Neuropsychological differentiation of progressive aphasic disorders

Jennifer M. Harris[1,2]*, Jennifer A. Saxon[1,2], Matthew Jones[1,2], Julie S. Snowden[1,2] and Jennifer C. Thompson[1,2]

[1]Manchester Academic Health Sciences Centre, Cerebral Function Unit, Greater Manchester Neuroscience Centre, Salford Royal NHS Foundation Trust, UK
[2]Division of Neurosciences and Experimental Psychology, Faculty of Biology, Medicine and Health, University of Manchester, UK

The differentiation of subtypes of primary progressive aphasia (PPA) remains challenging. We aimed to identify optimum neuropsychological measures for characterizing PPA, to examine the relationship between behavioural change and subtypes of PPA and to determine whether characteristic profiles of language, working memory, and behavioural changes occur in PPA. Forty-seven patients with PPA and multi-domain Alzheimer's disease (AD) together with 19 age-matched controls underwent a large battery of working memory and language tests. We found that simple tasks of sentence ordering, narrative production, and buccofacial praxis were particularly useful in differentiating non-fluent/agrammatic variant PPA (nfvPPA) from other PPA subtypes, whereas a test of single word comprehension was useful in detecting semantic dementia (SD). No individual tests were discriminating for logopenic variant PPA (lvPPA) relative to nfvPPA. LvPPA and multidomain AD exhibited similar language profiles. A principal components analysis revealed that characteristic PPA profiles extended beyond the realms of language, in particular, the presence of apraxia in nfvPPA, behavioural changes in SD, and working memory deficits in lvPPA. These findings suggest that not all tests are equally discriminatory for PPA and highlight the importance of a test profile in differentiating PPA. These results also support the view that lvPPA is a focal form of AD and emphasize the difficulties classifying lvPPA.

Current diagnostic recommendations for primary progressive aphasia (PPA) include three main subtypes: non-fluent/agrammatic (nfvPPA), characterized by agrammatism and/or apraxia of speech (AOS); logopenic (lvPPA), characterized by impaired repetition and word finding difficulties; and semantic (svPPA), characterized by anomia, impaired word comprehension, and impaired object recognition (Gorno-Tempini *et al.*, 2011). The terms nfvPPA and svPPA are commonly used interchangeably with the earlier designations progressive non-fluent aphasia (PNFA) and semantic dementia (SD; Neary *et al.*, 1998), although they are not precisely equivalent. In particular, the term SD acknowledges the multimodal nature of patients' semantic loss and the fact that the earliest presenting symptom may be in the visual rather than verbal domain. The three PPA

*Correspondence should be addressed to Jennifer M. Harris, Cerebral Function Unit, Greater Manchester Neuroscience Centre, Salford Royal Foundation Trust, Salford M6 8HD, UK (email: jenny.harris@manchester.ac.uk).

subtypes are associated with different distributions of atrophy: nfvPPA with left posterior fronto-insular atrophy, lvPPA with left posterior perisylvian or parietal atrophy, and svPPA with anterior temporal lobe atrophy (Gorno-Tempini *et al.*, 2011). Most patients with nfvPPA and svPPA/SD have frontotemporal lobar degeneration (FTLD) spectrum pathologies and most lvPPA patients have Alzheimer's disease (AD) pathology, although this is not invariably the case (see Harris & Jones, 2014 for a review).

Neuropsychological studies suggest that current classifications do not encapsulate the full range of PPA syndromes observed, and patients may fulfil the criteria for more than one PPA variant (Botha *et al.*, 2015; Harris *et al.*, 2013). Furthermore, while each PPA subtype is associated with characteristic deficits, a degree of overlap exists between the subtypes. Indeed, the core features of lvPPA also occur frequently in nfvPPA (Sajjadi, Patterson, Arnold, Watson, & Nestor, 2012; Wicklund *et al.*, 2014). These findings suggest that the characterization of PPA requires further refinement.

A potential source of variability in findings may lie in the choice of tests employed by clinicians and researchers. Thus, for example, in current classifications (Gorno-Tempini *et al.*, 2011) agrammatism is identified through tasks involving sentence production, yet different tasks may not have equal sensitivity or specificity. Indeed a recent review suggests that evaluation of agrammatism should include the assessment of comprehension and production of grammatical morphology, functional categories, verbs, and complex syntactic structures (Thompson & Mack, 2014). It would be important to determine optimum measures for detecting characteristic language deficits prospectively in a cohort of PPA patients.

Refinement of diagnosis may depend not only on identification of optimal language measures but also on the recognition of associated deficits. One such area worthy of consideration is praxis. AOS is a core feature of nfvPPA (Gorno-Tempini *et al.*, 2011), yet deficits may extend beyond the realm of speech to orofacial and/or limb apraxia (Joshi, Roy, Black, & Barbour, 2003; Rohrer, Rossor, & Warren, 2010; Tyrrell, Kartsounis, Frackowiak, Findley, & Rossor, 1991). Gestural apraxia might occur secondary to a central disorder of communication (Duffy & Duffy, 1981; Glosser, Wiener, & Kaplan, 1986). Apraxia might be predicted to be a more integral component of nfvPPA than of other forms of PPA.

Another domain of potential diagnostic importance is working memory. Phonological working memory has been suggested to play a pivotal role in the logopenic syndrome (Gorno-Tempini *et al.*, 2008; Meyer, Snider, Campbell, & Friedman, 2015), leading to patients' difficulty in sentence repetition. Yet, the degree to which standard tests of working memory are able to differentiate lvPPA from nfvPPA is unclear. NfvPPA patients might be expected to perform poorly on verbal working memory tasks because of their marked speech production problems, and indeed there is compelling evidence of phonological processing impairments in nfvPPA to suggest problems in verbal/phonological working memory (Libon *et al.*, 2007; Nestor *et al.*, 2003). On the other hand, they might reasonably do well on working memory tasks that do not make phonological demands. The examination of performance on a variety of verbal and visual working memory tasks would help to identify optimal measures to aid differentiation.

In addition to the associated cognitive deficits, accompanying behavioural changes might be of diagnostic relevance. NfvPPA and svPPA/SD are pathologically linked to behavioural variant frontotemporal dementia (bvFTD) which is the commonest clinical disorder associated with FTLD spectrum pathology and is characterized by changes in behaviour and personality. Language and behavioural symptoms can co-occur in disorders caused by FTLD pathology (Harris *et al.*, 2016). Patients with SD have been reported to

exhibit behavioural change, particularly stereotyped and repetitive behaviours (Rosen *et al.*, 2006; Snowden *et al.*, 2001), and behavioural change can also occur in nfvPPA (Rohrer & Warren, 2010). Increased apathy, anxiety, agitation, and depression have been described in lvPPA (Rohrer & Warren, 2010; Rosen *et al.*, 2006). However, since lvPPA is typically not associated with FTLD but rather with AD pathology, these patients might be expected to have differing behavioural change when compared to patients with nfvPPA and svPPA/SD. The presence of certain behavioural characteristics might therefore aid differentiation of PPA subtypes and warrants further investigation.

The link between lvPPA and AD pathology raises the question whether the language characteristics of lvPPA mirror those seen in early-onset AD, in which language problems typically constitute one component of a multi-domain disorder that includes also deficits in episodic memory, working memory, visual perception, and spatial function, (Smits *et al.*, 2012; Snowden *et al.*, 2007). Reports have thus far been mixed with some authors describing logopenic-type symptoms in non-focal AD patients (Harris *et al.*, 2015) and other authors describing a differing language profile in patients with AD (Ahmed, de Jager, Haigh, & Garrard, 2012).

In AD, long-term and working memory may breakdown separately (Stopford, Snowden, Thompson, & Neary, 2007). Working memory has been associated with language functioning (Caza & Belleville, 2008; Stopford, Snowden, Thompson, & Neary, 2008; Stopford *et al.*, 2007) but spatial span may also be impaired (Grossi, Becker, Smith, & Trojano, 1993; Trojano, Chiacchio, De Luca, & Grossi, 1994). A comparative study of lvPPA and AD showed poorer performance on tests of verbal working memory in lvPPA but similar performance in the two groups on tests of visuospatial working memory (Foxe, Irish, Hodges, & Piguet, 2013; Meyer *et al.*, 2015). Whether this finding generalizes to other lvPPA and AD cohorts, and whether working memory profile distinguishes lvPPA from nfvPPA remains to be established.

This study had several aims. First, we aimed to identify optimum language measures for differentiating SD, nfvPPA, and lvPPA, focussing on tests of naming, single word comprehension, sentence processing, narrative production, reading, spelling, and repetition that tap core features of PPA conditions. Second, we examined the potential diagnostic contribution of non-language measures, specifically in the domains of praxis, working memory, and behaviour. We included as a comparison group, patients with multidomain AD. We expected greater commonalities in language and non-language performance with lvPPA than other forms of PPA, but it was an open question whether distinct characteristics would be identified between lvPPA and AD. Third, we aimed to determine, through principal component analysis of performance measures, the degree to which core factors can be identified that have predictive value in distinguishing forms of PPA and to delineate optimal combinations of discriminating features.

Methods

Participants

Participants comprised 47 consecutive patients with a clinical diagnosis of nfvPPA (12), lvPPA (13), SD (8), and multi-domain AD (14) who attended a specialist early-onset dementia clinic and agreed to take part in the study. These participants included new referrals and follow-up patients. Most patients were seen within a year of first presenting to the clinic (mean 1.15 years, standard deviation 1.05 years). Participants with a history of alcohol abuse or head injury were excluded. Patients were diagnosed by experienced

neurologists based on detailed clinical history, neuroimaging results, and neurological examination, using guidelines published by Snowden *et al.* (2011), which have been shown, in clinico-pathological correlation studies, to yield high levels of diagnostic accuracy. Patients with nfvPPA and lvPPA met contemporary criteria (Gorno-Tempini *et al.*, 2011). All SD patients showed the language characteristics of svPPA (Gorno-Tempini *et al.*, 2011). However, as three patients showed early face and object recognition problems, in addition to their language disorder, and had greater right than left temporal lobe atrophy, the term SD (Neary *et al.*, 1998) is used to designate the group. Diagnoses were supported by neuropsychological examination using the Manchester Neuropsychological Profile (Snowden *et al.*, 2007, 2011; Thompson, Stopford, Snowden, & Neary, 2005). Nineteen age-matched controls were also recruited.

Demographic data are shown in Table 1. There was a significant association between gender and group (Fisher's $p = .026$). The lvPPA group included a higher proportion of males than the control group (Fisher's $p = .012$) and the AD group (Fisher's $p = .006$). There was a significant group difference in age, $F(4,61) = 7.357$, $p < .001$. The AD group was significantly younger than the other groups (vs. nfvPPA $p < .001$, vs. lvPPA $p < .001$, vs. SD $p = .011$, and vs. controls $p = .011$). The youthful age of the AD patients, in part, reflects a referral bias of younger patients to the neurology clinic but also an inherent bias towards early onset in AD presenting with multi-domain impairment.

All participants provided written informed consent to take part in the study. The study was approved by North West NRES committee (REC Refs: 12/NW/0883).

Neuropsychology

Participants underwent a neuropsychological test battery with a particular focus on language and working memory. For performance measures, see Table A1 in Appendix S1.

Language assessment included tests of naming, single word comprehension, sentence processing, narrative production, reading, and spelling.

Naming

- Object and action naming (Druks & Masterson, 2000).
- Manchester picture naming. This test involves naming forty line drawings from the Snodgrass and Vanderwart pictures (Snodgrass & Vanderwart, 1980).

Table 1. Demographics

Patient group	Gender (M:F)	Age at onset (years); mean (SD)	Age at testing (years); mean (SD)	Duration at testing	Family history of a similar condition in a first-degree relative; N (%)
NfvPPA (12)	7:5	66.71 (7.99)	70.67 (7.23)	4.00 (2.04)	3/11 (27.3)
LvPPA (13)	11:2	66.56 (6.95)	70.35 (6.39)	3.82 (2.20)	3/13 (23.1)
SD (8)	5:3	63.24 (3.77)	66.83 (2.88)	3.64 (1.16)	4/8 (50.0)
Multi-domain AD (14)	4:10	57.16 (5.84)	60.15 (5.75)	3.03 (1.44)	3/14 (21.4)
Controls (19)	7:12	n/a	65.51 (5.20)	n/a	n/a

Note. AD, Alzheimer's disease; F, female; LvPPA, logopenic variant primary progressive aphasias; M, male; nfvPPA, non-fluent variant primary progressive aphasia, SD, semantic dementia.

Single word comprehension

Manchester comprehension.   This involves matching a printed word with one of four pictures (the same 40 target items are used as in the Manchester naming test).

Sentence processing tasks

Modified PALPA 55 subtest Auditory sentence comprehension test (Kay, Lesser, & Coltheart, 1992) and PALPA subtest 58 Auditory comprehension of locative relations (Kay *et al.*, 1992).

Manchester sentence ordering.   A locally constructed task, which requires participants to order five individually printed words to make a sentence.

Manchester tense production.   In this locally constructed task, participants are shown action pictures (e.g., a boy kicking a ball) accompanied by the written word 'yesterday' or 'tomorrow'. Participants are asked to generate a descriptive sentence beginning with the word provided (e.g., Yesterday, the boy kicked the ball).

Measures of narrative production

Cookie theft picture.   Participants were recorded describing the picture (Goodglass & Kaplan, 1983). The number of phonetic errors, phonemic errors, fluency disruptions, length of utterance, number of dependent clauses per utterance, and percentage of well-formed sentences were calculated. More details are provided online (Table A1 in Appendix S1).

Reading tests
- Manchester reading. This test involves reading aloud the printed words used in the Manchester word-picture matching test.
- Modified PALPA subtest 36 Non-word reading.
- Modified PALPA test 31 Imageability/frequency reading.
- Spelling/sound regularity reading (Glushko, 1979).

Spelling

Written spelling.   Participants are requested to write 20 dictated words, drawn from the Manchester naming test.

   Other tests evaluated working memory, praxis, calculation, and behaviour.

Working memory

The tasks addressed both verbal (phonological) and visuospatial working memory. Verbal tasks encompassed those with written as well as spoken presentation and tasks requiring pointing as well as spoken responses.

- Verbal (phonological) tasks

  Digits: Forwards and reverse Digit span (Wechsler, 1981).

  Single words: Manchester word repetition. This test involves repetition of items from the Manchester naming/reading/comprehension tests.

  Word Sequences: Manchester immediate and delayed word repetition. This is a locally constructed test, which involves repeating one or two words with variable delays of zero and five seconds.

  Sentences: PALPA test 12 Sentence repetition (modified/shortened; Kay *et al.*, 1992). PALPA test 60 Pointing span for noun-verb sequences (Kay *et al.*, 1992).

  Modified Brown–Peterson task of verbal working memory (see Stopford, Thompson, Neary, Richardson, & Snowden, 2010). In this test, participants are presented visually with three words. They are asked to repeat the words either immediately, following a five second delay or following a five second delay during which the participant reads aloud numbers.

- Visuospatial tasks

  Visual patterns span (Della Sala, Gray, Baddeley, & Wilson, 1997), involving copying from memory grids of black and white squares to blank grids.

  Visual array comparison test constructed and modified from (Cowan *et al.*, 2005; Luck & Vogel, 1997) and programmed in E-Prime 2.0 (Psychology software tools inc, 2012). There are two subtests: colour and location. In both conditions, participants are briefly presented with one square and asked whether a second square is the same colour or in the same location as the first square. The arrays increase in size to a maximum of 10 squares.

Praxis

Orofacial and limb praxis were evaluated with the Manchester praxis screen, a locally constructed instrument taken from the Manchester neuropsychological profile, which is described previously (Snowden *et al.*, 2011). Participants are asked to carry out the actions described below. If participants are unable to carry out the action to command, they are shown the action to copy.

Orofacial praxis tasks consist of five actions, including tongue protrusion and coughing, three speech sounds (alternating repetitive vowel sounds, consonant sounds, and maintaining an extended phoneme), three emotional gestures (surprise, anger, and happiness), and three pantomimes (sniffing, sucking, and blowing).

Upper limb praxis tasks included four gestures and four pantomimes. Each action is performed with both left and right upper limbs.

Calculation

The Manchester calculation test involves 12 calculations; 6 administered verbally and 6 in writing.

Behaviour

A locally constructed behavioural questionnaire was given to relatives/carers to complete. The questionnaire includes questions aiming to evaluate changes in areas of behaviour, which are known to be affected in bvFTD and are described below. Each question is rated

on the basis of three options: increase, decrease, or no change. The behavioural domains have been found sensitive in distinguishing bvFTD from other forms of dementia (Bathgate, Snowden, Varma, Blackshaw, & Neary, 2001) and within subtypes of FTD (Snowden *et al.*, 2001) and are incorporated within contemporary diagnostic criteria for bvFTD (Rascovsky *et al.*, 2011):

- Social behaviour and interactions with others: interest and enjoyment being around others, social greetings and courtesies, amount of eye contact and frequency of personal questions, and comments of a complimentary or critical nature.
- Social emotions: happiness, sadness, fear, anger, guilt, surprise, disgust, embarrassment, empathy, laughter, and sense of humour.
- Response to environment: awareness of danger and response to painful and neutral stimuli.
- Eating and drinking: quantity and range of food eaten.
- Self-care: frequency of washing/bathing, changing clothes, and care about appearance.
- Hobbies, order, and routine: frequency of doing puzzles, TV quizzes, clockwatching, carrying out simple or complex repetitive behaviour, and hoarding.

Statistical analysis

Statistical analyses were conducted with SPSS version 22. A p value of <.05 was adopted.

Group comparisons of demographic data were carried out with ANOVAs and non-parametric equivalents as appropriate. Group comparisons on neuropsychological measures were analysed with Kruskal–Wallis tests. Due to the variation in ages and duration of symptoms across the cohort, group comparisons among the patient groups were also carried out with Quade's non-parametric rank analysis of covariance (ANCOVA), with age and duration of illness entered as nuisance covariates. *Post-hoc* Fisher's LSD tests were performed. A p value of <.05 was adopted.

Multiple *post-hoc* comparisons were corrected for using Bonferroni corrections (i.e., for comparisons of all groups, $p < .005$ was adopted and for comparisons of the patient groups $p < .0083$ was adopted).

Sensitivity, specificity, positive and negative predictive values of individual tests were calculated. The tests and groups were chosen on the basis of group comparisons. Any test where a patient group scored significantly worse relative to the other patient groups was included in the sensitivity and specificity analyses. Receiver operating characteristics curves were fitted to the data and Louden's index was used to determine cut-offs.

In order to delineate core factors underlying language, working memory, and behavioural deficits in these conditions, a principal components analysis (PCA) was carried out. A participant to variable ratio of 1.2 has yielded good results for PCA (Barrett & Kline, 1981). In order to have a reasonable participant to variable ratio, only scores from tests with both sensitivities and specificities greater than 50% were included in the analysis (see Table 4). For variables in which both 'total' and 'subtests' reached the threshold, for example, buccofacial praxis, only subtest variables were entered into the PCA. In total 25 variables were included in the PCA. Once missing data are taken into account, this study gives a 1.32 ratio. Factors above the inflection point on a scree plot were retained. In order to interpret factor loadings, a variance maximizing (varimax) rotation was performed. Factor loadings were used to gain individual participants' factor scores, which provide information about the participants' performance on the cognitive tests that cluster on said factor.

Individual participants' factor scores were used for a stepwise linear canonical discriminant analysis (LDA) to determine the strongest neuropsychological discriminators between the four groups (nfvPPA, lvPPA, SD, and multi-domain AD).

Results

Group comparisons

As expected, scores on many of the measures of working memory, speech and language, and praxis differed significantly in lvPPA and nfvPPA groups relative to healthy controls (data presented in Table A3 in Appendix S1). Only scores on tests of naming, comprehension, accuracy in reading aloud, and the percentage of nouns produced in narrative production and spelling differed between the SD group and healthy controls, in keeping with their semantic disorder. Scores on tests of naming, auditory sentence comprehension, spelling, several tests of repetition and auditory-visual working memory differed between AD and controls. Direct comparisons between patient groups are presented in Tables 2 and 3 and highlighted in the sections below. These data are corrected for age and duration of illness. Sensitivity, specificity, and positive and negative predictive values of individual tests are presented in Table 4.

Patients in all groups showed problems in naming and naming scores alone did not differentiate the groups. However, there were qualitative differences. SD patients named a higher proportion of actions relative to objects than all other patient groups (Table 2) and they made more semantic errors than nfvPPA patients (and Table A4 in Appendix S1). Indeed, the disproportionately poor naming of nouns was reasonably sensitive (87.5%) and specific (86.8%) to SD (Table 4). NfvPPA made more phonological errors on naming tests than SD patients (Table A4 in Appendix S1).

Agrammatism is a core feature nfvPPA; yet, scores on only a subset of sentence processing tasks were significantly worse in nfvPPA compared to the other patient groups. The Manchester sentence ordering test yielded the highest level of significance. Notably, however, not all conditions of the test were equally discriminating. Ordering five words according to a dictated sentence (dictation condition), and reading aloud of an ordered sentence (reading condition), were poorer in nfvPPA compared to all other patient groups. By contrast, on the standard, 'order' condition, in which patients were required to arrange sets of five words to form a sentence, nfvPPA scores were poorer than in lvPPA but not SD or AD. Indeed the 'order' condition had lower specificity (87.9%; Table 4) for detecting nvPPA, than the dictation condition (specificity 96.9%, sensitivity 66.7%). The reading condition had the highest sensitivity (91.7%) but the lowest specificity (78.1%).

NfvPPA patients performed more poorly than other groups on several measures of speech derived from narrative production (Table 2). These include a shorter mean length of utterance and more phonemic errors compared to all other groups, fewer dependent clauses per utterance compared to lvPPA and a lower percentage of well-formed sentences than SD (Table 2). Scores on a test of comprehension of complex syntax did not differ significantly between the patient groups.

Orofacial praxis differentiated nfvPPA from other patient groups, with overall scores on the Manchester orofacial praxis screen showing good specificity (77.1%), and sensitivity (100.0%). nfvPPA patients' deficits extended beyond the realms of AOS, although different orofacial tasks yielded different levels of sensitivity and specificity. Orofacial actions and pantomimes had the highest specificity (both 100.0%) but lower

Table 2. Group comparisons of measures of language function; median (range)

Measure	M (n)	SD (n = 8)	NfvPPA (n = 12)	LvPPA (n = 13)	AD (n = 14)	Quade's ANCOVA F (df = 3)	Controls (n = 19)
Naming							
Object and action naming: objects/50	0	25.5 (14–48)	47.0 (0–50)	44.0 (22–50)	45.5 (4–50)	2.303	50.0 (48–50)
Object and action naming: actions/50	0	30.0 (20–49)	42.0 (0–49)	45.0 (17–49)	42.5 (5–50)	0.681	50.0 (48–50)
Proportion action to object naming	1	1.2 (1.0–1.7)[a,b,c]	0.9 (0.1–1.0)[d]	1.0 (0.8–1.2)[d]	1.0 (0.7–1.3)[d]	11.101***	1.0 (1.0–1.0)
Manchester naming/40	0	21.0 (11–37)	36.5 (0–40)	36.0 (16–39)	36.5 (4–40)	2.518	40.0 (39–40)
Single word comprehension							
Manchester comprehension/ 40	0	38.5 (27–40)[a,b,c]	40.0 (40–40)[d]	40.0 (40–40)[d]	40.0 (38–40)[d]	9.286***	40.0 (40–40)
Sentence processing							
Auditory sentence comprehension/24	0	23.0 (11–24)	20.5 (10–24)	22.0 (15–24)	18.0 (7–23)	1.077	24.0 (23–24)
Auditory comprehension of locative relations /24	2	21.5 (5–24)	15.0 (7–24)	19.0 (7–24)	11.0 (6–24)	1.402	24.0 (19–24)
Manchester sentence ordering							
Order/10	2	8.0 (3–10)	1.0 (0–10)[b]	9.5 (4–10)[a]	9.0 (0–10)	4.492**	10.0 (7–10)
Reading/10	3	10.0 (10–10)[a]	3.5 (0–10)[b,c,d]	10.0 (6–10)[a]	10.0 (0–10)[a]	11.118***	10.0 (9–10)

Table 2. (*Continued*)

Differentiation of progressive aphasia

Measure	M (n)	SD (n = 8)	NfvPPA (n = 12)	LvPPA (n = 13)	AD (n = 14)	Quade's ANCOVA F (df = 3)	Controls (n = 19)
To dictation/10	3	10.0 (7–10)[a]	3.5 (0–10)[b,c,d]	10.0 (8–10)[a]	10.0 (0–10)[a]	6.262***	10.0 (10–10)
Time (s)	4	13.0 (8–28)[a]	29.1 (10–48)[d]	30.35 (11–55)	28.2 (14–75)	3.177*	6.2 (2–17)
Manchester tense production							
Uncued/20	7	17.0 (1–20)	18.0 (2–20)	19.0 (12–20)	19.0 (0–20)	0.845	20.0 (19–20)
Cued/20	7	18.0 (5–20)	18.0 (2–20)	20.0 (13–20)	19.0 (0–20)	1.356	20.0 (19–20)
Complete/20	2	20.0 (15–20)	13.0 (10–20)	20.0 (10–20)	20.0	1.934	20.0 (20–20)
Measures of narrative production: cookie theft description							
Words per minute	1	159.5 (89–217)[a,c]	47.8 (4–80)[b,c,d]	122.1 (38–152)[a]	116.9 (57–176)[a,d]	14.415***	145.1 (120–198)
Phonetic errors per 100 words	1	0.0 (0–0)	0.0 (0–2.5)	0.0 (0–0)	0.0 (0–0)	2.135	0.0 (0–0)
Phonemic errors per 100 words	1	0.0 (0–0)[a]	3.0 (0–67)[b,c,d]	0.0 (0–5)[a]	0.0 (0–5)[a]	6.393**	0.0 (0–0)
Fluency disruptions per 100 words	1	4.6 (1–22)[a]	31.3 (0–65)[d]	16.1 (3–44)	11.8 (0–64)	4.648**	6.8 (0–9)
Mean length of utterance (words)	1	10.9 (7–13)[a]	6.0 (0.0–9.6)[b,c,d]	10.0 (5.3–21.4)[a]	10.1 (5.7–17.7)[a]	5.454**	13.8 (9.4–22.7)
Number of dependent clauses per utterance	2	0.1 (0–0.5)	0.0 (0–0.1)[b]	0.3 (0–1.3)[a]	0.1 (0–0.7)	6.046**	0.5 (0.2–1.3)
Percent nouns	2	9.9 (8–19)[a]	19.9 (9–64)[d]	14.6 (9–26)	14.4 (6–23)	3.281*	19.6 (13–25)
Percent verbs	2	29.4 (22–36)	25.0 (14–38)	26.8 (16–32)	24.5 (17–32)	1.390	24.7 (19.9–30.7)
Proportion nouns to verbs	2	0.3 (0.2–0.9)[a]	0.7 (0.4–4.5)[d]	0.6 (0.4–1.1)	0.6 (0.3–1.0)	3.550*	0.8 (0.5–1.2)
Percentage well-formed sentences	1	100.0 (86–100)[a]	60.0 (0–100)[d]	71.4 (43–100)	80.0 (20–100)	4.481**	100.0 (85–100)
Reading							
Manchester reading/40	2	40.0 (31–40)	40.0 (33–40)[b]	40.0 (40–40)[a]	40.0 (31–40)	2.954*	40.0 (40–40)

Continued

Table 2. (*Continued*)

Measure	M (n)	SD (n = 8)	NfvPPA (n = 12)	LvPPA (n = 13)	AD (n = 14)	Quade's ANCOVA F (df = 3)	Controls (n = 19)
Imageability/frequency reading/40	0	38.0 (20–40)	37.0 (0–40)	39.0 (31–40)	39.0 (13–40)	1.834	40.0 (39–40)
Difference high/low frequency	0	1.5 (0–4)	1.0 (0–5)	0.0 (–3 to 2)	0.5 (–2 to 3)	2.422	0.0 (0–1)
Difference high/low imageability	0	2.0 (0–10)	1.0 (–1 to 5)	0.0 (0–7)	1.0 (0–9)	2.531	0.0 (0–1)
Spelling/sound regularity reading/20	0	19.0 (9–20)	18.0 (0–20)	19.0 (16–20)	19.0 (8–20)	0.581	20.0 (19–20)
Difference regular/exception	0	0.0 (–3 to 1)	0.0 (–2 to 4)	0.0 (–1 to 2)	0.0 (–3 to 2)	1.223	0.0 (–1 to 1)
Non-word reading/10	0	10.0 (3–10)	8.0 (0–10)	10.0 (6–10)	10.0 (1–10)	2.333	10.0 (5–10)
Spelling							
Manchester writing/20	5	13.0 (7–20)	12.0 (2–20)	19.0 (4–20)	14.5 (0–20)	0.550	20.0 (14–20)

Notes. df, degrees of freedom; lvPPA, logopenic variant primary progressive aphasia; m, missing; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; s, seconds; SD, semantic dementia.

*$p < .05$; **$p < .01$; ***$p < .0001$.

[a]Significant versus non-fluent/agrammatic patients.
[b]Significant versus logopenic patients.
[c]Significant versus AD patients.
[d]Significant versus SD patients. N.B. For *post-hoc* comparisons, significance is set at $p < .0083$.

Table 3. Group comparisons of working memory, praxis, and calculation; median (range)

	M (n)	SD (n = 8)	NfvPPA (n = 12)	lvPPA (n = 13)	AD (n = 14)	Quade's ANCOVA F (df = 3)	Controls (n = 19)
Working memory							
Digit span forwards	0	5.5 (3–8)[a]	4.0 (0–6)[b]	5.0 (2–6)	4.5 (2–8)	2.772	8.0 (5–9)
Digit span reverse	0	4.0 (2–6)[a,c]	2.0 (0–4)[b]	3.0 (1–4)	2.5 (1–4)[b]	6.514**	4.0 (3–8)
Manchester word repetition/40	1	40.0 (40–40)	40.0 (0–40)	40.0 (33–40)	40.0 (35–40)	3.100*	40.0 (40–40)
Manchester immediate and delayed word repetition/36	0	35.5 (21–36)	34.0 (0–36)	33.0 (6–36)	34.0 (5–36)	1.325	36.0 (35–36)
Immediate/18	0	18.0 (14–18)	17.0 (0–18)	17.0 (6–18)	18.0 (5–18)	1.424	18.0 (17–18)
Delayed/18	0	17.5 (7–18)	16.5 (0–18)	16.0 (0–18)	16.0 (0–18)	0.857	18.0 (17–18)
Sentence repetition/24	1	24.0 (23–24)[a]	14.0 (0–24)[b]	23.0 (0–24)	23.0 (0–24)	3.865*	24.0 (24–24)
Pointing span	1	4.5 (4–9)	5.0 (0–6)	4.0 (0–7)	3.0 (0–7)	1.536	8.0 (5–11)
Modified Brown–Peterson total/54	2	50.5 (35–54)[d]	44.5 (0–54)	36.0 (5–46)[b]	40.0 (0–54)	4.047*	53.5 (46–54)
Immediate/18	2	18.0 (16–18)[c,d]	16.0 (0–18)	15.0 (5–17)[b]	15.0 (0–18)[b]	5.100**	18.0 (17–18)
5-s delay/18	2	17.0 (13–18)[d]	15.0 (0–18)	8.0 (0–17)[b]	14.0 (0–18)	3.293*	18.0 (16–18)
Distraction & delay/18	2	16.5 (6–18)[d]	13.0 (0–18)	9.0 (0–16)[b]	11.0 (0–18)	2.960*	18.0 (12–18)
Visual patterns test	2	5.5 (3–9)[c]	5.5 (0–9)	5.0 (1–8)	3.5 (0–7)[b]	3.403*	6.0 (4–9)
Visual array comparison test: colour/10	4	4.0 (1–7)	4.0 (0–8)	3.5 (0–10)	1.5 (0–6)	1.829	6.0 (1–10)
Visual array comparison test: location/10	4	7.0 (0–10)	6.5 (0–10)	8.0 (0–10)	1.5 (0–5)	2.287	8.0 (2–10)
Praxis: Manchester praxis screen							
Orofacial/25	0	25.0 (22–25)[a]	20.0 (4–23)[b,c,d]	25.0 (21–25)[a]	25.0 (22–25)[a]	12.903***	25.0 (25–25)
Actions/10	0	10.0 (9–10)[a]	8.0 (4–10)[b,c,d]	10.0 (10–10)[a]	10.0 (9–10)[a]	8.069**	10.0 (10–10)
Sounds/speech praxis/3	0	3.0 (3–3)[a]	1.0 (0–3)[b,c,d]	3.0 (1–3)[a]	3.0 (2–3)[a]	23.325***	3.0 (3–3)

Continued

Table 3. (*Continued*)

	M (n)	SD (n = 8)	NfvPPA (n = 12)	lvPPA (n = 13)	AD (n = 14)	Quade's ANCOVA F (df = 3)	Controls (n = 19)
Emotions/6		6.0 (3–6)	5.0 (0–6)[d]	6.0 (3–6)[a]	6.0 (4–6)	4.351**	6.0 (6–6)
Pantomime/6		6.0 (6–6)[a]	6.0 (0–6)[b]	6.0 (5–6)	6.0 (4–6)	3.571*	6.0 (6–6)
Upper limb/32	0	29.0 (24–32)	26.5 (5–32)	32.0 (22–32)	28.0 (1–32)	1.110	32.0 (32–32)
Right total/16		14.5 (12–16)	13.5 (3–16)	16.0 (12–16)	14.5 (1–16)	1.003	16.0 (16–16)
Left total/16		14.5 (11–16)	13.5 (0–16)	16.0 (10–16)	13.5 (0–16)	1.027	16.0 (16–16)
Gesture total/16		15.0 (10–16)	14.5 (5–16)	16.0 (12–16)	15.5 (1–16)	1.191	16.0 (16–16)
Pantomime total/16		14.0 (12–16)	13.0 (0–16)	16.0 (9–16)	13.5 (0–16)	0.924	16.0 (16–16)
Calculation							
Manchester calculation test/12		12.0 (8–12)[a,d]	4.0 (1–12)[b]	6.0 (2–12)[b,c]	3.0 (0–10)[b,d]	11.035***	11.0 (7–12)

Notes. df, degrees of freedom; lvPPA, logopenic variant primary progressive aphasia; m, missing; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; s, seconds; SD, semantic dementia.
*p < .05; **p < .01; ***p < .0001.
[a]Significant versus non-fluent/agrammatic patients.
[b]Significant versus SD patients.
[c]Significant versus AD patients.
[d]Significant versus logopenic patients.

Table 4. Sensitivity, specificity, positive and negative predictive values of cognitive measures

Test (cut-off)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Semantic dementia versus other groups				
Manchester word picture comprehension test (<40/40)	62.5	92.3	62.5	92.3
Proportion action to object naming (>1.1)	87.5	86.8	58.3	97.1
Narrative: percent nouns (<11.5)	75.0	84.6	50.0	94.3
Narrative: proportion nouns to verbs (<0.4)	62.5	89.7	55.6	92.1
Behaviour: social behaviour (>5/9)	75.0	75.9	30.0	95.7
Behaviour: response to environment (>1/3)	25.0	93.1	33.3	90.0
Behaviour: hobbies, order and routines (>2/8)	75.0	72.4	27.3	95.5
Calculation (>8/12)	87.5	76.3	43.7	96.7
Non-fluent/agrammatic variant primary progressive aphasia versus other groups				
Manchester reading (<40/40)	40.0	91.4	57.1	84.2
Manchester sentence ordering: order (<4/10)	66.7	87.9	66.7	87.9
Manchester sentence ordering: reading (<10/10)	91.7	78.1	61.1	96.2
Manchester sentence ordering: to dictation (<6/10)	66.7	96.9	88.9	88.9
Narrative: phonemic errors per 100 words (>0.9)	81.8	80.0	56.3	93.3
Narrative: words per minute (<82.5)	100.0	85.7	68.8	100.0
Narrative: percentage well-formed sentences (<35.7%)	62.5	97.1	83.3	91.9
Narrative: mean length of utterance (<7.2 words)	81.8	82.9	60.0	93.5
Narrative: number of dependent clauses per utterance (<0.12)	100.0	62.9	40.9	100.0
Narrative: number of fluency disruptions per 100 words (>28.4)	63.6	88.6	63.6	88.6
Orofacial praxis total (<24/25)	100.0	77.1	60.0	100.0
Orofacial praxis actions (<9/10)	58.3	100.0	100.0	87.5
Orofacial praxis sounds (<3/3)	91.7	91.4	78.6	97.0
Orofacial praxis emotions (<6/6)	75.0	80.0	56.3	90.3
Orofacial praxis pantomimes (<4/6)	41.7	100.0	100.0	83.3
Logopenic variant primary progressive aphasia versus other groups				
Manchester immediate and delayed word repetition (<35/36)	76.9	52.9	38.5	85.7
Manchester immediate and delayed word repetition: immediate (<17/18)	38.4	76.5	38.5	76.5
Manchester immediate and delayed word repetition: delayed (<18/18)	76.9	38.2	32.3	81.3
Sentence repetition (<22/24)	46.2	69.7	37.5	76.7
Digit span forwards (<7)	100.0	14.7	31.0	100.0
Digit span reverse (<5)	100.0	5.9	28.9	100.0
Visual patterns span (<6)	84.6	34.4	34.4	84.6
Visual array comparison test: location (<1)	25.0	77.4	30.0	72.7
Visual array comparison test: colour (<7)	91.7	9.7	28.2	75.0
Pointing span (<5)	69.2	42.4	32.1	77.8
Brown–Peterson: total (<47/54)	100.0	50.0	39.3	100.0

Continued

Table 4. (*Continued*)

Test (cut-off)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Brown–Peterson: immediate (<18/18)	100.0	38.2	34.4	100.0
Brown–Peterson: delayed (<9/18)	54.5	79.4	46.2	84.4
Brown–Peterson: distraction (<17/18)	100.0	29.4	31.4	100.0
Logopenic variant primary progressive aphasia versus semantic dementia and non-fluent variant PPA				
Manchester immediate and delayed word repetition (<35/36)	76.9	60.0	55.6	80.0
Manchester immediate and delayed word repetition: immediate (<17/18)	38.5	75.0	50.0	65.2
Manchester immediate and delayed word repetition: delayed (<17/18)	61.5	60.0	50.0	70.6
Sentence repetition (<22/24)	46.2	68.4	50.0	65.0
Digit span forwards (<6)	84.6	30.0	44.0	75.0
Digit span reverse (<4)	76.9	35.0	43.5	70.0
Visual patterns span (<6)	84.6	50.0	55.0	81.8
Visual array comparison test: location (<1)	25.0	88.2	60.0	62.5
Visual array comparison test: colour (<7)	91.7	17.6	44.0	75.0
Pointing span (<5)	69.2	52.6	50.0	71.4
Brown–Peterson: total (<47/54)	100.0	65.0	61.1	100.0
Brown–Peterson: immediate (<18/18)	100.0	45.0	50.0	100.0
Brown–Peterson: delayed (<16/18)	81.8	60.0	52.9	85.7
Brown–Peterson: distraction (<17/18)	100.0	40.0	47.8	100.0

sensitivity (58.3% and 41.7% respectively). Perhaps unsurprisingly, production of repetitive and elongated speech sounds, that is, a measure of AOS, showed the best balance of specificity and sensitivity (91.7% and 91.4% respectively).

Patients with nfvPPA, lvPPA, and AD performed similarly on tests of working memory, whereas SD patients showed superior performance. NfvPPA patients performed worse than SD on digit span forwards and reverse conditions and on the sentence repetition test, whereas lvPPA patients performed worse than SD patients on all sections of the Brown–Peterson test. AD patients scored lower on the reverse digit span, immediate Brown–Peterson test, and the visual patterns test relative to SD patients. As working memory tests were expected to be useful in differentiating lvPPA from other groups, the sensitivity and specificity of these measures for lvPPA were calculated. The total score on the Brown–Peterson test showed the highest sensitivity for lvPPA (100.0%) but considerably lower specificity (50.0%). When multidomain AD patients were excluded from the analysis, the specificity increased to 65.0%. The only tests to reach over 70.0% specificity for lvPPA were the visual array comparison location test and the Manchester immediate word repetition test (77.4% and 76.5% respectively), but the sensitivities were very low (25.0% and 38.4%).

Behavioural data

Behavioural changes in the four patient groups are depicted in Figure 1 and Table A5 in Appendix S1. Behavioural data are absent from 7 patients. This was either because the

patient attended the appointment without an informant or else carers/relatives were distressed and it was deemed inappropriate to approach them.

Patients with SD exhibited more behavioural changes than the other patient groups, except in the domain of eating and drinking (Figure 1). There was no difference in frequency of behavioural changes in SD patients with predominantly right and predominantly left-sided atrophy (Figure A1 in Appendix S1). Behavioural changes were not exclusive to SD and some patients in each group exhibited changes in each category of behaviour evaluated. The only exception was that no patient with lvPPA exhibited altered 'response to environment'. Group differences reached significance for the following behavioural domains: 'response to environment' (Fisher's exact test, $p = .018$), 'social behaviour' (Fisher's exact test, $p = .038$) and 'hobbies, order and routine' (Fisher's exact test, $p = .015$). Changes in 'hobbies, order and routine' were more common in SD than nfvPPA, lvPPA, and AD (Fisher's exact test, $p = .044$, $p = .003$ and $.038$ respectively) and changes in patients' 'response to their environment' were more common in SD than lvPPA (Fisher's exact test, $p = .005$). Changes in 'social behaviour' were more common in SD than AD (Fisher's exact test, $p = .038$). Indeed, changes in these behavioural domains had relatively high sensitivities and specificities for SD (Table 4).

The breakdown of specific behavioural changes is shown in (Table A5 in Appendix S1). A large proportion of patients with nfvPPA, lvPPA, and AD exhibited a withdrawal in social behaviours and interaction with others, in particular, a relatively high proportion of lvPPA (44.4%) and nfvPPA (40.0%) patients enjoyed being with others less. In contrast, a high proportion of SD patients enjoyed being with others more (42.9%). Changes in social emotions were more prevalent in nfvPPA and SD patients than in lvPPA or AD.
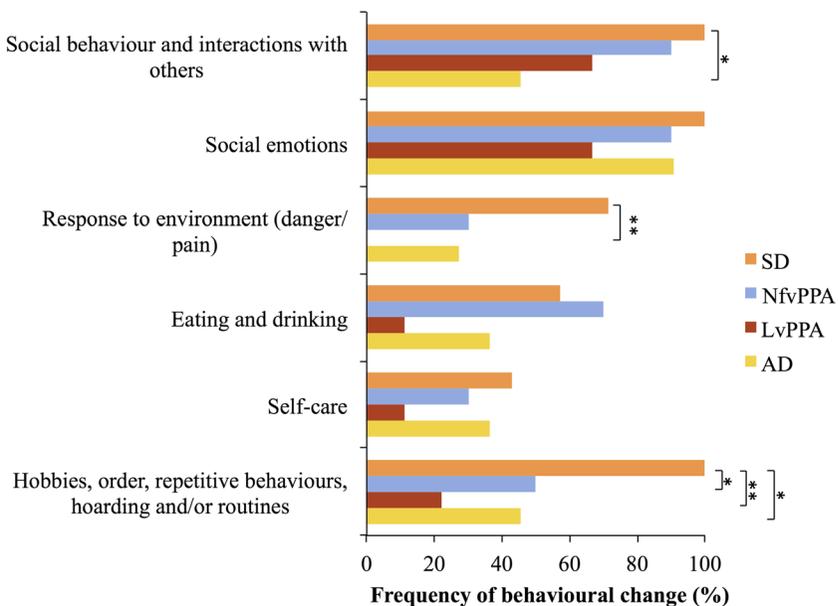

Figure 1. Behavioural change in the cohort. lvPPA, logopenic variant primary progressive aphasia; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; SD, semantic dementia; AD, multi-domain Alzheimer's disease. *$p < .05$, **$p < .01$. [Colour figure can be viewed at wileyonlinelibrary.com]

The majority of SD patients (57.1%) showed a reduction in the range of food they eat and an increase in the following features: reaction to painful stimuli (66.7%), clockwatching (57.1%), simple (71.4%) and complex (66.7%) repetitive behaviours, following a daily routine (57.1%), and enjoyment of puzzles (71.4%). In contrast, an increase in these features rarely occurred in the other patient groups. Nevertheless just under a third of nfvPPA patients liked TV quizzes and sweet food more than previously.

Principal components analysis

Fourteen patients had missing data on at least one of the 25 test variables due to anxiety/ the magnitude of their difficulties and had to be excluded from the PCA. The remaining 33 patients comprised 9 nfvPPA, 7 lvPPA, 7 SD, and 10 multi-domain AD. Evaluation of the sampling adequacy using the Kaiser–Meyer–Olkin revealed favourable results (0.504). The PCA yielded a 3-factor solution, which accounted for 55.700% of the variance in performance (F1 = 26.032%, F2 = 15.130%, F3 = 14.538%). The rotated (varimax) factor loadings for the cognitive assessments are shown in Table 5.

Tests of speech production, sentence processing, and buccofacial praxis loaded heavily onto factor one, together with one test of repetition. Tests of verbal/phonological working memory loaded heavily onto factor two. Single word comprehension, the proportion of actions versus objects named, and behavioural variables loaded heavily onto factor three.

Univariate analyses with Fisher's procedure employed for *post-hoc* pairwise comparisons revealed that scores on the 'speech production/grammaticality' factor and the 'semantic/behaviour' factor differed significantly in the three groups, $F(3,29) = 14.178$, $p < .001$ and $F(3,29) = 7.838$, $p = .001$ respectively. Patients with nfvPPA scored significantly lower on factor one (the 'speech production/grammaticality' factor) than patients in the other groups (all $p < .001$). Patients with SD scored higher on factor three (the 'semantic/behaviour' factor) than patients with nfvPPA, lvPPA, or AD ($p = .002$, $p < .001$ and $p < .001$ respectively). Factor two scores did not yield group differences.

Linear discriminant analysis

Scores for factors 1–3 for the 33 patients were entered into a LDA to determine how well the factors derived from the PCA were able to differentiate the three diagnostic groups.

Three discriminant functions were obtained. Two of the three discriminant functions were statistically significant, Wilks' $\lambda = .127$; $\chi^2 (9) = 58.905$; $p < .001$, Wilks' $\lambda = .486$; $\chi^2 (4) = 20.578$; $p < .001$ and Wilks' $\lambda = .986$; $\chi^2 (1) = 0.403$; $p = .525$ respectively.

The discriminant model correctly classified 72.7% of patients (88.9% of nfvPPA patients, 42.9% of lvPPA patients, 71.4% of SD, and 80.0% of multi-domain AD patients). The model showed 88.9% sensitivity and 100.0% specificity for diagnosing nfvPPA. The sensitivity for diagnosis of SD was 71.4% with a specificity of 96.2%. The sensitivity for diagnosis of lvPPA was 42.9% with a specificity of 96.2%. The sensitivity for diagnosis of multi-domain AD was 80.0% with a specificity of 69.6%.

Two patients with SD were predicted to be in the AD group. One patient with nfvPPA was predicted to be in the AD group. Four patients with lvPPA were predicted to be in the AD group. One patient with AD was predicted to be in the lvPPA group and a further patient with AD was predicted to be in the SD group.

While the model using the three factors was reasonably accurate at classifying nfvPPA and SD, it was unable to distinguish between the multi-domain AD and lvPPA groups.

Table 5. Factor scores

	Factor		
	Grammaticality/ speech production	Working memory	Semantic/ behavioural
Manchester immediate and delayed word repetition		0.760	
Brown–Peterson test: immediate		0.762	
Brown–Peterson test: delayed		0.805	
Visual patterns span			
Pointing span		0.775	
Manchester word picture comprehension test			−0.843
Proportion action to object naming			0.579
Narrative: percent nouns			
Narrative: proportion nouns to verbs			
Narrative: phonemic errors per 100 words	−0.715		
Calculation			
Manchester sentence ordering: order	0.768		
Manchester sentence ordering: reading	0.851		
Manchester sentence ordering: dictation	0.866		
Narrative: words per minute	0.732		
Narrative: mean length of utterance (words)			
Narrative: number of dependent clauses per utterance			
Narrative: fluency disruptions per 100 words	−0.772		
Narrative: percentage well-formed sentences	0.661		
Orofacial praxis: actions	0.710		
Orofacial praxis: sounds	0.848		
Orofacial praxis: emotions			
Behaviour: social Behaviour			0.871
Behaviour: response to environment			0.782
Behaviour: hobbies, order, and routine			0.823

Discussion

This study demonstrates three key findings in relation to PPA, which extend established knowledge. Firstly, they show that not all test measures within a language domain are equally valuable or discriminating. Secondly, they highlight features outside the language domain that contribute to the differentiation between subtypes of PPA. A PCA elicited three distinct factors that combined pure linguistic and extra linguistic features, which were useful in discriminating the groups. Thirdly, the findings show that despite high sensitivity of several measures to lvPPA they showed relatively poor specificity in discriminating lvPPA both from nfvPPA and from multidomain AD, highlighting the challenge for the diagnosis and classification of lvPPA. These aspects are considered in more detail below.

As expected, SD patients showed severely impaired naming. Yet, raw scores on naming tests did not differentiate SD from the other patient groups. A more useful marker was the relative magnitude of the naming impairment for nouns compared to that for verbs, which was significantly greater in SD compared to other groups. The Manchester comprehension test (word-picture matching), involving high frequency words, was highly discriminatory because SD patients alone showed reduced scores. A limitation is

that the test is sufficiently easy that it elicited ceiling level scores in some SD patients, and so may be insensitive to mild comprehension impairments. This finding highlights the importance of including for diagnostic purposes a variety of tests that range in level of difficulty.

NfvPPA was the only group to perform worse than controls and other patient groups on tests of grammar. Interestingly, however, production of grammatical sentences in picture description, a conventional measure of grammaticality, as well as a sentence completion using the correct verb tense, were less discriminating than the simple Manchester sentence ordering task involving the ordering of five words to form a grammatically correct sentence. Different conditions of the Manchester sentence ordering task were not equally discriminatory. The core 'order' condition, in which patients have to order five words to make a sentence, was reasonably sensitive to nfvPPA (i.e., most patients with nfvPPA exhibited reduced scores on this test), yet it was not as specific as some of the other conditions (i.e., patients in other groups also had reduced scores in this domain). The likely explanation is that performance could be compromised for reasons other than agrammatism. For example, SD patients might have difficulty understanding the component words of a sentence, whereas lvPPA and AD patients might be overloaded by task demands due to reduced working memory capacity. The 'dictation' condition, in which participants are dictated a full sentence and asked to order the words accordingly, increased specificity. The dictated sentence improved performance in other patient groups, while some nfvPPA patients remained unable to order the sentences correctly.

NfvPPA patients predictably performed poorly on tests of orofacial praxis relative to the other patient groups. Impaired production of repetitive and elongated speech sounds (orofacial praxis: sounds), that is, indicators of AOS, had high sensitivity and specificity for nfvPPA. Problems in orofacial praxis in nfvPPA extended beyond the realm of AOS, with impairments being demonstrated also in production of emotional gesture and orofacial actions, highlighting the association between gestural and spoken communication (Duffy & Duffy, 1981; Glosser *et al.*, 1986). Notably, on the PCA, tests of orofacial actions, sentence processing and narrative production loaded heavily onto the same factor (speech production and grammaticality), on which patients in the nfvPPA group had the lowest factor scores.

Behavioural changes, particularly changes in frequency of engagement in hobbies, increased preference for order and routines, repetitive behaviours, and hoarding, occurred more frequently in SD than the other patient groups. Indeed, an increase in repetitive behaviours and increased enjoyment of quizzes occurred in the majority of SD patients. Nevertheless, each core behavioural domain evaluated in this study was affected in some patients with nfvPPA. Most of the behavioural changes we observed are characteristic of bvFTD (Rascovsky *et al.*, 2011). Consistent with previous findings (Harris *et al.*, 2016), it is apparent that overlapping characteristics exist in these three syndromes predominantly predicated on FTLD pathology, that is, SD, nfvPPA, and bvFTD.

In this study, there were no significant differences in the behavioural profile of SD patients presenting with left and right predominant temporal lobe atrophy, and these behavioural features have been well documented (Bozeat, Gregory, Ralph, & Hodges, 2000; Green & Patterson, 2009; Lambon Ralph & Patterson, 2008; Liu *et al.*, 2004; Rohrer & Warren, 2010; Rosen *et al.*, 2006; Snowden *et al.*, 2001). Furthermore, a 'semantic and behavioural' factor emerged from the principal components analysis on which SD patients' scores differed from the other patient groups. The ubiquitous nature of behavioural changes in SD underscores the fact that this disorder extends beyond the

realm of semantic memory and calls into question whether it should be considered primarily a disorder of language. Similarities between patients with left and right predominant temporal lobe atrophy also raises the question of the usefulness of the contemporary distinction between syndromes associated, respectively, with left and right temporal lobe degeneration.

Individual test scores failed to show a clear pattern of deficits in lvPPA relative to the nfvPPA group. Impaired repetition is a central feature of lvPPA (Gorno-Tempini *et al.*, 2011) and may be predicated on phonological working memory impairment (Gorno-Tempini *et al.*, 2008). In this study, we performed a detailed evaluation of working memory including several tests of repetition. Performance on working memory tests was undoubtedly impaired in lvPPA relative to controls, and the Brown–Peterson measures, in particular, discriminated lvPPA from SD. However, impairments on working memory tests were also apparent in the nfvPPA and AD groups and the specificity of these measures was generally low for lvPPA. Indeed another factor analytic study of PPA found that repetition clustered with agrammatism and AOS, core features of nfvPPA (Sajjadi *et al.*, 2012). Given the marked speech production problems exhibited by patients with nfvPPA, it was perhaps unsurprising that they were impaired to a similar degree on tasks of verbal working memory as lvPPA patients. Our study supports the supposition that, in isolation, this feature has limited utility as a core diagnostic marker of lvPPA (Sajjadi *et al.*, 2012). Interestingly, the PCA elicited a 'working memory' factor which, together with a 'speech production and grammaticality' factor and a 'semantics and behaviour' factor, was able to differentiate lvPPA patients from nfvPPA and SD patients relatively well when evaluated with a linear discriminant analysis. Composite measures of working memory may therefore prove useful diagnostically in the classification of PPA.

The PCA analysis did not distinguish lvPPA from multi-domain AD. The findings suggest that common language and working memory deficits occur in lvPPA and multi-domain AD. Our findings differ from those of some previous studies, which have found differences between AD and lvPPA patients in the realm of verbal working memory (Foxe *et al.*, 2013; Meyer *et al.*, 2015) and language (Ahmed *et al.*, 2012). Differences in findings might reflect phenotypic variation in study cohorts, of which age is known to be one determinant (Snowden *et al.*, 2007). Differences in assessment methods might also be relevant. The study by Ahmed *et al.*, for example, involved analysis of speech samples rather than explicit measures of phonological short-term memory. Stage of illness might also be relevant. The finding by Foxe *et al.* (2013) and Meyer *et al.* (2015) of poorer phonological short-term memory in lvPPA were compared with AD, despite patients being matched for visual short-term memory performance might represent a transient distinction. It is of interest in this regard that longitudinal studies of lvPPA have indicated a convergence over time with the clinical symptoms of AD (Leyton, Hsieh, Mioshi, & Hodges, 2013) and a spread of atrophy consistent with AD (Brambati *et al.*, 2015)(Rohrer *et al.*, 2013). It is possible that at an earlier stage of disease greater differences might have been elicited between the two groups. However, the average number of years since disease onset was relatively low in the lvPPA group (mean 3.82 years) and in line with that cited in other studies of lvPPA (Foxe *et al.*, 2016; Krishnan *et al.*, 2017; Whitwell *et al.*, 2015; Win *et al.*, 2017). Moreover, the majority of patients were assessed within a year of their medical referral, so were still at a relatively early stage of illness. Further studies involving incident cases and longitudinal investigation of working memory in a spectrum of different AD subtypes with varying ages of onset would be useful.

The 'grammaticality and speech production' factor was the most useful factor in classifying the three patient groups. It has been suggested that the absence of frank

impairments in grammar and comprehension should be a core feature of lvPPA, rather than impaired repetition (Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Mesulam & Weintraub, 2014; Mesulam *et al.*, 2014). Our findings support the notion that grammaticality (together with speech production) is more effective than impaired repetition in differentiation of PPA. However, supporting criteria for lvPPA are almost exclusively made up of features denoting preserved areas of speech and language. The only other core feature, impaired single word retrieval, is a notoriously common feature across dementia syndromes, in this study, proved non-discriminatory. Thus, a change in the core criteria from 'impaired phrase repetition' to 'preserved grammaticality and speech production' would constitute denoting a disorder exclusively by *absence* of features, rather than the *presence* of characteristic features. The likely effect of this would be that any patient with PPA who does not have the defining features of the other two subtypes would be classified as lvPPA. While this would increase the sensitivity of the criteria for lvPPA, it would have a detrimental effect on the specificity, as mild cases of nfvPPA and svPPA and atypical PPA patients would probably fulfil criteria for lvPPA.

   The study has several limitations. Firstly, inevitably there is some circularity when evaluating classification of patients on the same areas of cognition that are used to reach a diagnosis. Nevertheless, clinical diagnoses were made independently by clinical history and observation and neurological examination, with supportive neuropsychological evaluation. Furthermore, most of the tests employed as part of this study are not routinely used in the clinic and some measures were purely experimental. Indeed, all patients with lvPPA exhibited impairments in sentence repetition during clinical diagnostic testing; yet, some patients performed at ceiling on the relatively undemanding PALPA sentence repetition task. The choice of the sentence repetition task might be criticized for being too easy. On the other hand, it did elicit impairments in the nfvPPA group sufficient to distinguish nfvPPA from SD. Sentence repetition is therefore unlikely to prove a useful diagnostic marker for lvPPA, to allow it to be distinguished from nvfPPA, irrespective of the level of difficulty of the repetition task. In addition, the individual-rotated factors elicited from the PCA included combinations of tests and behavioural measures that would not routinely be used in classification of patients. Secondly, by necessity of the prospective nature of the study, the sample size was relatively small ($n = 47$). The number of patients included in the PCA was smaller still ($n = 33$). However, as outlined in the methods, the ratio of participants to variables was acceptable (Barrett & Kline, 1981). Nevertheless, future confirmatory studies with larger numbers of participants would be useful. A third limitation is that, due to the relatively small sample, in order to have a reasonable participant to variable ratio for the PCA, the study did not involve an exhaustive assessment of non-linguistic and linguistic factors. Cognitive domains were chosen owing to their theoretical importance in a study of progressive aphasia; yet, there are some notable omissions. One such factor is episodic memory, which has been found to be significantly impaired in AD relative to lvPPA (Win *et al.*, 2017) and in lvPPA relative to nfvPPA (Piguet, Leyton, Gleeson, Hoon, & Hodges, 2015). In this study, standard episodic memory measures were omitted on the grounds that performance may be compromised secondarily by problems in language and working memory. However, further studies including carefully selected episodic memory variables would be interesting, as would the inclusion of other behavioural domains such as emotion processing and more detailed evaluation of connected speech, which may be useful in differential diagnosis of PPA (Piguet *et al.*, 2015; Wilson *et al.*, 2010). A final limitation relates to gender differences. The participants were consecutive referrals who met the selection criteria and agreed to participate. An unintended consequence was that the groups were not matched for

gender. In future studies it would be important to consider the possible influence of gender on differential performance patterns.

In conclusion, simple and brief tasks of sentence ordering, narrative production, buccofacial praxis, and single word comprehension are helpful in the discrimination of forms of PPA. Nevertheless, evaluating single tests in isolation has limitations. Namely, tests may lack sensitivity or specificity because they are too easy or because failure can arise for different underlying reasons. A test profile is important, as exemplified by the PCA. Characteristic profiles in PPA include non-language features, in particular, the presence of apraxia in nfvPPA, which extends beyond AOS, behavioural changes in SD, and working memory deficits in lvPPA. Notably, while factors elicited by the PCA were effective at differentiating nfvPPA, SD, and lvPPA, these measures were unable to differentiate lvPPA and multi-domain AD. The similarity in language profile in lvPPA and multidomain AD is important because it supports the contention that lvPPA is largely a focal, linguistic form of AD rather than FTLD. Nevertheless, lvPPA risks being a diagnosis of exclusion. The classification of forms of PPA that are distinct from nfvPPA and SD remains a challenge.

References

Ahmed, S., de Jager, C. A., Haigh, A. M., & Garrard, P. (2012). Logopenic aphasia in Alzheimer's disease: Clinical variant or clinical feature? *Journal of Neurology, Neurosurgery & Psychiatry*, *83*, 1056–1062. https://doi.org/10.1136/jnnp-2012-302798

Barrett, P. T., & Kline, P. (1981). The observation to variable ratio in factor analysis. *Personality Study and Group Behaviour*, *1*, 23–33.

Bathgate, D., Snowden, J., Varma, A., Blackshaw, A., & Neary, D. (2001). Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurologica Scandinavica*, *103*, 367–378. https://doi.org/ane236 [pii]

Botha, H., Duffy, J. R., Whitwell, J. L., Strand, E. A., Machulda, M. M., Schwarz, C. G., . . . Josephs, K. A. (2015). Classification and clinicoradiologic features of primary progressive aphasia (PPA) and apraxia of speech. *Cortex*, *69*, 220–236. https://doi.org/10.1016/j.cortex.2015.05.013

Bozeat, S., Gregory, C. A., Ralph, M. A., & Hodges, J. R. (2000). Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *Journal of Neurology, Neurosurgery and Psychiatry*, *69*(2), 178–186. https://doi.org/10.1136/jnnp.69.2.178

Brambati, S. M., Amici, S., Racine, C. A., Neuhaus, J., Miller, Z., Ogar, J., . . . Gorno-Tempini, M. L. (2015). Longitudinal gray matter contraction in three variants of primary progressive aphasia: A tenser-based morphometry study. *NeuroImage Clinical*, *8*, 345–355. https://doi.org/10.1016/j.nicl.2015.01.011

Caza, N., & Belleville, S. (2008). Reduced short-term memory capacity in Alzheimer's disease: The role of phonological, lexical, and semantic processing. *Memory*, *16*, 341–350. https://doi.org/10.1080/09658210701881758

Cowan, N., Elliott, E. M., Scott Saults, J., Morey, C. C., Mattox, S., Hismjatullina, A., & Conway, A. R. (2005). On the capacity of attention: Its estimation and its role in working memory and cognitive aptitudes. *Cognitive Psychology*, *51*(1), 42–100. https://doi.org/10.1016/j.cogpsych.2004.12.001

Della Sala, S., Gray, C., Baddeley, A., & Wilson, L. (1997). *Visual patterns test: A test of short term visual recall*. Bury St Edmunds, UK: Thames Valley Test Company.

Druks, J., & Masterson, J. (2000). *An object & action naming battery*. Philadelphia, PA: Psychology Press.

Duffy, R. J., & Duffy, J. R. (1981). Three studies of deficits in pantomimic expression and pantomimic recognition in aphasia. *Journal of Speech, Language, and Hearing Research*, *24*(1), 70–84. https://doi.org/10.1044/jshr.2401.70

Foxe, D. G., Irish, M., Hodges, J. R., & Piguet, O. (2013). Verbal and visuospatial span in logopenic progressive aphasia and Alzheimer's disease. *Journal of the International Neuropsychological Society*, *19*(3), 247–253. https://doi.org/10.1017/S1355617712001269

Foxe, D., Leyton, C. E., Hodges, J. R., Burrell, J. R., Irish, M., & Piguet, O. (2016). The neural correlates of auditory and visuospatial span in logopenic progressive aphasia and Alzheimer's disease. *Cortex*, *83*, 39–50. https://doi.org/10.1016/j.cortex.2016.07.003

Glosser, G., Wiener, M., & Kaplan, E. (1986). Communicative gestures in aphasia. *Brain and Language*, *27*, 345–359. https://doi.org/10.1016/0093-934X(86)90024-6

Glushko, R. J. (1979). Organization and activation of orthographic knowledge in reading aloud. *Journal of Experimental Psychology: Human Perception and Performance*, *5*, 674–691. https://doi.org/10.1037//0096-1523.5.4.674

Goodglass, H., & Kaplan, E. (1983). *Boston diagnostic aphasia examination (BDAE)*. Philadelphia, PA: Lea and Febiger.

Gorno-Tempini, M. L., Brambati, S. M., Ginex, V., Ogar, J., Dronkers, N. F., Marcone, A., . . . Miller, B. L. (2008). The logopenic/phonological variant of primary progressive aphasia. *Neurology*, *71*, 1227–1234. https://doi.org/10.1212/01.wnl.0000320506.79811.da

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., . . . Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, *76*, 1006–1014. https://doi.org/10.1212/wnl.0b013e31821103e6

Green, H. A. C., & Patterson, K. (2009). Jigsaws-A preserved ability in semantic dementia. *Neuropsychologia*, *47*, 569–576. https://doi.org/10.1016/j.neuropsychologia.2008.10.015

Grossi, D., Becker, J. T., Smith, C., & Trojano, L. (1993). Memory for visuospatial patterns in Alzheimer's disease. *Psychological Medicine*, *23*(1), 65–70. https://doi.org/10.1017/S003329170003885X

Harris, J. M., Gall, C., Thompson, J. C., Richardson, A. M., Neary, D., du Plessis, D., . . . Jones, M. (2013). Classification and pathology of primary progressive aphasia. *Neurology*, *81*, 1832–1839. https://doi.org/10.1212/01.wnl.0000436070.28137.7b

Harris, J. M., & Jones, M. (2014). Pathology in primary progressive aphasia syndromes. *Current Neurology and Neuroscience Reports*, *14*, 466. https://doi.org/10.1007/s11910-014-0466-4

Harris, J. M., Jones, M., Gall, C., Richardson, A. M. T., Neary, D., du Plessis, D., . . . Thompson, J. C. (2016). Co-occurrence of language and behavioural change in frontotemporal lobar degeneration. *Dementia and Geriatric Cognitive Disorders Extra*, *6*, 205–213. https://doi.org/10.1159/000444848

Harris, J. M., Thompson, J. C., Gall, C., Richardson, A. M., Neary, D., du Plessis, D., . . . Jones, M. (2015). Do NIA-AA criteria distinguish Alzheimer's disease from frontotemporal dementia? *Alzheimer's & Dementia*, *11*(2), 207–215. https://doi.org/10.1016/j.jalz.2014.04.516

Joshi, A., Roy, E. A., Black, S. E., & Barbour, K. (2003). Patterns of limb apraxia in primary progressive aphasia. *Brain and Cognition*, *53*, 403–407. https://doi.org/10.1016/S0278-2626(03)00116-7

Kay, J., Lesser, R., & Coltheart, M. (1992). *Psycholinguistic assessment of language processing in aphasia*. Hove, UK: Psychology Press.

Krishnan, K., Machuda, M. M., Whitwell, J. L., Butts, A. M., Duffy, J. R., Strand, E. A., . . . Josephs, K. A. (2017). Varying degrees of temporoparietal hypometabolism on FDG-PET reveal amyloid-positive logopenic primary progressive aphsia is not a homogeneneous clinical entity. *Journal of Alzheimer's Disease*, *55*, 1019–1029. https://doi.org/10.3233/JAD-160614

Lambon Ralph, M. A., & Patterson, K. (2008). Generalization and differentiation in semantic memory: Insights from semantic dementia. *Annals of the New York Academy of Sciences*, *1124*, 61–76. https://doi.org/10.1196/annals.1440.006

Leyton, C. E., Hsieh, S., Mioshi, E., & Hodges, J. R. (2013). Cognitive decline in logopenic aphasia: More than losing words. *Neurology*, *80*(10), 897–903. https://doi.org/10.1212/WNL.0b013e318285c15b

Libon, D. J., Xie, S. X., Moore, P., Farmer, J., Antani, S., McCawley, G., . . . Grossman, M. (2007). Patterns of neuropsychological impairment in frontotemporal dementia. *Neurology*, *68*, 369–375. https://doi.org/10.1212/01.wnl.0000252820.81313.9b

Liu, W., Miller, B. L., Kramer, J. H., Rankin, K., Wyss-Coray, C., Gearhart, R., . . . Rosen, H. J. (2004). Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. *Neurology*, *62*, 742–748. https://doi.org/10.1212/01.WNL.0000113729.77161.C9

Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature*, *390*, 279–281. https://doi.org/10.1038/36846

Mesulam, M. M., & Weintraub, S. (2014). Is it time to revisit the classification guidelines for primary progressive aphasia? *Neurology*, *82*, 1108–1109. https://doi.org/10.1212/WNL.0000000000000272

Mesulam, M. M., Weintraub, S., Rogalski, E. J., Wieneke, C., Geula, C., & Bigio, E. H. (2014). Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. *Brain*, *137*(Pt 4), 1176–1192. https://doi.org/10.1093/brain/awu024

Mesulam, M., Wieneke, C., Thompson, C., Rogalski, E., & Weintraub, S. (2012). Quantitative classification of primary progressive aphasia at early and mild impairment stages. *Brain*, *135*(Pt 5), 1537–1553. https://doi.org/10.1093/brain/aws080

Meyer, A. M., Snider, S. F., Campbell, R. E., & Friedman, R. B. (2015). Phonological short-term memory in logopenic variant primary progressive aphasia and mild Alzheimer's disease. *Cortex*, *71*, 183–189. https://doi.org/10.1016/j.cortex.2015.07.003

Neary, D., Snowden, J., Gustafson, L., Passant, U., Stuss, D., Black, S., . . . Benson, D. F. (1998). Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology*, *51*, 1546–1554. https://doi.org/10.1212/WNL.51.6.1546

Nestor, P. J., Graham, N. L., Fryer, T. D., Williams, G. B., Patterson, K., & Hodges, J. R. (2003). Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. *Brain*, *126*(Pt 11), 2406–2418. https://doi.org/10.1093/brain/awg240

Piguet, O., Leyton, C. E., Gleeson, L. D., Hoon, C., & Hodges, J. R. (2015). Memory and emotion processing performance contributes to the diagnosis of non-semantic primary progressive aphasia syndromes. *Journal of Alzheimer's Disease*, *44*, 541–547. https://doi.org/10.3233/JAD-141854

Psychology software tools inc. (Producer). (2012). E-Prime 2.0.

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., . . . Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, *134*(Pt 9), 2456–2477. https://doi.org/10.1093/brain/awr179

Rohrer, J. D., Caso, F., Mahoney, C., Henry, M., Rosen, H. J., Rabinovici, G., . . . Gorno-Tempini, M. L. (2013). Patterns of longitudinal brain atrophy in the logopenic variant of primary progressive aphasia. *Brain and Language*, *127*(2), 121–126. https://doi.org/10.1016/j.bandl.2012.12.008

Rohrer, J. D., Rossor, M. N., & Warren, J. D. (2010). Apraxia in progressive nonfluent aphasia. *Journal of Neurology*, *257*, 569–574. https://doi.org/10.1007/s00415-009-5371-4

Rohrer, J. D., & Warren, J. D. (2010). Phenomenology and anatomy of abnormal behaviours in primary progressive aphasia. *Journal of the Neurological Sciences*, *293*(1–2), 35–38. https://doi.org/10.1016/j.jns.2010.03.012

Rosen, H. J., Allison, S. C., Ogar, J. M., Amici, S., Rose, K., Dronkers, N., . . . Gorno-Tempini, M. L. (2006). Behavioral features in semantic dementia vs other forms of progressive aphasias. *Neurology*, *67*, 1752–1756. https://doi.org/10.1212/01.wnl.0000247630.29222.34

Sajjadi, S. A., Patterson, K., Arnold, R. J., Watson, P. C., & Nestor, P. J. (2012). Primary progressive aphasia: A tale of two syndromes and the rest. *Neurology*, *78*, 1670–1677. https://doi.org/10.1212/WNL.0b013e3182574f79

Smits, L. L., Pijnenburg, Y. A., Koedam, E. L., van der Vlies, A. E., Reuling, I. E., Koene, T., . . . van der Flier, W. M. (2012). Early onset Alzheimer's disease is associated with a distinct neuropsychological profile. *Journal of Alzheimer's Disease*, *30*(1), 101–108. https://doi.org/10.3233/jad-2012-111934

Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory*, *6*(2), 174–215. https://doi.org/10.1037/0278-7393.6.2.174

Snowden, J. S., Bathgate, D., Varma, A., Blackshaw, A., Gibbons, Z. C., & Neary, D. (2001). Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *Journal of Neurology, Neurosurgery and Psychiatry*, *70*, 323–332. https://doi.org/10.1136/jnnp.70.3.323

Snowden, J. S., Stopford, C. L., Julien, C., Thompson, J. C., Davidson, Y., Gibbons, L., . . . Mann, D. (2007). Cognitive phenotypes in Alzheimer's disease and genetic risk. *Cortex*, *43*, 835–845. https://doi.org/10.1016/S0010-9452(08)70683-X

Snowden, J. S., Thompson, J. C., Stopford, C. L., Richardson, A. M., Gerhard, A., Neary, D., & Mann, D. M. (2011). The clinical diagnosis of early-onset dementias: Diagnostic accuracy and clinicopathological relationships. *Brain*, *134*(Pt 9), 2478–2492. https://doi.org/10.1093/brain/awr189

Stopford, C. L., Snowden, J., Thompson, J. C., & Neary, D. (2007). Distinct memory profiles in Alzheimer's disease. *Cortex*, *43*, 846–857. https://doi.org/10.1016/S0010-9452(08)70684-1

Stopford, C. L., Snowden, J., Thompson, J. C., & Neary, D. (2008). Variability in cognitive presentation of Alzheimer's disease. *Cortex*, *44*(2), 185–195. https://doi.org/10.1016/j.cortex.2005.11.002

Stopford, C. L., Thompson, J. C., Neary, D., Richardson, A. M., & Snowden, J. (2010). Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia. *Cortex*, *48*, 429–446. https://doi.org/10.1016/j.cortex.2010.12.002

Thompson, C. K., & Mack, J. E. (2014). Grammatical impairments in PPA. *Aphasiology*, *28*, 1018–1037. https://doi.org/10.1080/02687038.2014.912744

Thompson, J. C., Stopford, C. L., Snowden, J., & Neary, D. (2005). Qualitative neuropsychological performance characteristics in frontotemporal dementia and Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *76*, 920–927. https://doi.org/10.1136/jnnp.2003.033779

Trojano, L., Chiacchio, L., De Luca, G., & Grossi, D. (1994). Exploring visuospatial short-term memory defect in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *16*, 911–915. https://doi.org/10.1080/01688639408402702

Tyrrell, P. J., Kartsounis, L. D., Frackowiak, R. S., Findley, L. J., & Rossor, M. N. (1991). Progressive loss of speech output and orofacial dyspraxia associated with frontal lobe hypometabolism. *Journal of Neurology, Neurosurgery and Psychiatry*, *54*, 351–357. https://doi.org/10.1136/jnnp.54.4.351

Wechsler, D. (1981). *Wechsler adult intelligence scale-revised*. New York, NY: Psychological Corporation.

Whitwell, J. L., Jones, D. T., Duffy, J. R., Strand, E. A., Machuda, M. M., Przybelski, B. S., . . . Josephs, K. A. (2015). Working memory and language network dysfunction in logopenic aphasia: A task-free

fMRI comparison to Alzheimer's dementia. *Neurobiology of Aging*, *36*, 1245–1252. https://doi.org/10.1016/j.neurobiolaging.2014.12.013

Wicklund, M. R., Duffy, J. R., Strand, E. A., Machulda, M. M., Whitwell, J. L., & Josephs, K. A. (2014). Quantitative application of the primary progressive aphasia consensus criteria. *Neurology*, *82*, 1119–1126. https://doi.org/10.1212/WNL.0000000000000261

Wilson, S. M., Henry, M. L., Besbris, M., Ogar, J. M., Dronkers, N. F., Jarrold, W., . . . Gorno-Tempini, M. L. (2010). Connected speech production in three variants of primary progressive aphasia. *Brain*, *133*(Pt 7), 2069–2088. https://doi.org/10.1093/brain/awq129

Win, K. T., Pluta, J., Yushkevich, P., Irwin, D. J., McMillan, C. T., Rascovsky, K., . . . Grossman, M. (2017). Neural correlates of verbal episodic memory and lexical retrieval in Logopenic Variant Primary Progressive Aphasia. *Frontiers in Neuroscience*, *11*, 330. https://doi.org/10.3389/fnins.2017.00330

Supporting Information

The following supporting information may be found in the online edition of the article:

Appendix S1. Supplementary material.