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ARTICLE

Speech production differences in English and Italian speakers with nonfluent variant PPA

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Abstract

Objective

To understand whether the clinical phenotype of nonfluent/agrammatic primary progressive aphasia (nfvPPA) could present differences depending on the patient's native language.

Methods

In this cross-sectional study, we analyzed connected speech samples in monolingual English (nfvPPA-E) and Italian speakers (nfvPPA-I) who were diagnosed with nfvPPA and matched for age, sex, and Mini-Mental State Examination scores. Patients also received a comprehensive neuropsychological battery. All patients and 2 groups of age-matched healthy controls underwent an MRI scan with 3D T1-weighted sequences. Connected speech measures and the other cognitive features were compared between patient groups. MRI variables, in terms of gray matter volume, were compared between each patient group and the corresponding controls.

Results

Compared to nfvPPA-E, nfvPPA-I had fewer years of education and shorter reported disease duration. The 2 groups showed similar regional atrophy compatible with clinical diagnosis. Patients did not differ in nonlanguage domains, comprising executive scores. Connected speech sample analysis showed that nfvPPA-E had significantly more distortions than nfvPPA-I, while nfvPPA-I showed reduced scores in some measures of syntactic complexity. On language measures, Italian speakers performed more poorly on syntactic comprehension.

Conclusions

nfvPPA-E showed greater motor speech impairment than nfvPPA-I despite higher level of education and comparable disease severity and atrophy changes. The data also suggest greater grammatical impairment in nfvPPA-I. This study illustrates the need to take into account the possible effect of the individual's spoken language on the phenotype and clinical presentation of primary progressive aphasia variants.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AMAP = adaptive maximum a posteriori; **ANOVA** = analysis of variance; **CAT12** = Computational Anatomy Toolbox; **FOV** = field of view; **GM** = gray matter; **lvPPA** = logopenic variant of primary progressive aphasia; **MMSE** = Mini-Mental State Examination; **MPRAGE** = magnetization-prepared rapid acquisition gradient echo; **nfvPPA** = nonfluent/agrammatic primary progressive aphasia; **nfvPPA-E** = English-speaking patients with nonfluent/agrammatic primary progressive aphasia; **nfvPPA-I** = Italian-speaking patients with nonfluent/agrammatic primary progressive aphasia; **PCC** = posterior cingulate cortex; **PPA** = primary progressive aphasia; **ROI** = region of interest; **SMA** = supplementary motor area; **svPPA** = semantic variant of primary progressive aphasia; **TE** = echo time; **TPM** = tissue probability map; **TR** = repetition time; **UCSF** = University of California, San Francisco; **VBM** = voxel-based morphometry; **WAB** = Western Aphasia Battery.

Current diagnostic guidelines for primary progressive aphasia (PPA) recognize 3 variants: nonfluent/agrammatic PPA (nfvPPA), semantic variant of PPA (svPPA), and logopenic variant of PPA (lvPPA).[1] These variants differ in terms of the affected language domains,[1] distribution of atrophy,[2] and pathologic substrates.[3] Education, bilingualism, rural dwelling, and intrinsic aspects of native language can influence language symptoms in neurodegenerative diseases.[4] The world languages show an enormous amount of variation, although this variation is restricted by a set of universal principles that are presently under investigation.[5–7] Phonology and orthography differences between English and Italian can affect reading deficits, as previously shown in dyslexia[8] and in few cases of semantic aphasia.[9–11] Similarly, we speculate that articulatory and morpho-syntactic differences between languages could affect speech production deficits in nfvPPA. For instance, English is a Germanic language mainly characterized by frequent consonant clusters,[12] while Italian is a Romance language, with prevalent consonant–vowel syllable structure and few consonant clusters.[13] On the other hand, Italian is a highly synthetic language, characterized by the extensive use of inflectional and derivational morphology.[13] Because PPA diagnostic criteria[1] were mostly defined by observations in native English speakers, difference in phenotypic presentation based on intrinsic language features could lead to possible misdiagnosis.

In this study, we compared connected speech samples in monolingual English and Italian speakers with a diagnosis of nfvPPA and compared patterns of speech and language errors between the 2 patient groups. Neuroanatomical differences were also analyzed. We hypothesized that, despite similar brain cortical damage, English-speaking patients with nfvPPA might show a higher number of distortions and motor speech errors, while Italian patients might show more morpho-syntactic difficulties.

Methods

Participants

Thirty-eight patients with nfvPPA (18 Italian native speakers and 20 English native speakers) were studied. Italian-speaking patients with nfvPPA (nfvPPA-I) were prospectively recruited at the Neurology Unit of the San Raffaele Hospital in Milan, Italy. English-speaking patients with nfvPPA (nfvPPA-E) were selected from 44 nfvPPA cases recruited at the Memory and Aging Center at University of California, San Francisco (UCSF) to be age-, sex- and Mini-Mental State Examination (MMSE)–matched with nfvPPA-I. We matched study groups for severity using MMSE, the only objective measure that was available at both sites. We also report disease duration but did not match for it since identification of first symptom, especially subtle linguistic impairment, is highly subjective and can be affected by education level and cultural and social context in each country.[4] Other inclusion criteria at both sites were clinical diagnosis of imaging-supported sporadic nfvPPA,[1] right-handedness, monolingual Italian or English current and native speakers, availability of an audiotaped picture description from the Western Aphasia Battery (WAB),[14] not mute, and sufficiently intelligible speech such that the intended target could be determined for the majority of words. In addition, people were excluded if they had significant medical illnesses or substance abuse that could interfere with cognitive functioning; any other systemic, psychiatric, or neurologic illnesses; or other causes of focal or diffuse brain damage, including cerebrovascular disorders on routine MRI.

Patients received a comprehensive evaluation including structured history and neurologic examination, neuropsychological testing, extensive battery of language tests, and MRI. Clinical diagnosis was based on history, neurologic evaluation, and review of neuroimaging findings (i.e., conventional MRI, CT, and/or PET scans). When available, a non–Alzheimer disease pathology was suggested by CSF biomarkers or amyloid PET. Sixty-nine right-handed age- and sex-matched monolingual Italian (n = 38) or English (n = 31) speakers were recruited as healthy controls at both centers among spouses of patients and by word of mouth. Healthy controls underwent a multidimensional assessment, including neurologic and neuropsychological evaluation, and were included only if results were in the normal range.

Standard protocol approvals, registrations, and patient consents

The local ethical standards committee on human experimentation approved the study protocol and all participants or their caregivers provided written informed consent prior to study inclusion.

Neuropsychological assessment

At each center, patients with nfvPPA underwent a comprehensive neuropsychological evaluation as described previously for Italian[15,16] and English[3,17] languages (table 1).

The evaluation of language included the examination of confrontation naming with subtests from the CaGi battery (nfvPPA-I) and the 15-item version of the Boston Naming Test (nfvPPA-E); object knowledge with the Pyramids and Palm Trees Test; single-word comprehension with word–picture matching tests from CaGi battery (nfvPPA-I) and a subtest of the WAB (nfvPPA-E); visual and auditory comprehension of syntactically complex sentences with the Token test, the subtests from the BADA battery (nfvPPA-I), and the syntax comprehension test (nfvPPA-E); and repetition with the subtest of Aachener Aphasie Test (nfvPPA-I) and a subtest of the WAB (nfvPPA-E). To evaluate connected speech production, patient speech samples were recorded while the patients described the image of the picnic picture subtest of the WAB.

Table 1 Demographic, clinical, and language features of patients with primary progressive aphasia and healthy controls

	nfvPPA-E	nfvPPA-I	*p* nfvPPA-E vs nfvPPA-I	95% CI
N	20	18	—	
Age, y	68.94 ± 6.27	69.18 ± 7.68	0.916	−4.42, 4.90
Female sex, n (%)	15 (75)	12 (67)	0.724	
Disease duration, y	3.85 ± 1.57	2.35 ± 1.06	0.002[a]	−2.38, −0.62
Education, y	16.10 ± 3.16	9.17 ± 5.27	<0.001[a]	−9.87, −4.00
MMSE	25.90 ± 2.97	24.44 ± 3.97	0.214	−3.80, 0.89
CSF, Aβ42[b]	—	753.82 ± 177.78	—	
CSF, t-tau[b]	—	285.27 ± 184.20	—	
CSF, p-tau[b]	—	42.32 ± 10.54	—	
Amyloid PET positive (%)	0 (0)	—	—	
Memory				
RAVLT, immediate	−2.00 ± 2.27	−1.82 ± 1.74	0.789	−1.20, 1.56
RAVLT, delayed	−1.09 ± 1.93	−0.84 ± 1.72	0.686	−1.00, 1.51
Complex figure, recall	−0.63 ± 1.49	−0.53 ± 1.36	0.834	−0.87, 1.07
Executive functions				
Digit span, backward	−1.79 ± 1.28	−1.69 ± 1.76	0.872	−1.13, 1.32
Phonemic fluency	−2.38 ± 0.68	−2.00 ± 0.71	0.109	−0.09, 0.85
Semantic fluency	−2.27 ± 1.21	−1.76 ± 1.37	0.250	−0.37, 1.37
Language				
Confrontation naming	−1.58 ± 1.78	−3.37 ± 5.16	0.190	−4.53, 0.96
Single word comprehension	−1.50 ± 2.25	−0.22 ± 1.29	0.050	0.01, 2.54
Object knowledge	−1.08 ± 1.82	−0.14 ± 1.24	0.110	−0.23, 2.11
Repetition	−10.11 ± 9.08	−7.05 ± 9.11	0.307	−2.94, 9.06
Syntactic comprehension, auditory	−0.35 ± 1.15	−16.13 ± 17.52	0.003[a]	−25.12, −6.43
Syntactic comprehension, visual	−2.90 ± 4.05	−10.26 ± 13.08	0.04[a]	−14.64, −0.09

Abbreviations: Aβ = β-amyloid; CI = confidence interval; MMSE = Mini-Mental State Examination; nfvPPA-E = English-speaking patients with nonfluent/agrammatic primary progressive aphasia; nfvPPA-I = Italian-speaking patients with nonfluent/agrammatic primary progressive aphasia; p-tau = phosphorylated tau; RAVLT = Rey Auditory Verbal Learning Test; t-tau = total tau.
Values are mean ± SD (or frequencies). CI denotes confidence intervals of differences. Cognitive scores are expressed as *z* scores based on normative values. *p* Values refer to *t* test models or Fisher exact test.
[a] Significant at $p < 0.05$.
[b] Data available for 11 (61%) nfvPPA-I. CSF cutoff = Aβ42 > 500 ng/L (values below are considered abnormal); t-tau = 0–450 ng/L and p-tau = 0–61 ng/L (values above are considered abnormal).

Quantitative analysis of speech samples

The speech sample was the picnic picture description component of the WAB.[14] Patients were instructed as follows: "Take a look at this picture, tell me what you see, and try to talk in sentences." Speech samples were audiorecorded using Audacity software (audacity.sourceforge.net) and analyzed according to a previously described quantitative procedure.[18] We investigated 4 different aspects of the speech samples: (1) speech rate and speech sound errors, (2) other disruptions to fluency, (3) lexical content, and (4) syntactic structure and complexity. Specifically, the following measures were recorded:

1. Speech rate and speech sound errors: total duration of the sample, duration of pauses, duration of the sample without pauses, total number of words, speech production rate (total number of words/duration of the sample without pauses), distortions, phonologic paraphasias and neologisms, motor speech rate ([number of distortions/number of words] × 100)
2. Other disruptions to fluency: false starts, filled pauses, repaired sequences, incomplete sequences
3. Lexical content: open class words, closed class words, verbs, nouns, open class proportion (open class words/closed class words), verb proportion (verbs/verbs + nouns)
4. Syntactic structure and complexity: number of utterances (i.e., a sequence of words not interrupted by a pause lasting more than 2 seconds, whose boundaries could be identified on the basis of prosodic cues; an utterance could then correspond to a word, a phrase, a part of a phrase or a sentence), number of sentences (i.e., a syntactic structure including at least a subject and a verb), number of words in sentences, mean length of sentence (number of words in sentences/number of sentences), proportion of sentences (number of sentences/number of utterances), number of embeddings, morphosyntactic errors, syntax production rate (number of words in sentences/number of words), morphosyntactic error rate (number of morphosyntactic errors/number of words in sentences), semantic errors.

MRI acquisition

In both centers, all participants underwent a brain MRI scan with 3D T1 sequences.

nfvPPA-I

Brain MRI scans were obtained using a 3.0T scanner (Intera, Philips Medical Systems, Best, the Netherlands). The following sequence was acquired: 3D T1-weighted fast field echo (repetition time [TR] 25 ms, echo time [TE] 4.6 ms, flip angle 30, 220 contiguous axial slices with voxel size 0.89 × 0.89 × 0.8 mm, matrix size 256 × 256, field of view [FOV] 230 × 182 mm^2).

nfvPPA-E

Brain MRI scans were obtained using 1.5T (Magnetom VISION; Siemens, Munich, Germany), 3.0T (Trio; Siemens), or 4.0T Bruker (Billerica, MA)/Siemens scanners. The following sequences were acquired: (1) 1.5T scanner: T1-weighted volumetric magnetization-prepared rapid acquisition gradient echo (MPRAGE) (TR 10 ms, TE 4 ms, flip angle 15, 154 contiguous coronal slices with voxel size 1 × 1 × 1.5 mm); (2) 3.0T scanner: T1-weighted volumetric MPRAGE (TR 23 ms, TE 2.98 ms, flip angle 9, 160 contiguous sagittal slices with voxel size 1 × 1 × 1 mm, FOV 256 × 256 mm^2); (3) 4.0T scanner: T1-weighted volumetric MPRAGE (TR 2330 ms, TE 3 ms, flip angle 7, 157 continuous sagittal slices with voxel size 1 × 1 × 1 mm^3).

MRI analysis

Whole-brain and region of interest (ROI) analyses were conducted to investigate potential differences between nfvPPA-E and nfvPPA-I vs controls and vs each other. For the neuroimaging portion of the study, 1 nfvPPA-E and 4 healthy participants in the Italian cohort failed the quality check and were excluded from the analyses.

Voxel-based morphometry (VBM) analysis

Structural MRI data were preprocessed using the Computational Anatomy Toolbox (CAT12; dbm.neuro.uni-jena.de/cat) in Statistical Parametric Mapping software (SPM12; www.fil.ion.ucl.ac.uk/spm/software/spm12) using MATLAB version R2017b. CAT12 classifies T1-weighted data as gray matter (GM), white matter, or CSF using an improved segmentation approach compared to the traditional unified segmentation,[19] based on an adaptive maximum a posteriori (AMAP) technique without the need for a priori information on the tissue probabilities. This means that the tissue probability maps (TPMs) are only used for spatial normalization, initial skull-stripping, and as initial segmentation estimate. The subsequent AMAP estimation is adaptive in the sense that local variations of the measures (i.e., means and variance) are modeled as slowly varying spatial functions.[20] This accounts not only for intensity inhomogeneities, but also for other local intensity variations. In addition, the segmentation approach uses a partial volume estimation with a simplified mixed model of a maximum of 2 tissue types.[21] GM probability maps were nonlinearly normalized to the Montreal Neurologic Institute space using DARTEL,[22] modulated by the Jacobian determinant of the deformations derived from the spatial normalization, and smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum.

ROI analysis

For each participant, mean GM volumes in left-lateralized ROIs were extracted. ROIs were obtained from the Juelich and Harvard-Oxford atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and were chosen independently from the VBM results and based on previous evidence: pars opercularis and pars triangularis of the inferior frontal gyrus, premotor cortex, anterior insula, pre–supplementary motor area (SMA), SMA, striatum, angular and supramarginal gyri, and finally the posterior cingulate cortex (PCC) as a control region.

Statistical analysis

Demographic, clinical, and cognitive data

Participant characteristics were compared between groups using *t* test models or Fisher exact test. In order to make the cognitive data comparable between groups, we transformed raw performance scores of the neuropsychological assessment into *z* scores by using normative data of age-, sex-, and education-matched populations of healthy Italian-speaking and English-speaking controls. The measures extracted from the speech samples were compared between groups as raw scores accounting for patients' years of education.

MRI data

VBM analysis

Inferential statistic was performed on the smoothed-modulated GM TPM using a voxel-by-voxel 2 × 2 analysis of variance (ANOVA) with 2 levels per factor (factor 1 = site – levels = UCSF, Milan; factor 2: group – levels = nfvPPA, healthy controls) including age, sex, whole brain total GM volume, and MRI scanner type (3.0T Philips; 1.5T and 3.0T Siemens; 4.0T Bruker/Siemens) as covariates. Each group of patients was compared against the matched healthy controls and a group × site interaction was performed in order to investigate differences between US and Italian patient groups. The statistical threshold was applied at $p < 0.05$ after family-wise error correction for multiple comparisons over the whole brain and k > 100 for cluster extent.

ROI analysis

A 2 × 2 ANOVA factorial design (the same as for VBM) was run for each ROI accounting for age, sex, whole brain total GM volume, and scanner type as covariates using MATLAB (Statistics and Machine Learning Toolbox). The same contrasts as for VBM were performed. The statistical threshold was set at $p < 0.05$ uncorrected and Bonferroni corrected for multiple comparisons over the number of tests performed (i.e., 10, one per each ROI; this set the corrected *p* value to 0.005 [0.05/10]).

Data availability

The dataset used and analyzed during the current study is available from the corresponding author upon request to qualified researchers (i.e., affiliated with a university or research institution/hospital).

Results

Demographic, clinical, and cognitive data

Table 1 shows demographic, clinical, and cognitive data. Patient groups were matched for age, sex, and performances on the tests assessing global cognition (MMSE), memory, and executive functions (table 1). nfvPPA-E had longer disease duration, while nfvPPA-I had fewer years of education and performed worse on tests assessing syntactic comprehension (table 1). The remaining language features were similar between groups.

Table 2 shows the quantitative features of connected speech production. The nfvPPA-E showed higher number of distortions and greater motor speech rate, while the nfvPPA-I presented with a higher number of phonologic paraphasias and utterances, and reduced mean length of sentences (table 2). Concerning distortions, nfvPPA-E produced a total of 187 distortions. Among those that were ascribable to recognizable words (n = 158), 140 (89%) were consonant (singleton or cluster) distortions, the remaining were vowel distortions. nfvPPA-I produced a total of 10 distortions; among those that were ascribable to recognizable words (n = 6), all were consonant (singleton or cluster) distortions.

MRI

VBM analysis

Table 3 and figure 1 show reduced GM volume in each group of patients compared to controls. In both groups, patients showed atrophy at the left hemisphere in the opercularis portion of the inferior frontal gyrus, pre-SMA, precentral gyrus, thalamus, insula, and hippocampus. Atrophy extended also to the left caudate nucleus in nfvPPA-I and to the left postcentral gyrus in the nfvPPA-E. We did not find a group × site significant interaction, thus no differences between patient groups were observed.

ROI analysis

Table 4 and figure 2 show the ROI volume reduction in patients compared with controls. In both groups, patients showed reduced GM volumes of the left pars opercularis of the inferior frontal gyrus, premotor cortex, anterior insula, pre-SMA, angular gyrus, and striatum. nfvPPA-E showed an involvement of the left supramarginal gyrus that was also near significance in the nfvPPA-I group. The remaining ROI volumes, including PCC, were similar to those of healthy controls. No group × site interaction was observed.

Discussion

We compared 2 cohorts of patients with nfvPPA who were native speakers of Italian or English with the aim of assessing the presence of language-specific phenotypic differences. During connected speech samples, nfvPPA-E showed higher numbers of distortions. nfvPPA-I had reduced mean length of sentences and showed greater difficulty in syntax comprehension. These findings occur in patients with similar cognitive impairment, disease severity, and brain atrophy, and while controlling for differences in education level. These results highlight the need of taking into consideration linguistic and cultural differences when evaluating patients with neurodegenerative disorders and suggest that PPA diagnostic criteria defined by symptoms of English-speaking patients might be less effective for diagnosing individuals speaking other languages.

nfvPPA-E produced more phonetic distortions, in terms of absolute numbers and in proportion of total number of produced words, compared to nfvPPA-I. This greater impairment

Table 2 Quantitative features of connected speech production

	nfvPPA-E	nfvPPA-I	*p* nfvPPA-E vs nfvPPA-I	95% CI
N	20	18		
Speech rate and speech sound errors				
Total duration	153.13 ± 82.68	124.22 ± 51.74	0.457	−38.56, 83.89
Duration of pauses	69.18 ± 42.62	62.97 ± 45.17	0.188	−12.69, 62.21
Duration of the sample without pauses	75.79 ± 86.29	61.25 ± 26.65	0.886	−59.53, 51.61
Total no. of words	99.15 ± 119.74	75.11 ± 30.04	0.681	−90.04, 59.45
Speech production rate	1.55 ± 0.62	1.33 ± 0.42	0.740	−0.38, 0.54
Distortions	9.84 ± 9.01	0.56 ± 1.69	0.001[a]	5.01, 16.34
Phonologic paraphasias and neologisms	0.84 ± 1.34	8.89 ± 10.23	0.028[a]	−13.27, −0.80
Motor speech rate	19.75 ± 21.41	0.95 ± 2.89	<0.001[a]	11.73, 37.85
Other disruptions to fluency				
False starts	1.95 ± 2.30	4.67 ± 8.42	0.169	−8.94, −1.63
Filled pauses	7.32 ± 7.10	4.72 ± 6.98	0.901	−5.63, −6.34
Repaired sequences	3.45 ± 4.41	7.50 ± 9.81	0.188	−10.77, 2.20
Incomplete sequences	0.50 ± 1.05	0.33 ± 0.49	0.674	−0.85, 0.56
Lexical content				
Open class words	37.10 ± 34.38	30.28 ± 11.23	0.676	−26.41, 17.34
Closed class words	62.05 ± 85.79	46.17 ± 24.99	0.717	−64.24, 44.66
Verbs	14.05 ± 16.89	10.22 ± 6.93	0.755	−12.76, 9.33
Nouns	31.95 ± 38.72	20.44 ± 9.59	0.975	−24.65, 23.90
Open class proportion	0.45 ± 0.16	0.43 ± 0.11	0.596	−0.09, 0.15
Verb proportion	0.29 ± 0.11	0.33 ± 0.21	0.582	−0.19, 0.11
Syntactic structure and complexity				
No. of utterances	15.20 ± 11.71	26.56 ± 9.05	0.004[a]	−22.84, −4.71
No. of sentences	10.40 ± 12.71	8.50 ± 5.57	0.467	−11.27, 5.28
No. of words in sentences	84.60 ± 122.51	40.44 ± 30.61	0.954	−77.61, 73.33
Mean length of sentences	7.05 ± 2.34	4.37 ± 1.59	0.032[a]	0.17, 3.57
Proportion of sentences	0.63 ± 0.36	0.34 ± 0.24	0.211	−0.10, 0.42
Embeddings	1.90 ± 3.58	1.44 ± 1.69	0.329	−3.46, 1.19
Morphosyntactic errors	4.30 ± 4.51	3.78 ± 3.44	0.095	−0.51, 6.08
Syntax production rate	0.69 ± 0.34	0.47 ± 0.31	0.527	−0.19, 0.36
Morphosyntactic error rate	0.19 ± 0.29	0.28 ± 0.79	0.487	−0.32, 0.67
Semantic errors	0.95 ± 1.32	2.17 ± 2.26	0.591	−1.93, 1.12

Abbreviations: CI = confidence interval; nfvPPA-E = English-speaking patients with nonfluent/agrammatic primary progressive aphasia; nfvPPA-I = Italian-speaking patients with nonfluent/agrammatic primary progressive aphasia.
Values are mean ± SD. CI denotes confidence intervals of differences. *p* Values refer to univariate general linear models that account for education. Speech production rate = total number of words/duration of the sample without pauses; motor speech rate = (number of distortions/number of words) × 100; open class proportion = open class words/closed class words; verb proportion = verbs/verbs + nouns; mean length of sentence = number of words in sentences/number of sentences; proportion of sentences = number of sentences/number of utterances; syntax production rate = number of words in sentences/number of words; morphosyntactic error rate = number of morphosyntactic errors/number of words in sentences.
[a] Significant at $p < 0.05$.

Table 3 Voxel-based morphometry

	Hemisphere	Coordinates			T score
		x	y	z	
nfvPPA-E vs healthy controls					
opIFG	Left	−53	8	20	4.6
Precentral gyrus	Left	−43	7	31	4.6
Postcentral gyrus	Left	−50	11	35	4.8
Insula	Left	−36	11	8	4.8
Pre-SMA	Left	−6	15	51	4.8
Thalamus	Left	−13	−16	12	3.5
Hippocampus	Left	−38	−24	−14	5.6
nfvPPA-I vs healthy controls					
opIFG	Left	−55	9	17	5.3
Precentral gyrus	Left	−39	1	42	5
Insula	Left	−40	9	5	5.7
Pre-SMA	Left	0	24	51	4
Thalamus	Left	−16	−12	15	7.8
Caudate nucleus	Left	−12	11	11	4.7
Hippocampus	Left	−36	−28	−9	4.4

Abbreviations: opIFG = pars opercularis of the inferior frontal gyrus; nfvPPA-E = English-speaking patients with nonfluent/agrammatic primary progressive aphasia; nfvPPA-I = Italian-speaking patients with nonfluent/agrammatic primary progressive aphasia; SMA = supplementary motor area.
Montreal Neurologic Institute coordinates of the significant clusters show gray matter loss in each group of patients with nfvPPA compared with healthy controls. Results are shown at $p < 0.001$ family-wise error corrected at peak level over the whole brain and k > 100 for cluster extent accounting for age, sex, scanner, and whole brain total gray matter volume. Color map represents T scores.

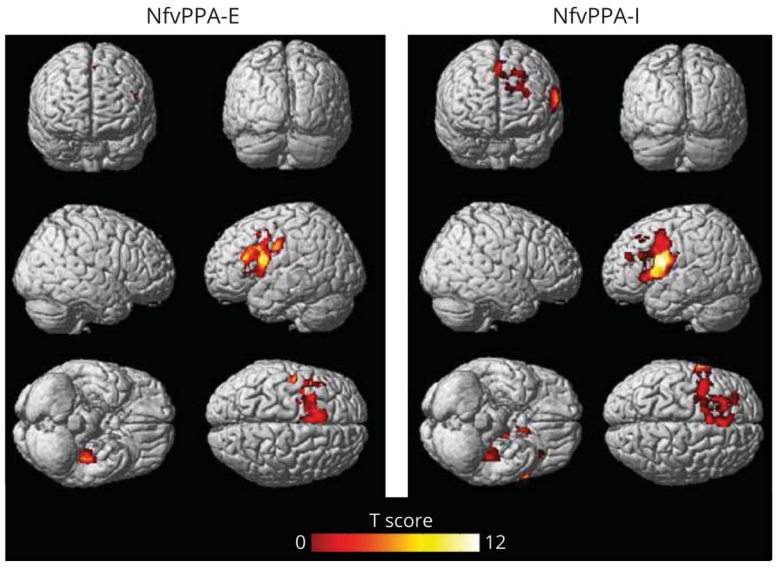
is compatible with the hypothesis that frequent consonant clusters typical of the English language might create a greater motoric challenge for a degenerating motor speech planning system. On the other hand, the prevalence of consonant–voxel sequences in Italian words might influence the greater number of phonologic paraphasias in nfvPPA-I. This issue is relevant for PPA differential diagnosis in Italian patients because, in the English description of the disorder,[18] phonologic paraphasias are considered more common in the logopenic variant.

We observed that, compared to English-speaking patients, nfvPPA-I showed reduced complexity of speech production by limiting the number of words in sentences, even after controlling for educational level. A similar argument as described above can apply and we speculate that this difference might reflect difficulties related to the higher demands of the highly synthetic Italian language compared to English. As we discuss below, the lower education level of the Italian cohort, although controlled for in the analyses, could be a confounding factor of this result.

The idea that language-specific features affect the clinical phenotypes of the same disorder in different languages has been reported previously. In developmental dyslexia, the Italian relatively transparent alphabetic system leads to better reading scores in Italian-speaking patients compared to English-speaking and French-speaking dyslexic patients, despite a similar pattern of altered brain activations.[23] Similarly, the same system influences the manifestation of reading errors in acquired language disorders,[9,10] such as svPPA with anterior temporal atrophy.[11] In svPPA, the more phonologically opaque alphabetic structure of English is reflected in the regularization errors that English-speaking patients make when reading atypically spelled words (e.g., "choir" for "quire" [kwaɪə]).[12] On the other hand, in Italian, the only irregularity in converting written words to utterances mainly regards stress assignment.[13] Word stress predominantly falls on the heavy penultimate syllable; words without a heavy penultimate syllable are phonologically unpredictable and thus necessitate being lexically/semantically marked.[9,10] Therefore, the typical errors that Italian patients with svPPA make when reading aloud are stress assignment errors (e.g., "tavòlo" for "tàvolo"). Gogi aphasia is another example of a unique presentation of a lexical/semantic reading disorder in Japanese speakers who make errors only in the nonphonetic kanji script.[24,25]

In the present study, nfvPPA-I had fewer years of education and shorter reported disease duration (despite similar disease

Figure 1 Gray matter atrophy detected by voxel-based morphometry in patients with nonfluent/agrammatic primary progressive aphasia (nfvPPA) compared with healthy controls



Brain regions show gray matter loss in each group of patients with nfvPPA compared with healthy controls. Results are overlaid on a 3D rendering of the Montreal Neurological Institute standard brain at $p < 0.05$ after family-wise error correction for multiple comparisons over the whole brain and k > 100 for cluster extent accounting for age, sex, scanner, and whole brain total gray matter volume. Color map represents T scores. E = English; I = Italian.

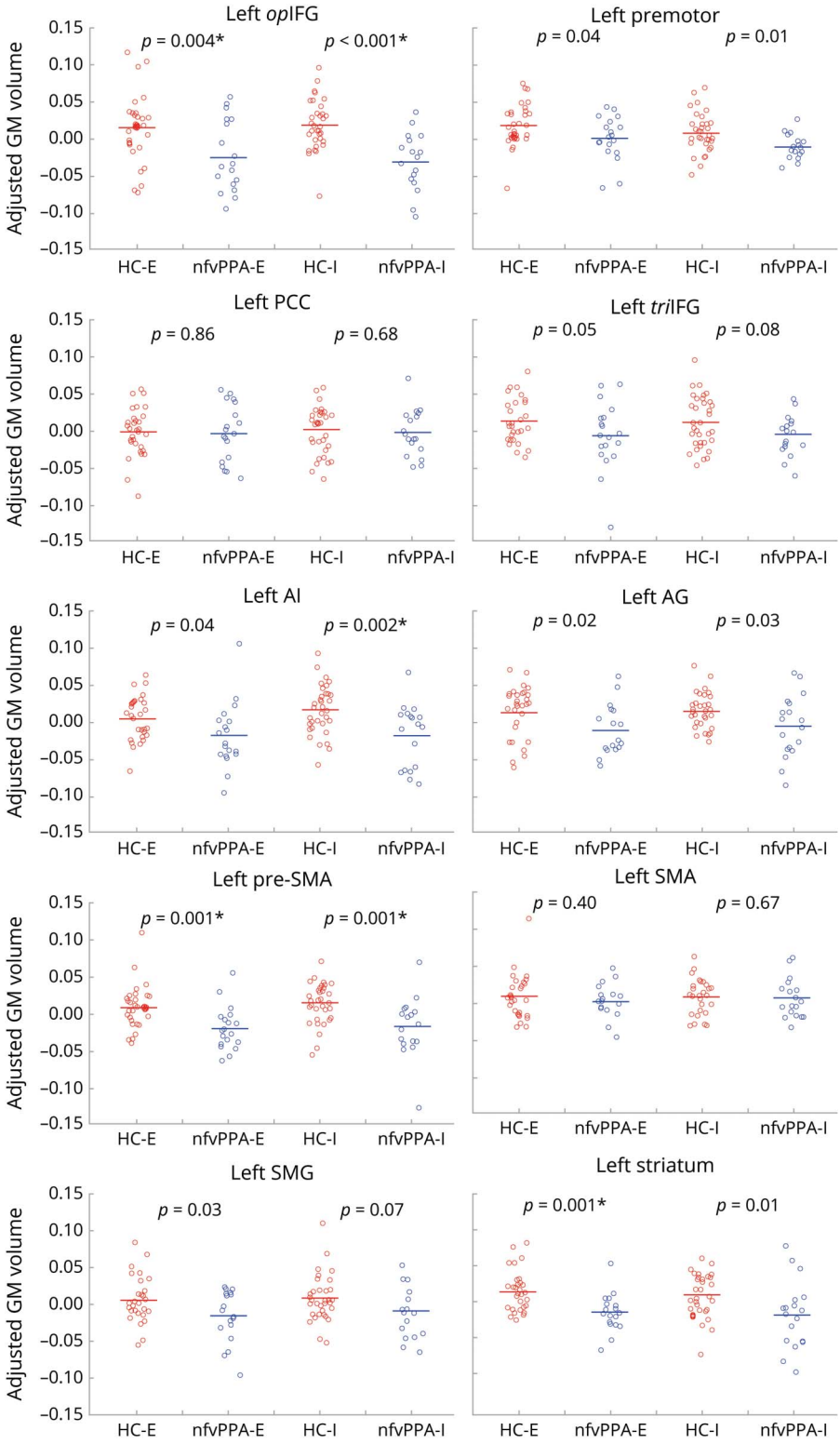
severity) compared to nfvPPA-E. Level of education is one of the main determinants of the so-called cognitive reserve, influencing disease duration and severity. While this difference can affect the results of the analyses, our main finding is that the group with lower education (the Italian group) showed milder, and in some case absent, motor speech impairment. Our study cannot provide evidence regarding the nature of cognitive reserve in our 2 experimental groups since patients were explicitly matched for age and general disease severity (MMSE). An effect of education on cognition and disease progression can be hypothesized since the Italian native speakers group reached similar disease severity as that of the US group in a shorter time. However, we cannot exclude a bias in the highly subjective estimation of symptom onset or that lower performances on syntactic production in nfvPPA-I is due to their lower education level.

Table 4 Gray matter volumes in left-lateralized a priori defined regions of interest in healthy controls and in patients with nonfluent variant of primary progressive aphasia for each of the study sites

	HC-E	nfvPPA-E	*p* Value–E	95% CI	HC-I	nfvPPA-I	*p* Value–I	95% CI
AG	0.39 ± 0.05	0.35 ± 0.04	0.02	0.003, 0.05	0.34 ± 0.04	0.31 ± 0.05	0.03	0.002, 0.04
Premotor	0.27 ± 0.03	0.24 ± 0.03	0.04	0.001, 0.04	0.21 ± 0.04	0.17 ± 0.02	0.01	0.01, 0.03
opIFG	0.36 ± 0.05	0.31 ± 0.05	0.004[a]	0.01, 0.07	0.34 ± 0.04	0.28 ± 0.04	<0.001[a]	0.03, 0.07
triIFG	0.35 ± 0.04	0.32 ± 0.05	0.05	−0.001, 0.04	0.31 ± 0.04	0.28 ± 0.04	0.08	−0.002, 0.04
AI	0.51 ± 0.04	0.47 ± 0.06	0.04	0.001, 0.04	0.49 ± 0.05	0.43 ± 0.05	0.002[a]	0.01, 0.06
PCC	0.34 ± 0.05	0.32 ± 0.04	0.86	−0.02, 0.02	0.31 ± 0.04	0.29 ± 0.04	0.68	−0.02, 0.02
Pre-SMA	0.32 ± 0.04	0.28 ± 0.03	0.001[a]	0.01, 0.05	0.29 ± 0.04	0.24 ± 0.04	0.001[a]	0.01, 0.05
SMA	0.29 ± 0.04	0.27 ± 0.03	0.40	−0.01, 0.02	0.26 ± 0.04	0.24 ± 0.04	0.67	−0.01, 0.02
SMG	0.36 ± 0.04	0.32 ± 0.04	0.03	0.002, 0.04	0.32 ± 0.05	0.28 ± 0.05	0.07	−0.001, 0.04
Striatum	0.35 ± 0.04	0.31 ± 0.03	0.001[a]	0.01, 0.04	0.30 ± 0.03	0.26 ± 0.05	0.01	0.01, 0.05

Abbreviations: AG = angular gyrus; AI = anterior insula; CI = confidence interval; E = English; HC = healthy controls; I = Italian; nfvPPA-E = English-speaking patients with nonfluent/agrammatic primary progressive aphasia; nfvPPA-I = Italian-speaking patients with nonfluent/agrammatic primary progressive aphasia; opIFG = pars opercularis of the inferior frontal gyrus; PCC = posterior cingulate cortex; SMA = supplementary motor Area; SMG = supramarginal gyrus; triIFG = pars triangularis of the inferior frontal gyrus.
Values of tissue probability are mean ± SD. CI denotes confidence intervals of differences. *p* Values refer to *t* test models accounting for age, sex, scanner, and whole brain total gray matter volume.
[a] *p* Values < 0.005 denote significance between groups at each site Bonferroni corrected for multiple comparisons (uncorrected *p* value/number of regions = 0.05/10).

Figure 2 Plots of gray matter (GM) volumes of regions of interest (ROIs) in patients with nonfluent/agrammatic primary progressive aphasia (nfvPPA) and healthy controls



Plots of GM volumes in a priori defined ROIs in healthy controls (in red) vs patients with nfvPPA (in blue) for each of the study sites. GM volume values represent the residuals of a general linear model (GLM) taking into account age, sex, scanner, and whole brain total GM volume. *p Values < 0.005 denote significance between groups at each site Bonferroni corrected for multiple comparisons (uncorrected p value/number of regions = 0.05/10), accounting for age, sex, scanner, and whole brain total GM volume. AG = angular gyrus; AI = anterior insula; E = English; HC = healthy controls; I = Italian; opIFG = pars opercularis of the inferior frontal gyrus; PCC = posterior cingulate cortex; SMA = supplementary motor area; SMG = supramarginal gyrus; triIFG = pars triangularis of the inferior frontal gyrus.

The current diagnostic criteria for PPA[1] are mainly based on deficits seen in the English-speaking patients. As a result, the criteria may not entirely capture the speech and language changes that occur in non-English native speakers. Specifically, nfvPPA diagnosis can be considered when 1 of the 2 core features, among agrammatism in language production and

presence of motor speech deficits (apraxia of speech and dysarthria), is satisfied.[1] Although a diagnosis of nfvPPA was still possible, most of the Italian cases presented in this study satisfied only 1 of these core features (agrammatism) despite similar pattern of brain atrophy. These results suggest the necessity to define or refine specific linguistic features (and criteria) that pertain to the patient's native and spoken language. Our results suggest that similar patterns of brain atrophy might be associated with different symptomatology depending on the patient's native language. Therefore, applying current PPA subvariants diagnostic criteria to patients speaking languages with different features than those of English might lead to misdiagnosis or at least diagnostic confusion. For example, orthographic semantic errors, rather than anomia, might be the first sign of svPPA in a pictographic language such as Chinese, while grammatical errors might be more common in patients with lvPPA speaking languages with complex morphosyntatic structures such as French or Italian. Our article is the first attempt to highlight these differences and we hope it will inspire collaborative international research that will lead to language-specific testing and diagnostic tools.

As mentioned above, the limitations of our study relate to the fact that we cannot exclude that difference in dementia severity, undetected anatomical involvement, and education level could play a role in our results. Finally, the lack of healthy control data for speech production is a limitation for a deep interpretation of our findings.

This study reveals the relevance of native language on the phenotype and clinical presentation of PPA and the need to consider cultural and language-specific effects during the diagnostic process.

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Continued

Appendix (continued)

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