Data-driven classification of patients with primary progressive aphasia

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A R T I C L E   I N F O

Keywords:
Primary progressive aphasia
Semantic dementia
Non-fluent aphasia
Logopenic aphasia
Frontotemporal dementia
Alzheimer's disease

A B S T R A C T

Current diagnostic criteria classify primary progressive aphasia into three variants—semantic (sv), nonfluent (nf) and logopenic (lv) PPA—though the adequacy of this scheme is debated. This study took a data-driven approach, applying k-means clustering to data from 43 PPA patients. The algorithm grouped patients based on similarities in language, semantic and non-linguistic cognitive scores. The optimum solution consisted of three groups. One group, almost exclusively those diagnosed as svPPA, displayed a selective semantic impairment. A second cluster, with impairments to speech production, repetition and syntactic processing, contained a majority of patients with nfPPA but also some lvPPA patients. The final group exhibited more severe deficits to speech, repetition and syntax as well as semantic and other cognitive deficits. These results suggest that, amongst cases of non-semantic PPA, differentiation mainly reflects overall degree of language/cognitive impairment. The observed patterns were scarcely affected by inclusion/exclusion of non-linguistic cognitive scores.

1. Introduction

Primary progressive aphasia (PPA) is an umbrella term which refers to a range of patients with neurodegenerative disease in whom language impairments are the most salient and clinically significant feature (Gorno-Tempini et al., 2011; Mesulam, 2001). This broad diagnostic class encompasses individuals in whom language impairments, clinical needs and underlying pathology are all diverse, and thus efforts have been made to sub-divide them into more homogeneous groups. Historically, two distinct PPA syndromes were recognised. In semantic variant PPA (svPPA, often termed semantic dementia), speech remains fluent and largely intact in both phonological and grammatical structure until late in progression; but loss of semantic knowledge results in difficulties in both language comprehension and production (Hodges & Patterson, 2007; Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden, Goulding, & Neary, 1989). Conversely, the defining symptoms of non-fluent/agrammatic variant PPA (nfvPPA) are effortful speech production, speech sound errors and agrammatism (Grossman et al., 1996; Knibb, Xuereb, Patterson, & Hodges, 2006; Ogar, Dronkers, Brambati, Miller, & Gorno-Tempini, 2007). Single-word comprehension typically remains intact in nfvPPA for a considerable time. Both syndromes have been linked with frontotemporal lobar degeneration (FTLD) pathology (Gorno-Tempini et al., 2011).

It has also been known for some time that a substantial proportion of PPA patients fail to show the typical features of either svPPA or nfvPPA, despite presenting with language deficits as the leading clinical symptom. Alzheimer disease (AD) pathology is more common among these individuals (Leyton et al., 2011). These findings led Gorno-Tempini et al. (2004) to propose a third variant – logopenic PPA (lvPPA) – characterised by poor sentence repetition and a loss of fluency that has been attributed to poor verbal working memory rather than the motor speech deficits observed in nfPPA (Gorno-Tempini et al., 2008).

This tripartite division of PPA patients was codified in a set of diagnostic recommendations that set out inclusion and exclusion criteria for each variant (Gorno-Tempini et al., 2011). Doubts have been raised, however, regarding the adequacy of these criteria to capture the full diversity of impairments in PPA. In a recent prospective study of 46 PPA patients, Sajjadi, Patterson, Arnold, Watson, and Nestor (2012) reported that rigorous application of the proposed diagnostic criteria identified only two patients whose linguistic profile was consistent with lvPPA. Furthermore, 41% of patients could not be classified at all, either because they did not meet the requirements for any of the variants or because they qualified for more than one. Studies from other centres have identified somewhat higher proportions of lvPPA patients among their samples but have also found substantial numbers of unclassifiable patients (16% in Gil-Navarro et al., 2013; 17% in Harris et al., 2013; 20% in Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; 24% in Ogar et al., 2008).

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In response to these findings, some authors have proposed a fourth “mixed PPA” class for patients who cannot otherwise be classified, usually because they exhibit a combination of semantic and grammatical impairments (Mesulam & Weintraub, 2014; Sajjadi et al., 2012). In a follow-up investigation by Sajjadi, Patterson, and Nestor (2014), the 14 mixed PPA patients were shown to have a left temporoparietal distribution of atrophy that closely resembled that previously reported for lvPPA. The authors suggested that AD was the most likely underlying pathology in these cases, but that the linguistic profile of Alzheimer-related aphasia is more diverse than that prescribed by the confines of the lvPPA diagnosis.

In the present study, we applied a novel analysis approach to the PPA cohort previously reported by Sajjadi et al. (2012). As discussed earlier, Sajjadi et al. investigated presentations of PPA through rigorous application of the currently accepted diagnostic criteria. Here, we approached the issue of PPA classification from a rather different, data-driven perspective. We applied statistical data-clustering methods that disregarded specific diagnostic criteria and instead grouped patients together if they showed a similar pattern of spared and impaired language and neuropsychological features. This allowed us to ask (a) how many distinct forms of PPA can be identified by a data-analytic technique that is blind to clinical diagnosis and (b) how well do these forms compare with the conventional diagnostic categories currently in use. While some previous studies have used data-clustering approaches to investigate structure within PPA (Knibb et al., 2006; Leyton, Ballard, Piguet, & Hodges, 2014; Machulda et al., 2013; Wicklund et al., 2014), the present study extends this approach in at least three important ways. First, unlike previous studies we used k-means clustering rather than hierarchical cluster analysis to group patients. Hierarchical cluster analysis works by grouping and separating patients at a number of different levels simultaneously. This provides a useful visual guide to the relationships between patients but with the limitation that it is difficult to determine which level of the hierarchy offers the most parsimonious account of the data. In contrast, the k-means technique partitions the cohort into a fixed number of clusters, with the number of clusters controlled by the researcher. The explanatory power of the clustering solution (in terms of percentage of variance explained) can be compared across solutions with different numbers of clusters, allowing the researcher to determine how many clusters are required to provide the most parsimonious account of the data (Jain, 2010). By using this technique, we were able to ask whether the tripartite system advocated by the consensus criteria was supported by the patterns of spared and impaired function in our PPA cohort.

The second advance is that we applied cluster analytic techniques to a large and heterogeneous sample of 43 PPA patients, including those with all of the three proposed variants and those with mixed PPA. This allowed us to assess the existence of coherent symptom groupings across the entire spectrum of PPA. In contrast, previous data-driven analyses have either focused only on lvPPA (Machulda et al., 2013), have excluded svPPA (Leyton et al., 2014) or have only considered unclassifiable patients (Wicklund et al., 2014).

Finally, we considered a wider range of linguistic, cognitive and speech production measures than were included in earlier data-clustering studies or in previous analyses by Sajjadi et al. (2012). In addition to performance on neuropsychological tests of language abilities, we included quantitative measures of connected speech. Speech production is an important part of the clinical picture in PPA and a valuable diagnostic tool, with characteristic changes in speech quality associated with each variant (Ash et al., 2013; Sajjadi, Patterson, Tomek, & Nestor, 2012b; Wilson et al., 2010). We also included tests of non-linguistic cognitive abilities. These do not feature in the current consensus criteria but a number of authors have noted that general cognitive deficits are more common in lvPPA or Alzheimer-related PPA, relative to the other variants (Leyton, Hiieh, Mioshi, & Hodges, 2013; Teichmann et al., 2013). Other studies have reported that non-verbal test scores do not discriminate between pathologically-confirmed cases of FTD and AD (Xiong et al., 2011). Thus, the potential diagnostic value of considering a patient’s extra-linguistic neuropsychological profile remains an open question. By comparing clustering results that included or excluded non-linguistic test scores, we were able to assess whether these measures improved the ability of the clustering algorithm to discriminate distinct forms of PPA.

2. Method
2.1. Participants
Our participants comprised 43 patients with a clinical diagnosis of PPA, prospectively recruited over a two-year period (2009–2011) from memory clinics held at Addenbrooke’s Hospital, University of Cambridge, UK. All patients met the basic criteria for PPA. Non-degenerative pathologies were excluded using MRI, except in three patients who had CT because MRI was contraindicated. These patients were first reported by Sajjadi et al. (2012), who classified them through strict application of the Gorno-Tempini et al. (2011) criteria, by which 14 patients were diagnosed with svPPA, 12 with nvfPPA and 2 with lvPPA. The remaining 15 patients could not be classified, either because they did not meet criteria for any of the proposed variants or because they fitted the criteria for more than one. We refer to these patients as mixed PPA.

In addition, 30 healthy controls were recruited, matched to the patient group for age and educational level. All were free of cognitive symptoms and neurological or psychiatric illnesses and performed normally on the Addenbrooke’s Cognitive Examination – Revised (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006).

2.2. Standard protocol approvals, registrations, and patient consents
Written informed consent was obtained from the participants and, where appropriate, their next of kin. The study was approved by the Cambridge regional ethics committee.

2.3. Neuropsychological and language assessments
Patients and controls completed a detailed neuropsychological battery described by Sajjadi et al. (2012; see Supplementary Tables 1 for full details). This was focused mainly on aspects of linguistic processing impaired in different forms of PPA: repetition and verbal short-term memory, syntax, verbal and non-verbal semantic knowledge and lexical retrieval. In addition, some tests of general cognitive function, visuospatial ability and episodic memory were included. These particular cognitive domains were targeted because it has been suggested that a continuum exists between lvPPA, posterior cortical atrophy and typical AD (Crutch, Lehmann, Warren, & Rohrer, 2013; Migliaccio et al., 2009). It was therefore possible that impairments to visuospatial function and/or episodic memory would be instrumental in distinguishing lvPPA patients from other PPA variants.

In addition, samples of connected speech were recorded from each participant during a picture description task and a semi-structured interview. These were analysed for their linguistic content as described elsewhere (Sajjadi, Patterson, Tomek, & Nestor, 2012a; Sajjadi et al., 2012b; see Supplementary Table 2 for details).

2.4. Statistical analyses
Data entering our analyses comprised scores on the neuropsychological tests and speech markers obtained through analysis of connected speech samples. Prior to analysis, error rates from the speech samples were arcsin-transformed to reduce skew. Where necessary (i.e., in the case of error rates and reaction times) scores were reversed so that higher values always signified better performance.
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