with behavioral symptoms.

Comparison of behavior changes at baseline

Table 2 shows CBI-R scores at baseline of each patient group. Patients with sv-PPA had more behavior changes compared with the two other variants of PPA. Most characteristic behavioral disturbances for sv-PPA were stereotypical behavior compared with nvf-PPA and lv-PPA, and empathy loss compared with lv-PPA (Table 2, each with $p < 0.01$). Semantic variant PPA patients also exhibited more changes in eating changes compared with nvf-PPA and lv-PPA ($p < 0.05$), and disinhibition compared with lv-PPA ($p < 0.05$). While apathy level tended to be more frequent in sv-PPA than in other PPA syndromes, the difference did

not reach statistical significance. No differences in behavioral disturbances were found between nvf-PPA and lv-PPA patients at baseline.

Memory was more affected in sv-PPA compared with nvf-PPA ($p < 0.01$). Caregivers often endorsed questions related to loss of memory for words, a typical feature of sv-PPA. Also, lv-PPA patients showed more memory problems compared with nvf-PPA patients ($p < 0.01$), in contrast to the similar levels of behavioral symptoms found at baseline in these two groups.

The level of impairment on subscales of daily life activities was found to be similar across PPA groups, except for lv-PPA having more difficulties with everyday skills compared with sv-PPA ($p < 0.05$). Hallucinations and delusions were uncommon in all PPA subtypes and when present were rated mild.

Comparing sv-PPA with bv-FTD showed that while behavioral symptom scores appeared higher in the bv-FTD group, only changes in eating habits reached statistical significance ($p < 0.05$). Examining other aspects of functioning revealed higher difficulties with everyday skills and sleep ($p < 0.01$) but less severe memory problems in patients with bv-FTD when compared with sv-PPA ($p < 0.05$).

Comparing lv-PPA with AD indicated similar levels of behavioral changes between the groups. While memory difficulties appeared more common in AD as compared with lv-PPA, this did not reach statistical significance.

Figure 1 shows the proportion of patients with a clinically relevant change in behavior at baseline and follow-up. At the first assessment, 74% of sv-PPA, 54% of nfv-PPA and 47% of lv-PPA exhibited one or more behavioral disturbances. In sv-PPA patients, stereotypical behavior, empathy loss and apathy had the highest prevalence and were prominent symptoms, occurring in 60% of patients or more. Disinhibition and changes in eating habits were found in around 40% of sv-PPA patients. In both nfv-PPA and lv-PPA groups, apathy was the most common symptom (46% and 38%). Other behavioral symptoms were found in less than one-third of these patients.

Progression of behavior changes

The levels of behavioral disturbances increased over time in each PPA subgroup (Table 3). For sv-PPA, stereotypical behavior (compared with both nfv-PPA and lv-PPA, $p < 0.01$) and empathy loss (compared with lv-PPA, $p < 0.01$) remained most discriminating behavior features. While baseline behavioral disturbances were similar in nfv-PPA and lv-PPA, patients with nfv-PPA had developed significantly more empathy loss 1 year later compared with lv-PPA ($p < 0.05$).

Further examination of the CBI-R subscales across PPA groups showed that memory remained less impaired in nfv-PPA compared with sv-PPA ($p < 0.01$) and lv-PPA, and that the decline in everyday skills was less pronounced in sv-PPA than in both nfv-PPA and lv-PPA groups ($p < 0.01$). Hallucinations and delusions remained rare symptoms in all patient groups.

When compared with bv-FTD, sv-PPA showed less changes in eating habits and apathy at follow-up ($p < 0.05$). Activities of daily life activities remained also less affected in sv-PPA

than in bv-FTD patients ($p < 0.01$). The evolution in behavioral changes, as well as on other domains of the CBI-R, in patients with lv-PPA was similar as compared with AD patients.

During follow-up, the vast majority of patients ($> 70\%$) in each PPA subgroup developed a clinically relevant change in at least one behavioral symptom (Figure 1). In sv-PPA, the frequency of stereotypical behavior increased to 80%, apathy to 70% and empathy loss to 67%. In nfv-PPA, the frequency of empathy loss increased to 60% after an interval of one year, compared with 33% in lv-PPA patients. Apathy became a prominent symptom in both nfv-PPA (68%) and lv-PPA (62%) during follow-up. Disinhibition, changes in eating habits and stereotypical behavior remained a relatively uncommon symptom both nfv-PPA and lv-PPA, found in about one third of these patients.

Across the subgroups of PPA, 38-50% of the patients who did not have behavior change at baseline developed them at follow-up (Table 4). In sv-PPA the risk of developing stereotypical behavior (50%) was the highest. Non-fluent variant PPA patients were mostly at risk for developing apathy and empathy loss (each around 40%) within 1 year, while this risk in lv-PPA patients was the highest for apathy (38%). The persistence of the behavioral disturbances over time in PPA patients was very high. Indeed, of the patients with clinically relevant change in any behavior symptom at baseline, almost all (95-97%) exhibited the same symptoms at follow-up.

DISCUSSION

This study compares the prevalence and severity of behavioral symptoms in a large cohort of PPA patients in early disease stages as well as their progression over a 1-year period. Among the different variants of PPA, sv-PPA patients presented with most behavior disturbances of the type that are characteristic of bv-FTD, including disinhibition, eating habit changes, stereotypical behavior and empathy loss. Earlier studies have also reported an increased frequency of such behavior phenomena in sv-PPA [14-16, 26, 27]. In addition to previous work, our results indicate that sv-PPA patients already show higher levels of behavioral changes than other PPA variants in the early stages of the disease (mild dementia severity). The analysis also demonstrate that behavioral disturbances are common symptoms in sv-PPA, nearly 75% of the sv-PPA patients had at least one behavioral change at first presentation.

The study also revealed differences in the behavior profile of nfv-PPA compared with lv-PPA. At baseline, the majority of nfv-PPA and lv-PPA did not exhibit behavioral disturbances and, when present, these did not differ between groups. Over time, however, nfv-PPA developed significantly higher rates of empathy loss compared with lv-PPA. This finding is in contrast to earlier work, which found a comparable profile of behavior changes between nfv-PPA and lv-PPA [14-16]. Previous studies, however, have used the Neuropsychiatric Inventory to assess behavior changes, an instrument which does not directly investigate the presence of empathy loss [28]. In addition, these studies have mostly used PPA criteria that predate those published in 2011, which implies that the separation between nfv-PPA and lv-PPA might have been less stringent. It has been shown that using the 2011 criteria assist with separating PPA patients with AD pathology by

reclassifying a sizable proportion of the previously diagnosed non-fluent PPA cases as lv-PPA [29].

The decline in empathy found in nfv-PPA supports earlier findings reporting decreased emotion recognition in this group [11, 30, 31]. Using the Ekman 60 Faces Test it was shown that nfv-PPA patients experience significant facial emotion recognition deficits compared with lv-PPA patients and controls [11]. Empathy is a multilayered phenomenon that includes the recognition of feelings and emotions of others. The impairment on this ability in nfv-PPA likely contributes to the diminished empathic responses observed in this group. Furthermore, imaging studies have highlighted the contribution of the anterior insula and inferior frontal gyrus in emotion processing, regions which have also been consistently associated with atrophy in nfv-PPA on the left side [32-34].

Considering the distinction between nfv- and lv-PPA, of note is that carers also reported more memory dysfunction on the CBI-R in lv-PPA compared with nfv-PPA. Although aphasia is by definition the most prominent feature of PPA, impairments in other aspects of cognition may also be present, which can help to differentiate between PPA subtypes. Recently, a study demonstrated that a combination of tasks for episodic memory, visuospatial function and recognition of facial emotion was able to classify correctly 87% of nfv- and lv-PPA patients at initial presentation [11]. Here, we show that these two PPA syndromes also differ with respect to behavioral changes. A lack of empathy, information that can be quickly gathered from an informant during consultation, can help improve diagnostic certainty, and is most relevant behavioral manifestation to consider compared with other FTD-like behavioral changes.

Reflecting common pathological substrates, lv-PPA presented a similar profile of behavior changes as observed in patients with typical AD. Apathy was the behavioral feature most commonly reported in both lv-PPA and AD. This finding is consistent with previous reports that apathy is among the most common behavior change early in the course of AD [35].

This study is the first to specifically report on the frequencies and evolution of behavior disturbances in the different subtypes of PPA over a 1-year period. As such, the results may inform physicians and carers of PPA patients about the likely long-term consequences of the disease, which is important when offering psycho-education and considering pharmacological treatment. Our findings indicate that emergence of behavioral disturbances over time in sv-PPA is very likely, even if not present at the initial presentation: 74% of sv-PPA patients exhibited one or more behavior disturbance at baseline, which increased to 84% during follow-up. Furthermore, the longitudinal data suggest that stereotypical behavior, lack of empathy and apathy are among the first behavioral symptoms to develop in sv-PPA whereas disinhibited behavior and altered eating habits are features that occur later in disease course. In both nfv-PPA and lv-PPA apathy was an important behavior symptom at baseline, occurring in around 40%, increasing to ~60% by the time of follow-up. In addition, patients with nfv-PPA are at sizable risk to develop empathy loss when the disease progresses from mild to moderate dementia severity, with frequencies of a clinically relevant change in this domain increasing from 32% to 60%. This is of relevance when discussing prognosis as it has been shown that lack of empathy is particular distressing for the caregivers [36]. Further, our findings indicate that when present at baseline, clinically relevant behavior changes are highly likely to be observed again at follow-up. It remains to be investigated whether other forms of

behavioral changes also become prevalent in nfv-PPA or lv-PPA in more advanced stages of the disease.

A PPA diagnosis requires a prominent, relatively isolated language deficit during the initial phases of the disease. However, as this study shows, many PPA patients will develop also behavioral impairments within a few years after clinical onset of PPA. Other PPA patients may develop additional prominent cognitive or motor deficits [\[10, 37\]](#). It has been suggested that for these patients who initially fulfilled the diagnostic criteria for PPA, but subsequently developed also prominent behavioral, cognitive or motor impairments, the designation of PPA-plus can be used [\[2\]](#).

A few caveats should be considered. Empathy is a complex social behavior and the CBI-R may not capture all of its nuances. Future studies with specific questionnaires developed to investigate empathy, such as the Interpersonal Reactivity Index, will be of interest [\[38\]](#). Nonetheless, the current findings align well with earlier observations of decreased performance on emotional recognition tasks in nfv-PPA patients. Secondly, patients in this study had a mild to moderate stage of dementia, when they most often present to the clinics. Longer follow-up studies will be required to provide better estimation of the long-term prognosis. Another possible limitation is that the diagnosis was based on clinical grounds, without pathological confirmation, although a sizable proportion of patients underwent a PiB-PET scan, a putative marker of AD, which corroborated the clinical diagnosis.

In summary, the study showed that the three subtypes of PPA differ in their profile of behavior disturbances, which can help differentiate between PPA subtypes. We confirmed

that FTD-like behavioral changes are most common in sv-PPA and we showed that these features are typically already present in the early stages of the disease. Further, we identified increased loss of empathy in nfv-PPA compared with lv-PPA. The courses described for the behavioral symptoms over 1 year, starting from mild stage of disease, can be helpful to estimate the prognosis of these symptoms in the different PPA variants. Notably, sv-PPA patients have a very high risk to develop behavior disturbances during the disease course and nfv-PPA patients often develop empathy loss. These findings have clinical implications and emphasize the value of behavioral assessment in PPA.

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TABLES AND FIGURES

Table 1: General clinical characteristics of patient groups.

	bv-FTD (n = 33)	sv-PPA (n = 30)	nfv-PPA (n = 22)	lv-PPA (n = 21)	AD (n = 31)	Group differences
Sex, % of male	79%	57%	46%	48%	52%	bv-FTD > sv-PPA, nfv-PPA, lv-PPA, AD
Age, years	63.2 (7.8)	63.6 (7.7)	65.5 (9.5)	65.7 (7.6)	61.6 (7.0)	NS
Symptom duration, months	4.0 (3.1)	4.4 (1.9)	2.3 (1.2)	3.5 (2.7)	2.6 (1.8)	sv-PPA > nfv-PPA, AD
Follow-up time, months	12.2 (2.1)	12.6 (1.3)	12.4 (1.7)	13.0 (1.6)	12.2 (1.6)	NS
CDR, /3						
at baseline	0.69 (0.28)	0.67 (0.24)	0.48 (0.29)	0.55 (0.35)	0.71 (0.25)	NS
at follow-up	1.11 (0.64)	0.81 (0.52)	0.66 (0.59)	0.67 (0.49)	0.79 (0.35)	bv-FTD > nfv-PPA, lv-PPA, AD
difference	-0.43 (0.49)	-0.17 (0.46)	-0.18 (0.50)	-0.17 (0.38)	-0.07 (0.35)	bv-FTD > AD
ACE-III, /100						
at baseline	78.5 (10.2)	61.7 (15.0)	76.9 (10.7)	61.3 (9.3)	71.5 (13.9)	bv-FTD > sv-PPA, lv-PPA, AD; sv-PPA < nfv-PPA, AD; nfv-PPA > lv-PPA; lv-PPA < AD
at follow-up	72.3 (16.3)	57.1 (15.7)	65.1 (22.5)	50.4 (14.9)	67.0 (14.1)	bv-FTD > sv-PPA, lv-PPA; sv-PPA < nfv-PPA, AD; nfv-PPA > lv-PPA; lv-PPA < AD
difference	-6.3 (11.0)	-6.6 (5.8)	-13.0 (18.0)	-11.9 (11.5)	-5.9 (6.2)	NS

Values represent means (standard deviations). NS indicates not significant; NA, not applicable; ACE-III, Addenbrooke's Cognitive Examination third version; CDR, clinical dementia rating scale

Table 2: Baseline CBI-R scores across patient groups.

	bv-FTD	sv-PPA	nfv-PPA	lv-PPA	AD
<i>Behavioural changes</i>					
Disinhibition	32.5 ^{C,D,E}	22.4 ^{d,e}	10.2 ^A	6.5 ^{A,b}	8.2 ^{A,b}
Eating habit changes	36.6 ^{b,C,D,E}	20.6 ^{a,c,d}	8.0 ^{A,b}	8.3 ^{A,b}	8.5 ^A
Stereotypical behavior	42.7 ^{C,D,E}	36.2 ^{C,D,E}	12.1 ^{A,B}	15.0 ^{A,B}	14.0 ^{A,B}
Apathy	49.2 ^{C,D,E}	39.4	22.0 ^A	22.6 ^A	23.1 ^A
Empathy loss	50.4 ^{C,D,E}	35.8 ^{c,D,E}	17.6 ^{A,b}	11.9 ^{A,B}	10.1 ^{A,B}
<i>Cognition</i>					
Memory	35.1 ^{b,C,e}	44.5 ^{a,C}	19.6 ^{A,B,D,E}	35.9 ^C	46.0 ^{a,C}
<i>Daily life activities</i>					
Everyday skills	24.6 ^b	14.4 ^{a,d}	17.7	28.5 ^b	25.9
Self care	5.7 ^{c,d}	1.7	0.6 ^a	0.6 ^a	3.8
Sleep	45.1 ^{B,c,d,e}	24.2 ^A	25.6 ^a	27.4 ^a	27.0 ^a
<i>Psychiatric features</i>					
Mood	29.0 ^{c,d,e}	20.4	16.2 ^a	15.5 ^a	17.1 ^a
Hallucin. and delusions	4.3	4.2	1.1	3.2	3.0
CBI-R Total	31.3 ^{C,D,E}	26.3 ^C	13.5 ^{A,B,e}	17.3 ^A	19.4 ^{A,c}

Results of pairwise comparisons: ^a vs bv-FTD, ^b vs sv-PPA, ^c vs nfv-PPA, ^d vs lv-PPA and ^e vs AD; lowercase letters if p-value < 0.05, capital letters if p-value < 0.01

Table 3: CBI-R scores at 1-year follow-up across patient groups.

	bv-FTD	sv-PPA	nfv-PPA	lv-PPA	AD
<i>Behavioral changes</i>					
Disinhibition	38.5 ^{C,D,E}	31.0 ^{c,D,e}	14.4 ^{A,b}	12.1 ^{A,B}	13.4 ^{A,b}
Eating habit changes	44.1 ^{b,C,D,E}	29.0 ^{a,d,e}	19.0 ^A	11.9 ^{A,b}	13.5 ^{A,b}
Stereotypical behavior	50.4 ^{C,D,E}	48.9 ^{C,D,E}	23.9 ^{A,B}	21.4 ^{A,B}	16.8 ^{A,B}
Apathy	63.4 ^{b,C,D,E}	46.1 ^a	39.4 ^A	36.1 ^A	29.3 ^A
Empathy loss	56.4 ^{c,D,E}	48.3 ^{D,E}	36.9 ^{a,d,e}	16.7 ^{A,B,c}	12.1 ^{A,B,c}
<i>Cognition</i>					
Memory	47.6 ^c	55.4 ^C	32.5 ^{a,B,d,E}	50.9 ^c	54.1 ^C
<i>Daily life activities</i>					
Everyday skills	41.1 ^B	22.6 ^{A,C,D}	42.5 ^B	42.6 ^B	34.1
Self care	19.5 ^{B,c,d}	5.8 ^A	10.2 ^a	4.5 ^a	9.1
Sleep	52.0 ^{B,C,D,E}	22.1 ^A	23.3 ^A	29.8 ^A	30.6 ^A
<i>Psychiatric features</i>					
Mood	30.1 ^E	28.1	24.7	22.3	18.8 ^A
Hallucin. and delusions	7.3	6.1	1.5	5.2	4.3
CBI-R Total	40.3 ^{C,D,E}	33.2	24.7 ^A	25.5 ^A	24.6 ^A

Results of pairwise comparisons: ^a vs bv-FTD, ^b vs sv-PPA, ^c vs nfv-PPA, ^d vs lv-PPA and ^e vs AD; lowercase letters if p-value < 0.05, capital letters if p-value < 0.01

Table 4: Proportion of patients developing clinically relevant changes between the first and second assessment.

	bv-FTD	sv-PPA	nv-PPA	lv-PPA	AD
Disinhibition	46%	17%	5%	5%	7%
Eating habit changes	36%	22%	11%	5%	4%
Stereotypical behavior	60%	50%	16%	14%	9%
Apathy	81%	11%	42%	38%	25%
Empathy loss	44%	9%	40%	13%	8%
Any behavioral change	NA	38%	50%	46%	40%

^a already 100% of bv-FTD patients are affected at baseline

Figure 1: Frequency of clinically relevant changes in patient groups at baseline and 1 year follow-up.

SUPPLEMENTARY DATA

Supplementary Table 1: CBI-R scores in non demented control individuals

Control individuals	
<i>Demographic characteristics</i>	
Number	35
Sex, % male	62.9
Age, mean (SD)	67.8 (6.8)
ACE-III score, mean (SD)	95.1 (3.0)
<i>CBI-R scores, mean (% with score ≥ 25)</i>	
Disinhibition	2.6 (0%)
Eating habit changes	1.9 (3%)
Stereotypic behavior	6.0 (6%)
Apathy	3.5 (6%)
Empathy loss	0.0 (0%)
Everyday skills	0.7 (0%)
Self care	0.0 (0%)
Sleep	14.2 (40%)
Memory	6.0 (0%)
Mood	3.2 (0%)
Hallucinations and delusions	0.2 (0%)
Total CBI score	3.4 (0%)