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Bilingualism in primary progressive aphasia: a retrospective study on clinical and language characteristics

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Abstract

BACKGROUND: Primary progressive aphasia (PPA) is a neurodegenerative disorder characterized by progressive deterioration of language. Being rare, reports of PPA in multilingual individual are scarce, despite more than half of the world population being multilingual.

METHODS: We describe clinical characteristics of 33 bilingual patients with PPA, including symptom presentation and language deficits pattern in their first (L1) and second language (L2), through a systematic literature review and new cases retrospectively identified in five countries.

RESULTS: Fourteen patients presented with nonfluent/agrammatic variant, six with semantic variant, and 13 with logopenic variant, with a median symptom onset of two years. Word-finding difficulties was the first symptom in 65% of all cases, initially noticed in L2, and not always the dominant language. Our group had 22 different languages as L1, and nine as L2. At the whole-group level there is a tendency for parallel impairment in both languages, in line with the shared bilingual neural substrate hypothesis, but each PPA variant shows some heterogeneity.

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DISCUSSION: Each PPA variant shows heterogeneity, warranting the need for comprehensive language and cognitive assessment across languages, as well as further clarification on the role of language mediators.

Keywords

Primary progressive aphasia; bilingualism; systematic review; retrospective study; language; dementia

Introduction

Primary progressive aphasia (PPA) is a neurodegenerative syndrome characterized by the progressive deterioration of language with the relative sparing of other cognitive functions, due to a selective distribution of neurodegeneration within specific language networks [1]. Based on this selective language network dysfunction, three clinical variants have been identified: (1) nonfluent/agrammatic variant (PPA-G), (2) semantic variant (PPA-S), and (3) logopenic variant (PPA-L) [1,2], generally associated with frontotemporal lobar degeneration (FTLD) or Alzheimer's disease (AD) [3]. Epidemiological data for PPA is limited, but is characterized by low prevalence and incidence rates [4,5]. It remains nonetheless surprising that only a few single cases of PPA have been reported in multilingual patients, considering that multilingualism is the norm for most individuals worldwide and will likely be increasing, due to globalisation and migration phenomena.

The study of the influence of multilingualism, particularly bilingualism, on the development and normal function of language and other cognitive domains has a long history [6] and has provided important insights into several cognitive and clinical questions. One topic that has received considerable attention is the study of bilingual patients with aphasia due to focal brain damage, most frequently because of stroke. In the last two centuries theorical models of multilingual aphasia focussed either on the influence of memory systems, or on the role of cognitive control. Both views reflect concepts on how the brain organises languages, either separated or sharing common neural networks [7]. There are three main hypotheses regarding the deterioration pattern of language processing in bilingual aphasia: (1) Ribot's law, which postulates that the mother language (L1) would be more resistant to progressive cognitive deterioration processes [8]; (2) Pitre's rule which defends that the dominant language would be greatly benefit from therapeutic intervention [8]; and (3) the shared neuronal substrate hypothesis, which argues for parallel deterioration of both languages [9].

Considerably fewer studies have evaluated language deficits in bilingual patients with neurodegenerative diseases [10], with the majority focusing on AD, specifically on deficits in semantic/lexical access. Earlier studies found that the non-dominant language is frequently more impaired in bilingual AD patients [11], although others have found a parallel impairment [9], which has been attributed to supra-linguistic deficits in executive cognitive control mechanisms [12].

The role of different mediators in multilingual aphasia should not be understated. Several possible factors have been identified, including, among others, the type of bilingualism (simultaneous vs. sequential; receptive vs. productive; additive vs. subtractive), degree and

balance of proficiency, age of acquisition, language characteristics and features (e.g. transparency, writing systems type, distance, degree of exposure, cognate vs non-cognate) and translation type [6,13,14], but their effects on language impairment in neurodegenerative disorders are still poorly understood.

Some studies also assessed bilingualism as a potential protective factor in neurodegenerative disorders. Despite some evidence on the association between bilingualism and later symptom onset in AD [16], possibly mediated through an increase in cognitive reserve and neuroplasticity, a recent study did not find an association between bilingualism and delayed symptom onset in PPA [18].

The aim of this retrospective study was to characterize the clinical manifestations of language decline in bilingual patients with PPA, with an emphasis on symptom onset, patterns of performance in different languages and identification of potential mediating factors.

Methods

We conducted a systematic literature search of multilingual PPA and complemented it with 20 new cases retrospectively identified in our centres. For the systematic review, medical electronic search engine (PubMed) was used to identify studies on PPA and multilingualism, using the following search terms: (primary progressive aphasia OR semantic dementia OR logopenic aphasia) in combination with (bilingualism OR multilingualism) in September 2017, yielding 14 publications. Reference lists of the identified publications were also reviewed. Eligibility criteria included peer-reviewed reports with individual data on multilingual PPA patients diagnosed according to current criteria [2], regardless of study type (cohort or case-report), PPA variant (nonfluent/agrammatic, semantic or logopenic), demographic or language characteristics. After screening, four records were excluded (two due to data duplication and two reported on a different aetiology (e.g. stroke) or disorder (e.g. non-primary aphasia due to AD)). In total, 13 previously published single cases were included in the analysis (cf. Supplementary Table 2, Supplemental digital Content 1, http://links.lww.com/CLINSPINE/A76, for references). Follow-up or interventional studies were included, but only data from the baseline assessment were collected. Additionally, twenty previously unpublished cases of multilingual patients with PPA were retrospectively identified in the databases of our centres (n=14 in Toronto, n= 2 in Braga, n= 2 in Madrid, n=1 in Washington and Aachen, respectively). Data from baseline assessments were collected from available clinical and research records. In all participating sites, diagnosis was established through interdisciplinary consensus, according to current criteria [2]. Patients were included in this study if diagnosed with PPA, regardless of variant, and classified as multilingual, which was broadly defined as the knowledge and use of two or more languages [19].

To minimise missing data, our design comprised the collection and analysis of L1 and L2, despite some patients being proficient in more than two languages. Most of the variables were categorized to allow for comparability (see Table 1 for definitions and operationalization details). Besides demographical characteristics (age, sex, educational

level, occupation), clinical characteristics included first symptom, age of onset, PPA diagnosis, medical history, family history, structural and functional imaging, cerebrospinal fluid AD biomarkers results). Structural and functional imaging data were based on available clinical reports or published descriptions. For the new 20 cases, images had also been reviewed by the interdisciplinary diagnostic consensus teams. We specifically coded data regarding first (L1) and second language (L2) features (dominance pattern, L2 age of acquisition, estimated proficiency level, L1 and L2 usage at time of diagnosis). As language assessment procedures varied across sites (for an overview, cf. Supplementary Table 1, Supplemental digital Content 1, http://links.lww.com/CLINSPINE/A76), severity of impairment, in naming, repetition, comprehension and semantic knowledge performance, was classified as normal, mild, moderate or severe, according to available standardized norms, when formal testing was conducted (in each language, when available) or qualitatively according to clinical assessment or available descriptions.

Results are largely descriptive given the study exploratory nature, variability in assessment methods and small sample sizes. We present frequency, percentage, mean values with standard deviation (SD) or median with interquartile range (IQR), depending on data characteristics. The study was authorized by the Ethic Committee of Hospital de Braga and conducted in agreement with the Helsinki Declaration.

Results

Demographics

We present data on 33 multilingual PPA patients, 13 from the literature review and 20 previously unpublished cases identified in our centres (cf. Supplementary Table 2, Supplemental digital Content 1, http://links.lww.com/CLINSPINE/A76 for an overview on individual characteristics). As shown in Table 2, twenty patients were male, and the mean age was 68.6 years (SD = 7.5). The majority were right-handed (left-handed n=3, information missing for three cases) and had completed tertiary education level (57.6%, secondary level 21.2%, primary level 9.1%, information missing for four patients), with a heterogeneous socio-cultural background, as evidenced by their occupational status (see Table 2), with a high frequency of management and teaching professionals.

Languages profile

The array of first and second languages is heterogeneous, including 22 different languages as L1 and nine languages as L2 (see Supplementary Table 2, Supplemental digital Content 1, http://links.lww.com/CLINSPINE/A76 for individual data). There were ten multilingual patients, eight of whom were fluent in a third language and two in a fourth or fifth additional language. Figure 1 depicts the frequency of L1 and L2 languages across patients. 72% of L1 languages belonged to the Indo-European language family, 14% to Sino-Tibetan, 9% to Uralic and 5% to Afro-Asiatic. 67% of L2 languages belong to the Indo-European language family and 11% to Afro-Asiatic, Sino-Tibetan or Japonic language families, respectively.

As shown in Table 3, L1 was the dominant language at time of assessment for 49% of patients. Most patients, even those with L2 perceived as dominant, used L1 on daily basis.

The majority had an early to middle age of L2 acquisition (33% early, 18% middle, and 24% late, with data missing for 3 patients). At the time of diagnosis, many patients used L2 daily, at work and/or at home, with only a minority using it occasionally. Based on qualitative information, most patients could be described as independent or proficient L2 users.

Clinical characteristics

Fourteen patients were diagnosed with nonfluent/agrammatic variant (PPA-G), 6 with semantic variant (PPA-S), and 13 with logopenic variant (PPA-L). As reported on Table 4, the median symptom onset was 2 years (range 1 to 6 years). The first symptom reported was word-finding difficulties in 67% of patients, anomia in 15%, effortful speech in 12% and comprehension problems in 6%. From the patients presenting with word-finding difficulties the majority had a diagnosis of PPA-L, followed by PPA-G and PPA-S. Most patients diagnosed with PPA-S presented initially with naming difficulties. Effortful speech was more frequently the first symptom of PPA-G. About half of published studies did not report data on previous medical history. A minority of patients had a history of traumatic brain injury and vascular risk factors. Information on learning disabilities was missing for almost all previously published patients. One patient reported a probable dyslexia. Nine patients had no information on family history, whereas nine (5 with PPA-L and 4 with PPA-G) had a positive family history of dementia. Excluding speech and language abnormalities, all patients had an otherwise normal neurological examination (missing data n=4). Apraxia of speech (AoS) was reported in 33% of patients, all classified as PPA-G.

Only two patients had no information on structural or functional imaging. Structural neuroimaging (n=27) showed predominantly left frontotemporal atrophy for PPA-G (n=7), predominately left anterior temporal atrophy for PPA-S (n=3), and predominately left temporo-parietal atrophy for PPA-L (n=3). Some cases (n=4) were described as showing global atrophy (PPA-G n=3, PPA-L n=1). Eleven patients had no reported neuroimaging structural abnormalities, the majority of which classified as PPA-L (n=7). Regarding functional neuroimaging (n=20), using fludeoxyglucose (^{18}F) positron emission tomography (FDG-PET) or single-photon emission computed tomography (SPECT), six patients presented with a normal pattern of perfusion in SPECT (PPA-G n= 2 and PPA-L n=4). Patterns of hypoperfusion or hypometabolism paralleled the atrophy patterns; left frontotemporal in PPA-G (n=4), left temporal in PPA-S (n=2), and left or bilateral temporoparietal dysfunction in PPA-L (n=3 or n=4, respectively). Five patients had information on brain amyloid specific biomarkers (cerebrospinal fluid – CSF - or PET imaging), of which three PPA-L patients presented with an AD-compatible CSF biomarker profile (n=2) or positive amyloid PET (n=1). The remaining two patients, classified as PPA-G, had either a negative amyloid PET, or a CSF biomarker profile not consistent with AD. Genetic testing was not available for any of the cases.

Language impairment profiles in L1 and L2

The first symptom was most frequently noticed in L2 (55% for the whole group). Regardless, there was a high degree of agreement (e.g. Spanish-Spanish) between the perceived dominant language and the language in which the first symptom was noticed (63%). Formal assessment in both languages was conducted in 45% of patients.

As shown in Figure 1, the pattern of language severity per domain in each language is heterogeneous. At the time of diagnosis, naming deficits were conspicuous, with similar impairment in both L1 and L2, except for PPA-G where, irrespective of language dominance at the time of testing, L2 appears to be more severely impaired. Comprehension deficits were more severe in L1 in PPA-S than in L2, whereas this pattern was reversed in PPA-G, although global profiles between languages were similar. Severity of repetition deficits were comparable between languages in the different PPA variants. Semantic knowledge performance seemed comparable between languages at the whole-group level, even though there appeared to be a tendency for more severely impaired semantic knowledge in L2 in the PPA-S and PPA-G groups than in L1. In the PPA-L group, deficits appear largely parallel when comparing L1 and L2 along the language domains.

Discussion

The aim of our study was to characterize clinical manifestations and language characteristics of multilingualism of patients with PPA. As shown by our systematic review, reports of multilingual patients with PPA are scarce and limited to single-case analyses. The data we present here represents the largest series assessing clinical and linguistic characteristics of multilingual PPA patients. Besides variability in the clinical and linguistic features of bilingual PPA cases, there is also considerable variability in data availability, which hinders comparisons with larger PPA studies in monolingual patients and limits generalization into different clinical and linguistic contexts.

Our case series is demographically in agreement with data from monolingual PPA reports. The higher frequency of male patients, as well as the mean age in our study, rendering its typical early-onset status, both reflect available epidemiological and clinical data [4]. The lack of comparison group of monolingual patients does not allow us to test the hypothesis of multilingualism as a potential protective factor. And although others have not confirmed the association between a delayed disease onset and bilingualism in PPA individuals [18], evidence from other neurodegenerative syndromes and aetiologies [20,21], warrants the need for future studies to include a monolingual PPA group. The high proportion of teachers in our sample (ca. 20% of the whole sample) is in consonance with a previous study [22] that identified an association between progressive speech and language disorders and the occupation of teaching. The significance of this finding regarding cognitive reserve and risk association remains unclear.

Only one patient had a reported history of a probable learning disability (dyslexia), which has been recognized as a risk factor for PPA [23]. Although medical history was unremarkable for most patients, the role of other possible risk factors, such as traumatic brain injury (for example, one of our PPA-L patients, with a previous history of traumatic brain injury, had an AD-consistent CSF biomarker profile) or cerebrovascular disease, has been less studied in PPA.

Besides the expected speech and language deficits, none of the patients showed significant abnormalities in the neurological examination: specifically, there were no findings suggestive of an associated syndrome within the FTLD spectrum, such as motor-neuron

disease or atypical parkinsonism syndrome, all of which may present at onset with a primary progressive aphasia variant. However, this may be overlooked in a cross-sectional study of baseline characteristics, highlighting the need for longitudinal assessments, especially when considering the variability in PPA clinical trajectory [1]. Only five cases had information on AD-specific biomarkers, which would certainly be informative, particularly for PPA-L cases, given its frequent association with AD pathology [24], as also shown in our data.

We focused our analysis on language impairment profiles based on naming, comprehension, semantic knowledge and repetition tasks. Information on other language domains, such as grammar, although important for correct diagnostic classification [2,25], were scarce, therefore representing an important limitation. Word-finding was the most frequent first symptom, regardless of variant diagnosis, which is not surprising given it is a quite frequent complaint in clinical context, heterogeneous in nature and associated with several neurodegenerative aetiologies, presumably through different cognitive mechanisms and brain network vulnerabilities [26].

The general pattern of language impairment does appear to agree with the shared bilingual neural substrate hypothesis, as at least at the whole-group level, as there was a tendency for parallel deterioration in both languages, in agreement with recent works on AD [9,27,28]. However, the results must be interpreted with caution given the methodological limitations of the study, particularly its limited sample size and lack of control over important linguistic mediating factors. These mediators, such as proficiency levels or the role of language distance, may partially explain differences in patterns of involvement in L1 and L2. As for example, the eventual case of a more severe deficit in comprehension in L2 in the PPA-S group could be explained by a decrease in lexical-semantic access and retrieval, mediated by a combination of mediators presumably associated with L2 (e.g., lower proficiency, later age of acquisition, rarer usage and low cumulative exposition) [14]. Future studies should consider the dynamic aspect of most linguistic mediators, such as proficiency, and include other sources of information, such as measures of cumulative proficiency and dominance. There is some evidence from stroke aphasia that L2 age of acquisition may interact with proficiency and dominance, but overall it has been suggested that proficiency level and current language use may be more reliable determinants in bilingual aphasia, than age of acquisition, at least in specific language processes, such as lexical access [14]. Such dynamic aspects between language mediators are yet to be thoroughly researched in models of language impairment caused by neurodegenerative disorders, such as PPA.

Being a retrospective clinical-based study, most of the data was categorized to facilitate data comparability. This leads to a clear loss of range and statistical limitations, but also possible generalization restrictions, depending on how variables were operationalized. Similarly, through this reductionist approach, possible mediators may lose informative value when only assessed cross-sectionally. This limitation also relates to the difficulty in comparing data from different sources (previously published cases and new cases). Therefore, caution in the interpretation of results is warranted, as perspectives may differ in conceptual and methodological approaches.

Although diverse, particularly for L1, the array of languages included in this study is surely biased, as it does not even represent the most frequently spoken languages in the world or even the most frequent language families. As others have argued [29], such a complex issue calls for the need of a worldwide global view, bearing in mind the complex interaction between multilingualism, cultural and educational factors, migration and dementia.

Nonetheless, the lack of attention given to multilingual PPA is probably associated with several issues, namely the lack of multilingual resources – both clinicians, and assessment tools. There are surely biases associated with how the language assessments themselves were conducted which hinder result interpretation. Formal language assessment in both languages was done for less than half of the patients in our sample. This may itself be a source of bias as available instruments are rarely validated in a multilingual context or this clinical population. We assume that for the remaining cases, the published data were derived mostly from qualitative assessments, based on third-party and patient reports, and from clinical examinations and impressions, which represents a source of considerable bias. The language and cultural background of the examiner may lead to over or underestimation of language deficits in L1 and L2. Beside measures of proficiency [30], there are as well as a few tools developed for the evaluation of language in multilingual contexts, such as the Bilingual Aphasia Test, but these may nonetheless not by sensitive enough to detect subtle deficits, as in mild PPA. The recent development of new tools specifically designed to assess language impairment in neurodegenerative disorders and primary progressive aphasia [31–33] will potentially become useful resources for multilingual PPA, once they are validated into different cultural and linguistic contexts.

The current lack of multilingual resources may also result in diagnostic delays. The shortest symptom onset time in our sample was two years, so we can assume that, at least, for a subsample of patients with longer disease duration, impairment in other cognitive domains was likely. Nevertheless, most studies reviewed here did not describe patient's performance on other cognitive domains, although information on non-verbal functions may improve discrimination between clinical syndromes [34]. The lack of information on other cognitive domains, may have been due to the severity of language impairment, which limits assessment of other cognitive domains with traditional language-based neuropsychological tools. The absence of information on other cognitive domains or behavioural symptoms also makes it difficult to explore the role of executive functions [6], and specifically, executive control, as has been evaluated in bilingual aphasia due to stroke.

Despite several methodological limitations regarding data availability and biases, this work shows that the pattern of impairment in multilingual PPA patients is heterogeneous, with possible discrepancies between first and second languages, thus warranting the need for specific language assessment in both languages. Fundamentally, this study identifies current obstacles for a better understanding of multilingualism in PPA and substantiates the need for a global, prospective and longitudinal study.

The importance of a careful characterization of multilingual PPA patients goes beyond a better understanding of brain-language relationships or reliable clinical classification in predicting underlying pathology. It also comprises significant implications at the therapeutic

level, as some efforts have been undertaken to investigate the efficacy of speech therapy in multilingual PPA [35] following encouraging evidence on monolingual PPA [36–38]. Language deficits have significant implications on the quality of life of patients, and despite the lack of research on the subject, it is nonetheless an area in which early therapeutic interventions, mainly through compensatory strategies, have a recognized benefit [39]. In an increasingly multilingual world, there will be an increasing need for a multilingual approach to assessment and management in PPA, in attempts to improve the reliability of clinical diagnosis and facilitate access to therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mesulam M-M. Primary progressive aphasia and the language network: The 2013 H. Houston Merritt Lecture. Neurology. 2013;81(5):456–462. doi:10.1212/WNL.0b013e31829d87df. [PubMed: 23897873]
2. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76(11):1006–1014. doi:10.1212/WNL.0b013e31821103e6. [PubMed: 21325651]
3. Grossman M Primary progressive aphasia: clinicopathological correlations. Nat Rev Neurol. 2010;6(2):88–97. doi:10.1038/nrneurol.2009.216. [PubMed: 20139998]
4. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. Int Rev Psychiatry. 2013;25(2):130–137. doi:10.3109/09540261.2013.776523. [PubMed: 23611343]
5. Coyle-Gilchrist ITS, Dick KM, Patterson K, et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology. 2016;86(18):1736–1743. doi:10.1212/WNL.0000000000002638. [PubMed: 27037234]
6. Costa A, Sebastián-Gallés N. How does the bilingual experience sculpt the brain? Nat Rev Neurosci. 2014;15(5):336–345. doi:10.1038/nrn3709. [PubMed: 24739788]
7. Bak TH. The impact of bilingualism on cognitive ageing and dementia: Finding a path through a forest of confounding variables. Linguist Approaches to Biling. 2016;6(1–2):205–226. doi:10.1075/lab.15002.bak.
8. Pearce JMS. A note on aphasia in bilingual patients: Pitres' and Ribot's laws. Eur Neurol. 2005;54(3):127–131. doi:10.1159/000089083. [PubMed: 16244484]
9. Costa A, Calabria M, Marne P, et al. On the parallel deterioration of lexico-semantic processes in the bilinguals' two languages: Evidence from Alzheimer's disease. Neuropsychologia. 2012;50(5):740–753. doi:10.1016/j.neuropsychologia.2012.01.008. [PubMed: 22261401]
10. Paradis M Bilingualism and neuropsychiatric disorders. J Neurolinguistics. 2008;21(3):199–230. doi:10.1016/j.jneuroling.2007.09.002.
11. Mendez MF, Perryman KM, Pontón MO, Cummings JL. Bilingualism and dementia. J Neuropsychiatry Clin Neurosci. 1999;11(3):411–412. http://www.ncbi.nlm.nih.gov/pubmed/17125807. [PubMed: 10440021]
12. Stilwell BL, Dow RM, Lamers C, Woods RT. Language changes in bilingual individuals with Alzheimer's disease. Int J Lang Commun Disord. 2016;51(2):113–127. doi:10.1111/1460-6984.12190. [PubMed: 26477451]

13. Groot AMB. Language and Cognition in Bilinguals and Multilinguals: An Introduction. New York, NY: Psychology Press; 2011.
14. Khachatryan E, Vanhoof G, Beyens H, Goeleven A, Thijs V, Van Hulle MM. Language processing in bilingual aphasia: a new insight into the problem. Wiley Interdiscip Rev Cogn Sci. 2016;7(3): 180–196. doi:10.1002/wcs.1384. [PubMed: 26990465]
15. Bak TH, Nissan JJ, Allerhand MM, Deary IJ. Does bilingualism influence cognitive aging? Ann Neurol. 2014;75(6):959–963. doi:10.1002/ana.24158. [PubMed: 24890334]
16. Bialystok E, Craik FIM, Freedman M. Bilingualism as a protection against the onset of symptoms of dementia. Neuropsychologia. 2007;45(2):459–464. doi:10.1016/j.neuropsychologia. 2006.10.009. [PubMed: 17125807]
17. Schweizer TA, Ware J, Fischer CE, Craik FIM, Bialystok E. Bilingualism as a contributor to cognitive reserve: Evidence from brain atrophy in Alzheimer's disease. Cortex. 2012;48(8):991–996. doi:10.1016/J.CORTEX.2011.04.009. [PubMed: 21596373]
18. Alladi S, Bak TH, Shailaja M, et al. Bilingualism delays the onset of behavioral but not aphasic forms of frontotemporal dementia. Neuropsychologia. 2017;99:207–212. doi:10.1016/ j.neuropsychologia.2017.03.021. [PubMed: 28322905]
19. Edwards J Bilingualism and Multilingualism: Some Central Concepts In: Bhatia TK, Ritchie WC, eds. The Handbook of Bilingualism and Multilingualism. Second Blackwell Publishing Ltd; 2013:5–25.
20. Craik FIM, Bialystok E, Freedman M. Delaying the onset of Alzheimer disease: Bilingualism as a form of cognitive reserve. Neurology. 2010;75(19):1726–1729. doi:10.1212/WNL. 0b013e3181fc2a1c. [PubMed: 21060095]
21. Bak TH, Robertson I. Biology enters the scene—a new perspective on bilingualism, cognition, and dementia. Neurobiol Aging. 2017;50:iii–iv. doi:10.1016/j.neurobiolaging.2016.10.020. [PubMed: 27866671]
22. Josephs KA, Papenfuss SM, Duffy JR, et al. Occupational differences between Alzheimer's and aphasic dementias: implication for teachers. Am J Alzheimers Dis Other Demen. 2013;28(6):612–616. doi:10.1177/1533317513494455. [PubMed: 23838322]
23. Rogalski E, Johnson N, Weintraub S, Mesulam M. Increased frequency of learning disability in patients with primary progressive aphasia and their first-degree relatives. Arch Neurol. 2008;65(2): 244–248. doi:10.1001/archneurol.2007.34.Increased. [PubMed: 18268195]
24. Teichmann M, Kas A, Boutet C, et al. Deciphering logopenic primary progressive aphasia: a clinical, imaging and biomarker investigation. Brain. 2013;136(11):3474–3488. doi:10.1093/brain/ awt266. [PubMed: 24108322]
25. Mesulam M-M, Wieneke C, Thompson C, Rogalski E, Weintraub S. Quantitative classification of primary progressive aphasia at early and mild impairment stages. Brain. 2012;135(Pt 5):1537–1553. doi:10.1093/brain/aws080. [PubMed: 22525158]
26. Rohrer JD, Knight WD, Warren JEJD, Fox NC, Rossor MN, Warren JEJD. Word-finding difficulty: a clinical analysis of the progressive aphasias. Brain. 2008;131(Pt 1):8–38. doi:10.1093/brain/ awm251. [PubMed: 17947337]
27. Nanchen G, Abutalebi J, Assal F, Manchon M, Démonet J-FF, Annoni J-MM. Second language performances in elderly bilinguals and individuals with dementia: The role of L2 immersion. J Neurolinguistics. 2017;43:49–58. doi:10.1016/j.jneuroling.2016.09.004.
28. Calabria M, Cattaneo G, Marne P, et al. Language deterioration in bilingual Alzheimer's disease patients: A longitudinal study. J Neurolinguistics. 2017;43:59–74. doi:10.1016/j.jneuroling. 2016.06.005.
29. Bak TH, Alladi S. Bilingualism, dementia and the tale of many variables: Why we need to move beyond the Western World. Commentary on Lawton et al. (2015) and Fuller-Thomson (2015). Cortex. 2016;74:315–317. doi:10.1016/J.CORTEX.2015.04.025. [PubMed: 26537794]
30. Marian V, Blumenfeld HK, Kaushanskaya M. The Language Experience and Proficiency Questionnaire (LEAP-Q): Assessing Language Profiles in Bilinguals and Multilinguals. J Speech, Lang Hear Res. 2007;50(August):940–967. doi:10.1044/1092-4388(2007/067). [PubMed: 17675598]

31. Catricalà E, Gobbi E, Battista P, et al. SAND: a Screening for Aphasia in NeuroDegeneration. Development and normative data. Neurological Sciences. 2017:1–15.
32. Savage S, Hsieh S, Leslie F, Foxe D, Piguet O, Hodges JR. Distinguishing subtypes in primary progressive aphasia: application of the Sydney language battery. Dement Geriatr Cogn Disord. 2013;35(3–4):208–218. doi:10.1159/000346389. [PubMed: 23467307]
33. Ivanova I, Salmon DP, Gollan TH. The multilingual naming test in Alzheimer's disease: clues to the origin of naming impairments. J Int Neuropsychol Soc. 2013;19(3):272–283. doi:10.1017/S1355617712001282. [PubMed: 23298442]
34. Butts AM, Machulda MM, Duffy JR, Strand EA, Whitwell JL, Josephs KA. Neuropsychological Profiles Differ among the Three Variants of Primary Progressive Aphasia. J Int Neuropsychol Soc. 2015;21(06):429–435. doi:10.1017/S1355617715000399. [PubMed: 26067425]
35. Meyer AM, Snider SF, Eckmann CB, Friedman RB. Prophylactic treatments for anomia in the logopenic variant of primary progressive aphasia: cross-language transfer. Aphasiology. 4 2015 http://www.tandfonline.com/doi/abs/10.1080/02687038.2015.1028327. Accessed January 19, 2016.
36. Henry ML, Rising K, DeMarco AT, Miller BL, Gorno-Tempini ML, Beeson PM. Examining the value of lexical retrieval treatment in primary progressive aphasia: Two positive cases. Brain Lang. 2013;127(2):145–156. doi:10.1016/j.bandl.2013.05.018. [PubMed: 23871425]
37. Jokel R, Kielar A, Anderson ND, et al. Behavioural and neuroimaging changes after naming therapy for semantic variant primary progressive aphasia. Neuropsychologia. 2016;89:191–216. doi:10.1016/j.neuropsychologia.2016.06.009. [PubMed: 27297727]
38. Jokel R, Graham NL, Rochon E, Leonard C. Word retrieval therapies in primary progressive aphasia. Aphasiology. 2014;28(8–9):1038–1068. doi:10.1080/02687038.2014.899306.
39. Fried-Oken M, Mooney A, Peters B. Supporting communication for patients with neurodegenerative disease. NeuroRehabilitation. 2015;37(1):69–87. doi:10.3233/NRE-151241. [PubMed: 26409694]

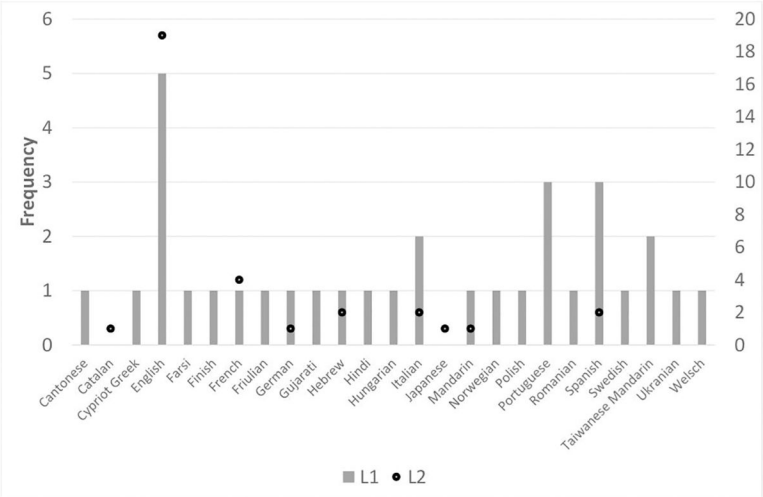

Figure 1. Frequency of L1 and L2 languages

Figure 1 depicts the frequency of L1 (first language) and L2 languages. In total 22 including 22 different languages are represented. English was the most common first language (L1), followed by European Portuguese and Spanish. Most patients' second language (L2) was English (n=19), and besides four French second language-speakers, other second languages included Spanish (n= 2), Italian (n=2), Hebrew (n=2), Catalan, German, Mandarin, and Japanese.

Table 1.

Variable definitions and categories used for data coding

Variable	Categories	Definition/Operationalization
Demographics		
Educational level	Primary	After preschool and before secondary education (usually 4 years)
	Secondary	Lower and junior secondary education (usually 5+3 years)
	Tertiary	Undergraduate and postgraduate education (University, Trade schools, College)
Occupation	Occupation status code	International Standard Classification of Occupations (ISCO)
Clinical characteristics		
First symptom	Wordfinding	Perceived first language symptom, as reported by the patient and/or informant
	Naming	
	Comprehension	
	Effortful Speech	
PPA diagnosis	PPA-G	Nonfluent/agrammatical variant based on current diagnostic criteria
	PPA-S	Semantic variant based on current diagnostic criteria
	PPA-L	Logopenic variant based on current diagnostic criteria
Structural imaging (brain MR/CT)	Normal	Based on clinical or published reporting. Classified as normal, if no abnormalities are reported or considered within normative range.
	Atrophy	Classified as atrophy present if report includes description of global atrophy or specific atrophy pattern (independent of hemispheric predominance)
Functional imaging (brain PET(SPECT)	Normal	Based on clinical or published reporting. Classified as normal, if no abnormalities are reported or considered within normative range.
	Abnormal	Classified as abnormal present if report includes description of hypoperfusion or hypometabolism, independent of pattern or hemispheric predominance. Does not include amyloid-PET imaging results.
Language characteristics		
Dominance	L1, L2 or both	Perceived language usage and knowledge at the time of diagnosis, by patient and/or informant
First symptom language	L1, L2 or both	Language in which the first symptom was noticed by the patient and/or informant
L2 age of acquisition	Early	Childhood
	Middle	Adolescence to early adulthood
	Late	Adulthood
Estimated L2 proficiency	0 (no proficiency)	Interagency Language Roundtable (IRL) scale
	1 (elementary proficiency)	
	2 (limited working proficiency)	
	3 (professional working proficiency)	
	4 (full professional proficiency)	
	5 (native or bilingual proficiency)	
Language usage	Daily at work	Language usage (L1 and L2) at time of diagnosis according to patient and/or informant
	Daily at home	
	Daily at home & work	
	Occasionally	
	Rarely	

Notes. PPA = Primary progressive aphasia; L1 = First language; L2 = Second language

Table 2.

Demographic characteristics per PPA variant

Demographic characteristics	PPA variant			
	Whole Group (=33)	PPA-G (n=14)	PPA-S (n=6)	PPA-L (n=13)
Male sex	60%	62%	83%	46%
Educational level (median, IQR)	3 (1)	2 (1)	3 (0)	3 (0)
Occupational Status (ISCO)				
Managers (ISCO 11)	5 (12%)	2	1	2
Production and specialized services (ISCO 13)	1 (3%)	0	0	1
Science and engineering professionals (ISCO 21)	2 (7%)	1	1	0
Health professionals (ISCO 22)	1 (3%)	1	0	0
Teaching professionals (ISCO 23)	7 (21%)	1	1	5
Legal, social and cultural professionals (ISCO 26)	3 (7%)	1	0	2
Science and engineering associated professionals (ISCO 31)	2 (7%)	2	0	0
Health associated professionals (ISCO 32)	2 (7%)	2	0	0
General and keyboard clerks (ISCO 41)	1 (3%)	0	0	1
Personal service workers (ISCO 51)	2 (7%)	1	0	1
Metal, machinery and related trade workers (ISCO 72)	2 (7%)	1	1	0
Handicraft and printing workers (ISCO 73)	1 (3%)	0	1	0
Stationary plant and machine operators (ISCO 81)	1 (3%)	0	0	1
Cleaners and helpers (ISCO 91)	1 (3%)	1	0	0
n/a	2 (7%)	1	1	0

Notes. Educational level was defined as 1= Primary 2= Secondary 3= Tertiary. PPA-G = Primary progressive aphasia – Agrammatic/Nonfluent variant, PPA-S = Primary progressive aphasia – semantic variant, PPA-L = Primary progressive aphasia – logopenic variant, IQR = Interquartile Range, ISCO = International Standard Classification of Occupations, n/a = not available

Table 3.

Language (L1 and L2) characteristics per PPA variant

	PPA variant			
Language characteristics	**Whole Group (=33)**	**PPA-G (n=14)**	**PPA-S (n=6)**	**PPA-L (n=13)**
Age of exposure L2				
Early	15 (33%)	6 (43%)	2 (33%	7 (54%)
Middle	6 (18%)	4 (28.5%)	0 (0%)	2 (15%)
Late	9 (24%)	4 (28.5%)	1 (17%)	4 (31%)
n/a	3 (9%)	0 (0%)	3 (50%)	0 (0%)
Dominant language at time of diagnosis				
L1	15 (49%)	5 (36%)	5 (83%)	5 (39%)
L2	13 (42%)	6 (43%)	1 (17%)	7 (54%)
Both L1 & L2	5 (9%)	4 (14%)	0 (0%)	1 (7%)
First symptom language				
L1	8 (24%)	3 (21%)	2 (33%)	3 (23%)
L2	18 (55%)	8 (57%)	2 (33%)	8 (62%)
Both L1 & L2	5 (15%)	3 (21%)	0 (0%)	2 (15%)
n/a	2 (0%)	0 (0%)	2 (33%)	0 (0%)

Notes. PPA-G = Primary progressive aphasia – Agrammatic/Nonfluent variant, PPA-S = Primary progressive aphasia – semantic variant, PPA-L = Primary progressive aphasia – logopenic variant, L1 = First language, L2 = Second language

Table 4.

Clinical characteristics per PPA variant

	PPA variant			
Clinical characteristics	**Whole Group (=33)**	**PPA-G (n=14)**	**PPA-S (n=6)**	**PPA-L (n=13)**
Age at onset, mean (SD)	68.55 (7.49)	68.86 (7.74)	66.17 (5.27)	69.31 (7.85)
Symptom onset time, median (IQR)	2 (1)	2 (1)	2.5 (1.75)	3 (1.25)
Apraxia of Speech (AoS), n (%)	7 (21%)	7 (50%)	0 (0%)	0 (0%)
First symptom				
Word finding, n (%)	22 (67%)	8 (57%)	2 (33%)	12 (92%)
Comprehension, n (%)	2 (6%)	0 (0%)	1 (17%)	1 (8%)
Naming, n (%)	5 (15%)	2 (14%)	3 (50%)	0 (0%))
Effortful speech/Articulation, n (%)	4 (12%)	4 (29%	0 (0%)	0 (0%)
Structural imaging (brain MR/CT)				
Normal, n (%)	11 (33%)	3 (21%)	1 (17%)	7 (53%)
Atrophy, n (%)	17 (51%)	10 (71%)	3 (50%)	4 (31%)
Not available, n (%)	5 (15%)	1 (7%)	2 (33%)	2 (23%)
Functional imaging (brain PET/SPECT)				
Normal, n (%)	8 (24%)	2 (15%)	2 (33%)	4 (31%)
Abnormal, n (%)	12 (36%	5 (35%)	0 (0%)	7 (54%)
Not available, n (%)	13 (40%)	7 (50%)	4 (67%)	2 (15%)

Notes. PPA-G = Primary progressive aphasia – Agrammatic/Nonfluent variant, PPA-S = Primary progressive aphasia – semantic variant, PPA-L = Primary progressive aphasia – logopenic variant, SD= standard deviation, MR = magnetic resonance, CT= computerized tomography, PET= Positron emission tomography, SPECT= Single-photon emission computed tomography