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Reading difficulties in primary progressive aphasia in a regular language-speaking cohort of patients

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ABSTRACT

Reading impairment is an important feature in Primary Progressive Aphasia (PPA). The Spanish orthography entails completely regular spelling to sound correspondences, so reading disorders may be different to English. In the current study, reading, phonological and semantic abilities of 35 patients with the three variants of PPA, and 13 healthy volunteers were assessed. Brain metabolism was concomitantly obtained from each participant using ^{18}F-fluorodeoxyglucose positron emission tomography imaging. Two main patterns of impairment were identified: difficulties in nonwords reading with preservation of exception words in agrammatic and logopenic aphasia, and the inverse pattern in semantic dementia. Left frontal and left parietotemporal regions were associated to nonwords reading, while the anterior temporal lobe was related to reading of exception words. These results support the usefulness of examining reading abilities in the differential diagnosis of PPA variants, and suggest potential types of words that could be used in Spanish to assess these patients.

1. Introduction

Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome in which the first clinical manifestation involves a language disorder (Mesulam et al., 2014). The first reference to this disease dates from 1982 (Mesulam, 1982), and two variants were initially distinguished: nonfluent aphasia, and fluent or semantic dementia. In recent years, a new variant termed logopenic aphasia has also been described (Gorno-Tempini et al., 2004). Although progressive loss of language is common to all three variants, presentation of symptoms differs from one subtype to the other, mainly due to differences in the specific topography of brain damage (Mesulam, 2001; Matías-Guiu and García-Ramos, 2013). In this regard, nonfluent aphasia, or the so-called agrammatic variant, is associated to atrophy of the posterior frontal area and the insula in the left hemisphere, around Broca's area (Brambati et al., 2009); conversely, atrophy in the fluent variant, or semantic dementia, is located in the anterior temporal region, mainly in the left hemisphere (Chan et al., 2001); atrophy in the logopenic variant is mainly limited to the posterior temporo-parietal area on the left hemisphere (Gorno-Tempini et al., 2004).

A group of experts defined the features that characterize each of the three types of PPA (Gorno-Tempini et al., 2011). All three variants exhibit reading impairment (acquired dyslexia). However, there are few studies that have been specifically designed to analyze reading disorders in PPA (Woollams et al., 2007; Brambati et al., 2009; Woollams and Patterson, 2012). Dyslexia itself seems to be different in each variant; for instance, semantic PPA patients have difficulties in reading irregular words (*e.g.* “sew”, which should be pronounced like “sow” and not “sue”), similar to what is observed in surface dyslexia, whilst logopenic and agrammatic PPA patients exhibit greater difficulties in reading unfamiliar words and nonwords, as it happens in phonological dyslexia. Interpretation of these impairments suggests that the former cannot correctly make use of the semantic route, whilst the latter cannot use the sublexical route. Consequently, reading difficulties could be used as another differential symptom for diagnosing each of the PPA variants (Brambati et al., 2009).

It is interesting to evaluate these reading disorders in regular languages and, specifically, Spanish-language is a good model to analyze the reading difficulties of languages with transparent ortographies (Kwork et al., 2016). Transparent orthographies are those in

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which each grapheme corresponds to a phoneme, and one can read it as it is written. This is the opposite of opaque orthographies, such as English. In Spanish, there are few publications in PPA (Gil-Navarro et al., 2013; Matías-Guiu et al., 2014, 2015a), and to the best of our knowledge, reading disorders have not been specifically studied. Given the differences in the correspondence between orthography and phonology and the use of lexical and sublexical processes in reading among English and Spanish (Cuetos and Barbón, 2006; Kwork et al., 2017), some variances could be hypothesized. These facts may lead to some differences in the characteristics of reading disorders or, at least, in the stimuli needed to examine patients.

The main aim of this study was to examine the difficulties that Spanish patients with each of the three variants of PPA exhibit regarding the ability of reading. In this regard, ideally, the gold standard would be to use nonwords to evaluate the sublexical route, whilst irregular words should be used for evaluation of the lexical route. However, irregular words are lacking in Spanish, since all words can be read by transforming graphemes into phonemes, and, for instance, surface dyslexia may be unnoticeable. A potential alternative could be to use foreign words which are commonly used in Spanish (*e.g.*, Hollywood, Google, Renault, *etc.*) (Wilson and Martínez-Cuitiño, 2012). However, these words entail the limitation that they may be familiar for the younger people, but not for the older ones. Another possibility could be to use words in which the stress mark has been deleted. This could represent an interesting approach, given the fact that, in Spanish, stress is governed by rules or pointed out by a stress mark placed over the vowel in the stressed syllable. The stress mark indicates the exception to general rules. For instance, around 64% of Spanish words are stressed on the penultimate syllable (Morales-Font, 2014), and the vast majority of these words end in a vowel, or in "n" or "s". In these words, the stress mark is not necessary. However, words which are stressed on the antepenultimate syllable are very uncommon, and appear in only 8% of cases (Morales-Font, 2014), so all words which are stressed on the antepenultimate syllable need a stress mark (*e.g.*, *cámara*, *bóveda*, *etc.*). If the stress mark is deleted in these words and patients are not familiar with them, they will tend to stress the penultimate syllable (*caMAra, boVEda*, *etc.*). A similar strategy has been previously used in Italian (Rozzini et al., 1997; Colombo et al., 2000). Therefore, in order to assess our first aim and evaluate the reading abilities of patients with each variant of PPA, four types of stimuli were used: regular words, foreign words, words without a stress mark and nonwords. Besides, patients were evaluated with several phonological and semantic tasks, to be able to establish correlations between reading disorders and semantic and phonological abilities.

The second objective of our study was to identify the neurological basis of reading different kinds of words, by correlating difficulties in these activities and brain metabolism measured by neuroimaging. In this regard we know that in the agrammatic variant, atrophy and hypometabolism usually begin at the left posterior fronto-insular area (Gorno-Tempini et al., 2004), also affecting the phonological processing. In semantic dementia, on the other hand, atrophy and hypometabolism usually begin in the anterior temporal region of the left hemisphere (Chan et al., 2001), affecting the ventral circuit responsible for reading familiar words, both regular and irregular. In this case, a more extensive area of atrophy entails greater difficulties in reading irregular words, and greater semantic deficits will be observed in these patients. Finally, in the logopenic variant, atrophy and hypometabolism usually begin at the left temporoparietal area (Gorno-Tempini et al., 2008; Matías-Guiu et al., 2015b), affecting the dorsal pathway responsible for reading nonwords; therefore, a greater atrophy in this region would imply increased difficulties with these stimuli, and a larger deficit in phonological processing. To achieve this second objective ^{18}F-fluorodeoxyglucose positron emission tomography imaging (FDG-PET) was obtained from both patients and healthy subjects.

Our hypothesis was that patients with semantic dementia may have difficulties in reading foreign words and words without stress marks, whilst agrammatic and logopenic patients may have difficulties in reading nonwords. We attempted to find a potential association between scores in reading foreign words and words without stress marks and scores in the semantic tasks on one hand, and the relationship between scores in nonword reading and phonological tasks on the other. We also aimed to find a correlation between scores in reading of each type of word and brain metabolism.

2. Methods

2.1. Participants

Forty-eight subjects were enrolled in this study: 35 patients with PPA (11 with the agrammatic variant, 5 with semantic dementia and 19 with the logopenic subtype) and 13 healthy volunteers. All patients were prospectively recruited from the Department of Neurology of the Hospital Clínico San Carlos (Madrid, Spain) between June 2014 and February 2016. Spanish was the first language for all patients, and only two patients had non-balanced bilingualism. A full clinical and medical history, together with a comprehensive neurological, neuropsychological and language assessment, was performed in all patients, who were then classified into a specific PPA subtype, according to current consensus criteria (Gorno-Tempini et al., 2011). In all cases, the PPA variant was further confirmed with FDG-PET imaging. Controls had no neurological disorders or systemic diseases which could potentially cause neurological impairment. All controls underwent a complete cognitive assessment and ^{18}F-FDG PET imaging, both of which yielded normal results. Table 1 shows the socio-demographic characteristics of the four groups of participants. There were no differences between groups in age, gender and years of education.

The study was approved by the Clinical Research Ethics Committee of the Hospital Clínico San Carlos. All participants signed an informed consent form prior to inclusion in the study.

Table 1
Main demographic and neuropsychological data for each group: mean raw scores (SD).

	PNFA = 11	SD = 5	LPA = 19	Controls = 13
Age (years)	70.4 (8.9)	66.8 (5.2)	76.9 (8.3)	68.9 (12.1)
Gender (F/M)	4/7	3/2	12/7	6/7
Years of education	9.4 (4.9)	14.4 (3.6)	12.1 (5.2)	11.5 (4.0)
MMSE	23.3 (6.2)	22.0 (8.7)	21.8 (6.4)	28.3 (1.7)
FAQ	5.7 (8.2)	6.4 (6)	3.4 (3.5)	0 (0)
CDR	0.4 (0.2)	0.5 (0)	0.4 (0.2)	0(0)
PASS (total score)	5.5 (3.7)	7.4 (5.1)	3.7 (2.8)	0 (0)
Rey Figure (copy)	25.3 (3.8)	32.8 (2.2)	20.9 (8.3)	29.6 (8.1)
Rey Figure (memory 30 min)	8.6 (2.5)	7.5 (3.6)	6.7 (2.3)	9.6 (2.0)
ToL (correct moves)	2.1 (2.7)	2.5 (2.0)	1.7 (1.9)	3.7 (2.4)
VOSP (d-p) (20)	18.3 (2.4)	17.2 (4.8)	18.7 (1.3)	19.3 (1.2)
Boston Naming Test (60)	34 (13)	6 (5.6)	28.0 (12.5)	47.5 (7.3)
Category verbal fluency	6.5 (3.7)	4.2 (4.0)	7.1 (3.2)	17.3 (4.9)
Letter verbal fluency	2.1 (1.5)	6.2 (4.4)	6.6 (3.6)	14.6 (5.3)
Action verbal fluency	3.5 (2.4)	7.0 (5.5)	9.5 (4.2)	16.0 (6.2)
Repetition (syllables) (8)	7.2 (1.5)	8.0 (0.0)	7.7 (0.7)	8.0 (0.0)
Repetition (pairs of syllables)(8)	6.5 (2.3)	7.8 (0.4)	6.9 (1.7)	8.0 (0.0)
Repetition (words) (10)	9.8 (0.6)	9.8 (0.4)	9.6 (0.7)	10.0 (0.0)
Repetition (sentences) (60)	47.8 (9.5)	48.0 (21.4)	38.7 (17.1)	60.0 (0.0)
Buccofacial praxis (20)	16.4 (3.9)	19.2 (1.0)	19.2 (1.8)	20.0 (0.0)

MMSE: Mini-Mental State Examination. FAQ: Functional Activities Questionnaire. CDR: Clinical Dementia Rating. PASS: Progressive Aphasia Severity Score; ToL: Tower of London.
VOSP (d-p): Visual Object Perception Battery (discrimination of position).