The relationship between behavioral changes, cognitive symptoms, and functional disability in primary progressive aphasia: a longitudinal study

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ABSTRACT

BACKGROUND The contribution of behavioral changes to functional decline is yet to be explored in PPA. Objectives: (1) investigate functional changes in two PPA variants (semantic and non-fluent), at baseline and after 12 months; (2) investigate baseline differences in behavioral changes between groups, and (3) explore predictors of functional decline after a 12-month period.

METHODS A longitudinal study involving 29 people with PPA (18 svPPA; 11 nfvPPA) seen annually in Sydney/Australia was conducted. 114 functional and behavioral assessments were included for within (repeated-measures ANOVA; annual rate of change; multiple regression analyses) and between group analyses (pair-wise comparisons).

RESULTS Functional profiles in svPPA and nfvPPA were similar in people with up to 5 years of disease duration. Behavioral changes were marked in svPPA patients (stereotypical behavior and apathy) but did not predict annual rate of change of functional abilities; global cognitive scores at baseline did. Despite mild behavioral changes in nfvPPA (disinhibition, apathy), these were significant predictors of annual rate of functional change.

CONCLUSIONS The presentation and interplay of behavioral changes and functional disability differs in svPPA and nfvPPA. These varying factors should be taken into account when considering prognosis, disease management, and selection of outcome measures for interventions.

INTRODUCTION

Primary progressive aphasia (PPA) refers to three primary clinical variants: semantic (svPPA), non-fluent (nfvPPA), and logopenic variant (lvPPA). SvPPA patients maintain fluent speech but have severe impairments in expressive and receptive single-word comprehension, which impair recognition of objects and people. In contrast, communication in nfvPPA involves effortful, halting speech with grammatical and speech production errors leading to non-fluent communication. LvPPA has a distinct pattern of speech disruption with overlaps with nfvPPA, however, in contrast to svPPA and nfvPPA is primarily pathologically associated with Alzheimer's disease.[1-3]

In PPA, assessment of language often outweighs assessment of functional disability. Functional deficits are defined as disability in activities of daily living (ADLs), comprising change in a number of daily tasks of varying levels of complexity.[4] Current diagnostic criteria for PPA states that ADLs are relatively well maintained during the initial phase of the condition.[1,5] Over time however, PPA becomes similar to all dementia syndromes, where localized language and cognitive dysfunction evolves into generalized dementia affecting multiple functional domains and leading to care facility placement.

Recently, it has been described that decline in everyday function in LPA is initially limited to instrumental ADLs, in contrast to nfvPPA which shows more generalized decline across both basic and instrumental ADLs.[6] Similarly longitudinal functional changes may be more marked in nfvPPA than in svPPA, but the factors behind these are not well known.[7-10] While the relationship between behavioral symptoms and functional decline in LPA and nfvPPA has been compared, this relationship is yet to be understood in nfvPPA in comparison to svPPA, which is particularly intriguing in light of unremarkable behavioral changes in nfvPPA.

This study aimed to (1) characterize functional deficits in svPPA and nfvPPA; (2) examine longitudinal functional deficits in relation to cognitive and behavioral symptoms; (3) identify predictors of functional disability in svPPA and nfvPPA over a 12-month period.

METHODS

Participants

Twenty-nine participants (svPPA=18; nfvPPA=11) were consecutively recruited via convenience sampling from the FRONTIER Research Group in Sydney, and assessed either in the clinic, home or care facility on two separate occasions approximately one year apart (M=1.4y ± 0.6) between November-2007 and December-2011. A total of 114 functional and behavioral assessments were completed across the 29 participants over the study time period and included for the analyses. Participants were included at baseline if (1) they fulfilled current criteria for svPPA or nfvPPA;[1] (2) had a reliable proxy informant to report on everyday functioning and behavior (informants were judged reliable if they either lived with or regularly saw the patient, and if they were able to clearly articulate functional and behavioural information pertaining to the patient); (3) did not have any major physical impairment such as requiring mobility aids; (4) did not have major depressive symptoms as measured by the DASS-21 [11,12] and (5) had a longitudinal assessment within 18 months. People with a diagnosis of lvPPA were excluded from this study based on a combination of a neurological clinical assessment, neuropsychological data and in vivo β–amyloid imaging. Of note, in the nfvPPA group, 2/11 participants were later re-diagnosed with atypical Parkinsonian syndromes (Corticobasal Syndrome, CBS, or Progressive Supranuclear Palsy, PSP). Due to the already small participant numbers in this study, these participants were retained for the analyses. Finally, 7/11 from the nfvPPA subgroup, and 8/18 in the svPPA subgroup have died since this study was conducted.

A multidisciplinary consensus based on a neurological clinical assessment (JRH) and a comprehensive neuropsychological battery was used for the diagnosis. Estimated disease duration was calculated at time of diagnosis based on reported onset of symptoms by the informant.

Instruments

Functional assessment

The Disability Assessment for Dementia (DAD) was used to assess level of functioning in activities of daily living (ADLs).[13] The DAD is an informant-based measure evaluating 23 instrumental activities of daily living (IADLs) and 17 to basic self-care (BADLs) and has been extensively used in frontotemporal dementia (FTD) studies.[7,9,14] IADL domains include: “meal preparation”, “telephoning”, “going on an outing”, “finance and correspondence”, “medications”, and “leisure and housework”; BADL domains evaluate “hygiene”, “dressing”, “continence”, and “eating”. Questions that are not applicable are excluded to avoid activity bias (e.g. finances; cooking). Total DAD score is reported as a percentage of remaining ability, where lower scores represent greater impairment.

In order to further distinguish clinical differences between subgroups, total DAD, BADL and IADL sub-scores were included in the analysis. All caregivers were interviewed by experienced research occupational therapists (EM, COC or CK) at baseline and follow-up visits.

Behavioral assessment

The Cambridge Behavioral Inventory Revised (CBI-R) is a caregiver-based assessment that measures and discriminates behavior across ten domains.[15] For each of the 45 items, the caregiver is required to rate behavioral changes on a four-point scale (0=never,

1=a few times per month, 2=a few times per week, 3=daily, and 4=constantly), where higher scores indicate higher frequency of abnormal behaviors.

Given the FTD focus on this study, only four domains were included: 'memory and orientation', 'abnormal behaviour/disinhibition', 'stereotypic and motor behaviors' and 'apathy'.[16] Two people with svPPA did not have complete baseline and follow-up assessments.

Brief cognitive assessment

A brief screening tool sensitive to the early stages of dementia was used at baseline. The Addenbrooke's Cognitive Examination Revised (ACE-R) assesses five cognitive domains: 'attention and orientation', 'memory', 'verbal fluency', 'language', and 'visuospatial' abilities.[17] Total score is 100, where higher scores reflect greater cognitive ability. The 88/100 cut off yields 94% sensitivity and 89% specificity for diagnosing dementia, and the tool has been reported as useful in tracking PPA progression.[18]

Data analyses

Data were analyzed using the Statistical Package for Social Sciences 21.0 (SPSS). Participants were categorized according to length of symptoms at baseline. Two categories were created: 'early stage' referred to disease duration of less than five years; 'moderate stage' participants had five or more years of disease. The five-year cut-off was used in this sample for two reasons: firstly, all recruited svPPA patients [5], already had a disease duration longer than two years by the time they presented at the clinic for their baseline visit. Secondly, many patients from both the svPPA and nfvPPA subgroups were still managing a majority of their ADLs despite having at least 5 years of disease duration. Therefore a five-year cut-off was deemed more suitable to represent 'moderate stage' for this study. The

baseline analyses (functional deficits and behavioral changes) focused on the early stage (svPPA, n=11/18; nfvPPA, n=11/11). The longitudinal analyses and the linear regression analysis included all participants. Of note, all moderate stage participants belonged to the svPPA group.

Demographic data were analyzed using parametric independent samples *t* tests. Kolmokorov-Smirnov tests were used to determine normality of distribution of main variables of interest at baseline, and non-parametric measures were used to take into account the skewness of the data distribution in some of these variables. Mann-Whitney U tests were performed to analyze dementia subgroup differences within the 'early' stages in regards to functional deficits and behavioral change. At follow-up, all variables of interest were normally distributed. Repeated-measures ANOVA were used to investigate effect of diagnosis and time on total DAD, IADLs and BADLs scores. For these longitudinal analyses diagnostic sub-groups were analyzed as a whole (svPPA=18/18; nfvPPA=11/11) for more appropriate statistical inferences.

In order to investigate which baseline scores could predict annual rate of change in functional scores, a forced entry multiple regression using the Enter method was performed for both the svPPA and nfvPPA subgroups. A forward sequential regression approach was used to conserve power given the small sample size. Annual rate of change in function was calculated by subtracting the follow-up total DAD score from the baseline total DAD score for each participant. The annual rate of change was used as the dependent variable, with five baseline scores used as independent variables. The choice of these variables was largely based on the differences between diagnostic groups at baseline: ACE-R, CBI-R memory score; CBI-R stereotypical behavior score; CBI-R apathy score; DAD total score. A series of regressions were run using differing block variations of entering variables to estimate the best model for predicting the annual rate of change.

RESULTS

Demographics

There were no differences observed between svPPA and nfvPPA for age or total years of education at baseline (all *p's*>.05; Table 1). Length of symptoms was significantly longer for svPPA ($p<.0001$), whereas ACE-R scores were higher for nfvPPA ($p<.05$). Notably, 3/18 (16.7%) of svPPA patients had predominantly right-sided temporal atrophy, and 2/11 (18.2%) of nfvPPA patients had apraxia of speech.

(Insert Table 1 about here)

Functional status at baseline assessments (first visit to research institute)

In the svPPA sub-group, 11/18 participants were in the 'early stage', as defined by up to 5 years of disease duration, whereas all participants with a diagnosis of nfvPPA were included in the 'early stage' category due to their shorter length of history (Table 1).

Overall ADL function was similar between svPPA and nfvPPA, as shown by the DAD total score (Figure 1, Panel A). When these scores were broken down into more complex instrumental (Figure 1, Panel B) and basic ADLs (Figure 1, Panel C), the similarity between groups remained. Interestingly, the outlier participant (very low functional scores) from the nfvPPA group in each of these figures went on to later develop an atypical Parkinsonian syndrome (CBS) (Figure 1).

(Insert figure 1 about here)

Behavioral changes at baseline

In parallel to functional disability, we also explored behavioral differences between the two PPA groups according to the duration of their symptoms since disease onset, in order to understand their potential contribution to ADL dysfunction. Early in the disease ('early stage'), svPPA scored significantly higher in memory impairment than nfvPPA (U=15, z=-2.829, p<.005). Higher levels of stereotypical behavior (U=26.5, z=-2.035, p<.05), and apathy (U=20.5, z=-2.439, p<.05) were also found in svPPA. The differences between both groups was substantial across these two domains, with 60% of patients from the svPPA group showing marked deficits, compared with only 9% of patients from the nfvPPA group. Lastly, there were no significant differences for disinhibition scores between the PPA groups, with both groups demonstrating mild-moderate degree of changes. Interestingly, patients with nfvPPA who went on to develop an atypical Parkinsonian syndrome (CBS or PSP) tended to demonstrate higher scores on behavioral dysfunction at baseline (Figure 2).

(Insert figure 2 about here)

Longitudinal functional decline

On average, follow-up assessments were conducted one year apart (M=1.4y ± 0.6). Repeated-measures ANOVA revealed an effect of time for total DAD score, IADL and BADL scores for both svPPA and nfvPPA. Critically, there were no interactions between time and diagnoses on any of these three analyses, confirming that both diagnostic groups showed similar decline on these three scores at the follow-up visit (Figure 3, Panels A, B, C).

(Insert figure 3 about here)

What factors can predict functional scores at follow-up?

For svPPA, a model trend emerged from the multiple regression for annual rate of change in functional (DAD) scores ($F_{(13)}$=3.71, p=.05) consisting of (i) total DAD score at baseline, and (ii) ACE-R score at baseline. This model explained 36.4% of the variance of the annual rate of change in functional scores (p<.05) (Table 2), with most of the variance (35.5%) explained by the ACE-R score at baseline.

Other models in this regression, containing forward sequentially added scores for apathy, stereotypical behavior and memory deficits in separate blocks were not significant.

(Insert Table 2 about here)

For nfvPPA, a significant model to predict annual rate of change in functional scores emerged from the multiple regression consisting of (i) CBI apathy and CBI stereotypical behavior, and (ii) total DAD score at baseline. This model explained 67.8% of the variance of the annual rate of change in DAD scores (p<.01) (Table 3). In this model, apathy and stereotypical behaviors made a very small but significant contribution (2.3% variance), whereas 65.5% of the variance was explained by the functional score at baseline (Table 3). ANOVA confirmed the statistical significance of this model ($F_{(7)}$=4.91, p<.05). The sequential addition of global cognitive scores or memory deficits did not change the model.

Of note, everyday memory deficits did not factor as a significant predictor of annual rate of change in ADL for either svPPA or nfvPPA patients in any of the regression analyses.

(Insert Table 3 about here)

DISCUSSION

This study demonstrated that decline (over a 12-month period) in ADL function can be largely predicted by cognitive scores in svPPA, and a combination of behavioral and functional scores in nfvPPA. It also confirmed that both PPA subgroups maintain a mild degree of functional impairment in the initial 5 years of the disease, but present distinct profiles of behavioral changes. Patients with svPPA show marked stereotypical behavior and apathy, but these do not seem to strongly predict functional decline.

Baseline global cognitive score was found to be the strongest predictor of functional decline at follow-up for svPPA patients. Predictors of functional decline in nfvPPA, however, comprised a different model: a combination of baseline functional level, apathy and stereotypical behavior. It is interesting that baseline total ADL score was a predictive factor of functional decline in nfvPPA but not in svPPA patients. Possible reasons include differences in disease stage at baseline between the two groups, or the well described slower rate of disease progression in svPPA.[8,19] In fact different patterns of ADL decline have been described between nfvPPA and svPPA patient groups with matched disease duration.[7] Regardless of the reasons for the different predictors of functional decline for these groups, these dissimilar factors should be taken into account when planning intervention strategies. For instance, given baseline functional performance predicts functional decline in nfvPPA, addressing any functional limitations should be a focus of treatment when patients present at the clinic. For example, if a nfvPPA patient presents with impairments in initiating and planning their basic ADLs, a supportive intervention may include setting up the requirements for an activity and assisting the person to sequence through the steps of the activity with verbal prompting.

Our finding that a combination of behavioral and functional scores are the best predictors for functional decline in the nfvPPA group diverges from the Alzheimer's literature, where reports have identified cognitive and behavioral factors as the key predictors

of ADL decline.[20,21] A possible reason for this divergence is the use of different assessments in comparison to current published studies. Additionally, the discrepancy in factors predicting ADL decline in AD and FTD variants might be a reflection of dissimilar pathologies as well as differences in affected neuroanatomical areas. Indeed, our group of nfvPPA patients included 2/11 with apraxia of speech. It is possible that the inclusion of different forms of nfvPPA may have impacted on the results. Future studies should include a larger sample of nfvPPA patients to allow subtype analysis.

The identification of variables that do not contribute to functional decline is also critical in understanding changes over time. Behavioral changes are often evident at presentation in patients with svPPA, resembling behavioral variant FTD, but these behavioral changes do not seem to be relevant in predicting functional decline in svPPA. While marked behavioral changes are present in svPPA, they seem to somehow allow for continued participation in activities, albeit in a very rigid manner, instead of hindering their performance.[22-24] While there was a trend for global cognition to contribute to around a third of the variance in functional decline, the remaining factors which contribute to functional decline in svPPA remain unclear. The lack of behavioral factors contributing to ADL decline in the present study is, however, in contrast with a recent longitudinal study, which reported that increasing levels of apathy were correlated with declining ADL function in svPPA.[24] This is likely to be explained by the differences in methodological approach, i.e., cross sectional and longitudinal. Another important consideration is the inclusion of 3/18 patients who had predominantly right-sided temporal lobe atrophy. For patients in the earlier stages of disease this may have impacted on their clinical presentation, with right-sided patients exhibiting worse behavioural symptoms than patients with predominantly left-sided temporal lobe atrophy. With progression however, the clinical profile of these subtypes becomes similar as left-sided svPPA also exhibit behavioural symptoms.[25,26]

Paradoxically, semantic deficits appear not to be a main contributing factor to functional decline, given that they appear very early in the disease and at a time when ADL function is very well preserved. The investigation of other factors affecting function in svPPA deserves future studies.

The differences in behavioral changes in svPPA and nfvPPA are noteworthy and raise two critical points.[27-32] Firstly, people with svPPA have marked behavioral dysfunction, which at present, is overshadowed by the emphasis on the semantic deficits that characterize the syndrome. These marked behavioral changes are not part of the current diagnostic criteria but in many instances are of greater concern and distress to families than the well-reported semantic deficits.[33] Secondly, people with nfvPPA also demonstrate mild-moderate degrees of behavioral changes, such as apathy, which are equally underreported.[30,34] A proportion of the nfvPPA group with behavioral changes in the present study later developed an atypical Parkinsonian syndrome (CBS or PSP) as a secondary condition.[35-37] Although less severe than in svPPA, the behavioral changes observed in nfvPPA should be closely monitored for better disease management and prognosis. Interestingly, a recent paper reported no differences in levels of apathy between svPPA and nfvPPA groups.[38] This is likely to be explained by the use of different assessment tools; the CBI-R has been shown to be highly sensitive to behavioral changes in the FTD spectrum.[39]

The present study also confirmed that functional abilities remain virtually intact for most PPA patients up to 5 years from disease onset, while behavioral changes are present from an early stage, most notably in svPPA. These findings reinforce the notion that assessment and monitoring of deficits in PPA should include a combination of tools measuring functional, behavioral, and cognitive deficits for a global and accurate characterization of impairments in PPA and care management.[40,41]

The nfvPPA group had circumscribed length of symptoms, which impeded a comparative analysis between both PPA groups in the later stages of the disease (those with longer history of symptoms). It is possible that the results of this study may have been different if the nfvPPA group had a 5-year disease duration similar to the svPPA group. In fact, a study comparing the rate of functional decline between FTD variants found that nfvPPA patients who had an average disease duration of 5 years declined faster than a svPPA group with a similar disease duration.[7] Future studies should investigate predictors of functional decline in PPA subgroups with matched disease durations. Nonetheless, this shorter disease duration is of clinical relevance in itself, and a number of reasons could explain this difference in PPA group composition. The most plausible reason is that nfvPPA leads to a more aggressive disease progression,[8] and are not referred to research centers later in the disease course. This pattern of shorter time from disease onset to presentation for assessment in nfvPPA has been previously reported.[35,42] Further, it is possible that in the earlier stages of disease the non-fluent language impairments are more obviously disruptive than the anomia seen in svPPA, so patients with nfvPPA are brought in for diagnosis sooner. Alternatively, by the time people with nfvPPA have a longer disease history (beyond 5 years), they might have developed additional symptoms that lead to a revised diagnosis of atypical Parkinsonian syndrome (CBS or PSP).[43] Indeed, this occurred in a proportion (18%) of nfvPPA patients in this study.

Some limitations in this study include the relatively small sample size,[44] which was related to the need to restrict to participants who had complete data at the follow-up visits. Still, this sample size is in line with other published longitudinal studies in PPA. Another potential limitation is the use of proxy reporting measures to assess ADL function and behavioral symptoms, which may increase the likelihood of response bias in the data.[45,46] Assessment by proxy, however, is the most common approach used in dementia studies.

In summary, this study demonstrated that functional profiles in svPPA and nfvPPA are rather similar in people with up to 5 years of disease duration. Behavioral changes are very marked in svPPA but do not predict annual rate of change in disability; instead, global cognitive scores at baseline do. Despite the less marked nature of behavioral changes in nfvPPA, they make a significant contribution to functional disability, with functional scores at baseline making the strongest contribution to functional decline in nfvPPA. The dissimilar factors behind functional decline in PPA should be taken into account when considering prognosis, referring to specialist community services and in designing well-targeted interventions.

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REFERENCES

1. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF and others. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006-1014.
2. Leyton CE, Villemagne VL, Savage S, Pike KE, Ballard KJ, Piguet O, Burrell JR, Rowe CC, Hodges JR. Subtypes of progressive aphasia: Application of the international concensus criteria and validation using B-amyloid imaging. Brain 2011;134:3030-3043.
3. Mesulam M, Wicklund A, Johnson N, Rogalski E, Leger GC, Rademaker A, Weintraub S, Bigio EH. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. Ann Neurol 2008;63:709-719.
4. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-186.
5. Mesulam MM. Primary progressive aphasia. Ann Neurol 2001;49:425-432.
6. Jang J, Cushing N, Clemson L, Hodges JR, Mioshi E. Activities of daily living in progressive non-fluent aphasia, logopenic progressive aphasia and Alzheimer's disease. Dement Geriatr Cog Disord 2012;33:354-360.
7. Mioshi E, Hodges JR. Rate of change of functional abilities in frontotemporal dementia. Dement Geriatr Cog Disord 2009;28:419-426.
8. Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR. Clinical staging and disease progression in frontotemporal dementia. Neurology 2010;74:1591-1597.
9. Mioshi E, Kipps CM, Dawson K, Mitchell J, Graham A, Hodges JR. Activities of daily living in frontotemporal dementia and Alzheimer disease. Neurology 2007;68:2077-2084.
10. Wicklund AH, Johnson N, Rademaker A, Weitner BB, Weintraub S. Profiles of decline in activities of daily living in non-Alzheimer dementia. Alzheimer Dis Assoc Disord 2007;21:8-13.
11. Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav Res Ther 1995;33:335-343.
12. Ng F, Trauer T, Dodd S, Callaly T, Campbell S, Berk M. The validity of the 21-item version of the Depression Anxiety Stress Scales as a routine clinical outcome measure. Acta Neuropsychiatr 2007;19:304-310.

13. Gelinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: The Disability Assessment for Dementia. Am J Occup Ther 1999;53:471-481.
14. Mioshi E, Hodges JR, Hornberger M. Neural correlates of activities of daily living in frontotemporal dementia. J Geriatr Psychiatry and Neurol 2013;26:51-57.
15. Wear HJ, Wedderburn CJ, Mioshi E, Williams-Gray CH, Mason SL, Barker RA, Hodges JR. The Cambridge Behavioural Inventory revised. Dement Neuropsychol 2008;2:102-107.
16. Rascovsky K, Hodges JR, Knopman D, mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EGP, Onyike CU and others. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456-2477.
17. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): A brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry 2006;21:1078-1085.
18. Leyton CE, Hornberger M, Mioshi E, Hodges JR. Application of the Addenbrook's Cognitive Examination to diagnosis and monitoring of progressive primary aphasia. Dement Geriatr Cog Disord 2010;29:504-509.
19. Hodges JR, Patterson K. Semantic dementia: A unique clinicopathological syndrome. Lancet Neurol 2007;6:1004-1014.
20. Mortimer JA, Ebbitt B, Jun SP, Finch MD. Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. Neurology 1992;42:1689-1696.
21. Zahodne LB, Manly JJ, MacKay-Brandt A, Stern Y. Cognitive declines precede and predict functional declines in aging and Alzheimer's disease. PloS One 2013;8:e73645.
22. O'Connor CM, Ahmed S, Mioshi E. Functional disability in primary progressive aphasia. Aphasiology 2014;28:1131-1149.
23. O'Connor CM, Clemson L, Brodaty H, Gitlin LN, Piguet O, Mioshi E. Enhancing caregivers' understanding of dementia and tailoring activities in frontotemporal dementia: Two case studies. Disabil Rehabil 2016;38:704-714.
24. O'Connor CM, Clemson L, Hornberger M, Leyton CE, Hodges JR, Piguet O, Mioshi E. Longitudinal change in everyday function and behavioral symptoms in frontotemporal dementia. Neurol Clin Pract 2016.

25. Kumfor F, Landin-Romero R, Devenney E, Hutchings R, Grasso R, Hodges JR, Piguet O. On the right side? A longitudinal study of left- versus right-lateralized semantic dementia. Brain 2016; 139:986-998.
26. Kashibayashi T, Ikeda M, Komori K, Shinagawa S, Shimizu H, Toyota Y, Mori T, Ishikawa T, Fukuhara R, Ueno S and others. Transition of distinctive symptoms of semantic dementia during longitudinal clinical observation. Demen Geriatr Cog Disord 2010;29:224-232.
27. Bozeat S, Gregory CA, Ralph MAL, Hodges JR. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? J Neurol Neurosurg Psychiatry 2000;69:178-186.
28. Cathery-Goulart MT, Knibb JA, Patterson K, Hodges JR. Semantic dementia versus nonfluent progressive aphasia: Neuropsychological characterization and differentiation. Alzheimer Dis Assoc Disord 2012;26:36-43.
29. Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. Brain 1992;115:1783-1806.
30. Marra C, Quaranta D, Zinno M, Misciagna S, Bizzarro A, Masullo C, Daniele A, Gainotti G. Clusters of cognitive and behavioural disorders clearly distinguish primary progressive aphasia from frontal lobe dementia, and Alzhiemer's disease. Dement and Geriatr Cogn Disord 2007;24:317-326.
31. Nyatsanza S, Shetty T, Gregory C, Lough S, Dawson K, Hodges JR. A study of stereotypic behaviours in Alzheimer's disease and frontal and temporal variant frontotemporal dementia. J Neurol Neurosurg Psychiatry 2003;74:1398-1402.
32. Rosen HJ, Allison SC, Ogar JM, Amici S, Rose K, Dronkers N, Miller BL, Gorno-Tempini ML. Behavioural features in semantic dementia vs other forms of progressive aphasias. Neurology 2006;67:1752-1756.
33. Hsieh S, Leyton C, Caga J, Flanagan E, Kaizik C, O'Connor CM, Kiernan MC, Hodges JR, Piguet O, Mioshi E. The evolution of caregiver burden in frontotemporal dementia with and without amyotrophic lateral sclerosis. J Alzheimers Dis 2015;49:875-885.
34. Rohrer JD, Ridgway GR, Crutch SJ, Hailstone J, Goll JC, Clarkson MJ, Mead S, Beck J, Mummery C, Ourselin S and others. Progressive logopenic/phonological aphasia: Erosion of the language network. Neuroimage 2010;49:984-993.
35. Kertesz A, Blair M, McMonagle P, Munoz DG. The diagnosis and course of frontotemporal dementia. Alzheimer Dis Assoc Disord 2007;21:155-163.

36. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain 2005;128(9):1996-2005.
37. Kertesz A, Davidson W, Munoz DG. Clinical and pathological overlap between frontotemporal dementia, primary progressive aphasia and corticobasal degeneration: the Pick complex. Dement Geriatr Cogn Disord 1999;10:46-49.
38. Singh TD, Duffy JR, Strand EA, Machulda MM, Whitwell JL, Josephs KA. Neuropsychiatric symptoms in primary progressive aphasia and apraxia of speech. Dement Geriat Cogn Disord 2015;39:228-238.
39. Lillo P, Mioshi E, Zoing MC, Kiernan MC, Hodges JR. How common are behavioural changes in amyolateral sclerosis? Amyotroph Lateral Scler 2011;12:45-51.
40. Desai AK, Grossberg GT, Sheth DN. Activities of daily living in patients with dementia: clinical relevance, methods of assessment and effects of treatment. CNS Drugs 2004;18:853-875.
41. Mohs RC, Schmeidler J, Aryan M. Longitudinal studies of cognitive, functional and behavioural change in patients with Alzheimer's disease. Stat Med 2000;19:1401-1409.
42. Hsieh S, Hodges JR, Leyton CE, Mioshi E. Longitudinal changes in primary progressive aphasias: Differences in cognitive and dementia staging measures. Dement Geriatr Cogn Disord 2012;34:135-141.
43. Kertesz A, Martinez-Lage P, Davidson W, Munoz DG. The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. Neurology 2000;55:1368-1375.
44. Schneider A, Hommel G, Blettner M. Linear regression analysis—part 14 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2010;107:776-782.
45. Wagmiller RL. A fixed effects approach to assessing bias in proxy reports. Int J Public Opin Res 2009;21:477-505.
46. Jonas C, Schiffczyk C, Lahmeyer C, Mueller F, Riepe MW. Staging dementia using proxy-reported activities of daily living. Dement Geriatr Cogn Disord 2011;32:111-117.

Table 1. Comparison of age, gender, education, disease duration and ACE-R scores across nfvPPA and svPPA participants at baseline. Means; standard deviation (SD) in parentheses.

	svPPA (n = 18)	nfvPPA (n = 11)	*p* values
Age years	65.3 (8.4)	66.6 (11.4)	.726ǂ
Gender (M/F)	12/6	9/2	.376†
Education years	12.1 (3.6)	13.3 (4.3)	.426ǂ
Disease duration	5.1 (2.2)	2.6 (1)	< 0.001ǂ
Baseline ACE-R score	56.8 (15.6)	71.7 (16.9)	< 0.05ǂ

Abbreviations: svPPA=semantic variant primary progressive aphasia; nfvPPA=non-fluent variant primary progressive aphasia; ACE-R=Addenbrooke's Cognitive Examination-Revised; ǂ*t* tests; †Chi square test

Table 2. Multiple regression model of annual rate of change in total DAD in people with svPPA (n=16)

Independent Variable	Unstandardized Beta coefficient	Std. Error	*t*	Sig.	R^2	F change in R^2
(Constant)	-33.013	19.962	-1.654	.122	N/A	N/A
DAD Total	-.366	.241	-1.523	.152	.009	.120
ACER	.839	.312	2.693	.018	.364	7.251*

*p<.05

DAD = Disability Assessment for Dementia; ACER = Addenbrooke's Cognitive Examination Revised

Table 3. Multiple regression model of annual rate of change in total DAD for people with nfvPPA (n=11)

Independent Variable	Unstandardized Beta coefficient	Std. Error	*t*	Sig.	R^2	F change in R^2
(Constant)	-127.280	29.313	-4.342	.003	N/A	N/A
CBI Apathy	.738	.268	2.752	.028	.023	.095
CBI Stereotypical	-.706	.250	-2.823	.026		
DAD Total	1.206	.320	3.770	.007	.678	14.215*

* $p<.01$

DAD = Disability Assessment for Dementia; CBI = Cambridge Behavioral Inventory

FIGURE LEGENDS

Figure 1:

Title: Comparison of baseline DAD functional scores across svPPA and nfvPPA

Legend: Baseline comparisons of functional disability across 'early stage' svPPA (11/18) and nfvPPA (11/11) participants using Mann-Whitney U tests. (A) baseline total DAD scores; (B) baseline IADL scores; (C) baseline BADL scores. SvPPA=semantic variant primary progressive aphasia; nfvPPA=non-fluent variant primary progressive aphasia; DAD=Disability Assessment for Dementia; BADL=basic activities of daily living; IADL=instrumental activities of daily living. Circled points represent a patient who later went on to develop an atypical Parkinsonian syndrome (CBS or PSP).

Figure 2:

Title: Comparison of baseline CBI behavioral scores across svPPA and nfvPPA

Legend: Baseline comparisons of behavioral changes across 'early stage' svPPA (11/18) and nfvPPA (11/11) participants using Mann-Whitney U tests. Scores of 50% or higher were considered to represent 'marked behavioral changes'. SvPPA=semantic variant primary progressive aphasia; nfvPPA=non-fluent variant primary progressive aphasia; CBI=Cambridge Behavioral Inventory-Revised. Circled points represent a patient who later went on to develop an atypical Parkinsonian syndrome (CBS or PSP).

Figure 3:

Title: Comparison of longitudinal DAD functional scores across svPPA and nfvPPA

Legend: Longitudinal comparisons (A, B, C) across both diagnostic subgroups as a whole (svPPA=18/18; nfvPPA=11/11) using repeated-measures ANOVA. (A) longitudinal change in total DAD scores; (B) longitudinal change in IADL scores (C) longitudinal change in BADL scores. SvPPA=semantic variant primary progressive aphasia; nfvPPA=non-fluent variant primary progressive aphasia; DAD=Disability Assessment for Dementia; BADL=basic activities of daily living; IADL=instrumental activities of daily living.