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Handedness and language learning disability differentially distribute in progressive aphasia variants

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Primary progressive aphasia is a neurodegenerative clinical syndrome that presents in adulthood with an isolated, progressive language disorder. Three main clinical/anatomical variants have been described, each associated with distinctive pathology. A high frequency of neurodevelopmental learning disability in primary progressive aphasia has been reported. Because the disorder is heterogeneous with different patterns of cognitive, anatomical and biological involvement, we sought to identify whether learning disability had a predilection for one or more of the primary progressive aphasia subtypes. We screened the University of California San Francisco Memory and Aging Center's primary progressive aphasia cohort ($n = 198$) for history of language-related learning disability as well as hand preference, which has associations with learning disability. The study included logopenic ($n = 48$), non-fluent ($n = 54$) and semantic ($n = 96$) variant primary progressive aphasias. We investigated whether the presence of learning disability or non-right-handedness was associated with differential effects on demographic, neuropsychological and neuroimaging features of primary progressive aphasia. We showed that a high frequency of learning disability was present only in the logopenic group ($\chi^2 = 15.17$, $P < 0.001$) and ($\chi^2 = 11.51$, $P < 0.001$) compared with semantic and non-fluent populations. In this group, learning disability was associated with earlier onset of disease, more isolated language symptoms, and more focal pattern of left posterior temporoparietal atrophy. Non-right-handedness was instead over-represented in the semantic group, at nearly twice the prevalence of the general population ($\chi^2 = 6.34$, $P = 0.01$). Within semantic variant primary progressive aphasia the right-handed and non-right-handed cohorts appeared homogeneous on imaging, cognitive profile, and structural analysis of brain symmetry. Lastly, the non-fluent group showed no increase in learning disability or non-right-handedness. Logopenic variant primary progressive aphasia and developmental dyslexia both manifest with phonological disturbances and posterior temporal involvement. Learning disability might confer vulnerability of this network to early-onset, focal Alzheimer's pathology. Left-handedness has been described as a proxy for atypical brain hemispheric lateralization. As non-right-handedness was increased only in the semantic group, anomalous lateralization mechanisms might instead be related to frontotemporal lobar degeneration with abnormal TARDBP. Taken together, this study suggests that neurodevelopmental signatures impart differential trajectories towards neurodegenerative disease.

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Abbreviations: FTLD = frontotemporal lobar degeneration; PPA = primary progressive aphasia

Introduction

Primary progressive aphasia (PPA), described by Marsel Mesulam in 1982, was initially described as a syndrome related to left-hemisphere anatomical damage and non-Alzheimer's pathology. The nosology of the disorder has evolved and PPA is currently defined as a collection of clinical syndromes each with a specific pattern of anatomical damage affecting unique aspects of language (Fig. 1; Gorno-Tempini *et al*., 2004, 2011).

The logopenic variant of PPA affects the temporoparietal junction leading to profound phonological impairments and word finding difficulties. The non-fluent/agrammatic variant of PPA involves the left posterior, inferior frontal gyrus, creating motor, speech and syntactic deficits. The semantic variant of PPA is associated with anterior temporal lobe atrophy with profound loss of semantic knowledge. Distinctive pathology is associated with each of the PPA clinical/anatomical subtypes: Alzheimer's disease with the logopenic variant of PPA, frontotemporal lobar degeneration (FTLD) with abnormal tau pathology or abnormal TARDBP accumulation type A with non-fluent variant PPA, and FTLD with abnormal TARDBP type C with semantic variant PPA (Gorno-Tempini *et al*., 2011).

Why specific language networks show differential vulnerability to neurodegeneration remains unknown. In an attempt to address this issue, Rogalski *et al*. (2008) reported an over-representation of learning disability in patients with PPA and their first-degree relatives. They also reported three cases of structural lesions associated with PPA—an individual who underwent a temporal lobe neurosurgical procedure as a child and two individuals with left hemicranial hypoplasia, who all later developed progressive disorders of language (Alberca *et al*., 2004; Rogalski *et al*., 2008). These neurodevelopmental or acquired abnormalities in the language network were interpreted as possible risk factors for PPA as a whole; however, as this is not a unitary disorder, it would follow that these factors might differentially influence specific clinical presentations, patterns of anatomical involvement and/or pathological subtypes.

Developmental dyslexia, defined as reading and spelling difficulty out of proportion to general intelligence, is the most common developmental language learning disability affecting ~5–10% of children (Shaywitz, 1998). The most common clinical phenotype is a phonological processing disturbance causing difficulties in acquiring written language abilities. In contrast to, or perhaps because of, their language processing difficulties, many dyslexic individuals have been found to possess enhanced visuospatial and artistic abilities (Wolff and Lundberg, 2002; Von Karolyi *et al*., 2003).

Dyslexia is highly heritable and several identified genetic risk factors play known roles in neuronal migration (Darki *et al*., 2012). Dyslexic individuals display structural variations in white matter tracts and grey matter architecture as well as functional hypometabolism of the left temporoparietal regions, most notably in the posterior middle temporal gyrus, superior temporal sulcus and angular gyrus (Horwitz *et al*., 1998; Darki *et al*., 2012; Richlan *et al*., 2012). Dyslexia may be associated with an increased rate of non-right-handedness and a trend towards brain symmetry, especially in the planum temporale (Geschwind and Behan, 1982; Geschwind and Galaburda, 1985). Although these associations remain contentious, there are some recent genetic associations providing greater evidence that language-related learning disabilities are linked to neural organization of language and hand preference (Scerri *et al.,* 2011).

Handedness is one of the earliest markers of neural organization, brain development and functional asymmetry (McCartney

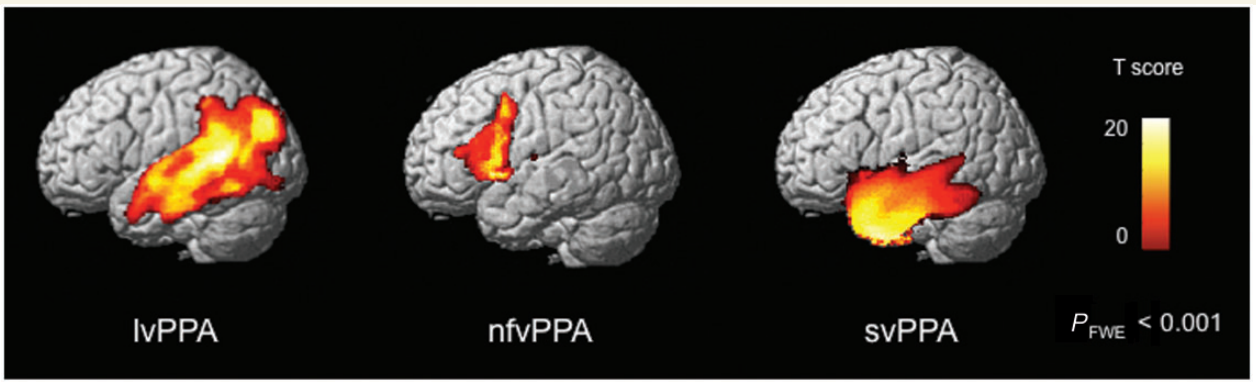

Figure 1 Pattern of atrophy in patients with PPA variants versus controls. Statistical parametric maps show patterns of grey matter atrophy in logopenic variant PPA (lvPPA; $n = 24$), non-fluent variant PPA (nfvPPA; $n = 40$) and semantic variant PPA (svPPA; $n = 58$) compared with their relative healthy control groups matched for age, gender, scan and sample size. Voxel-based morphometry results are thresholded at a family-wise error rate of $P < 0.001$. FEW = familywise error rate.

and Hepper, 1999). Up to 8–10% of the population is non-right-handed (McManus, 1991; Perelle and Ehrman, 1994). Structurally, non-right-handed individuals have greater symmetry of frontal and temporal regions (Geschwind *et al*., 2002), particularly the planum temporale (Steinmetz *et al*., 1991; Snyder *et al*., 1995). Functionally, language activation in near all right-handed and most non-right-handed people is left lateralized. The frequency of anomalous language activation, right lateralized or bilaterally distributed, is thus higher in non-right-handed than in right-handed populations (Geschwind *et al*., 2002; Szaflarski *et al*., 2002). These structural and functional differences are hypothesized to be responsible for increased rates of certain cognitive and biological features in non-right-handed people, including enhancements in musical, mathematical and visuospatial abilities and increased frequency of developmental language-related learning disabilities (Geschwind and Behan, 1982; Geschwind and Galaburda, 1985).

In this report, we investigated the association of hand preference and the presence of language-related learning disability in each of the three main variants of PPA as a means of exploring the effect of neurodevelopmental factors on the vulnerability of different language networks to neurodegenerative disease.

Logopenic, non-fluent and semantic variant primary progressive aphasia

Materials and methods

Study population

We studied all patients who met consensus diagnostic criteria for PPA (logopenic, non-fluent and semantic variant PPA; Gorno-Tempini *et al*., 2011) seen through the research programmes of the University of California San Francisco Memory and Aging Center. We identified 209 patients with PPA, 198 patients (48 logopenic variant, 54 non-fluent variant and 96 semantic variant) that had accessible clinical charts with handedness and of these, 189 patients (48 logopenic variant, 51 non-fluent variant and 90 semantic variant) who had past medical history information present for review for history of learning disability.

For history of learning disability, charts were screened for evidence of developmental cognitive impairments in speaking or reading, including diagnoses of dyslexia and/or stuttering, and histories of delay in speaking or reading. We did not assess for developmental behavioural delays such as autism or attention deficit disorder. Handedness was classified in a dichotomous manner as either right-handed or non-right-handed (which included patients who displayed ambidextrous/mixed-hand preference, forced right, and left handed individuals).

An additional sample of 35 patients with semantic variant PPA from the Mayo Clinic, Jacksonville, 34 of whom had hand preference recorded in the same manner, were included as an independent sample in the handedness experiment.

Cognitive, speech and language evaluation

Participants underwent neuropsychological screening and speech and language assessment. Neuropsychological screening and history determined whether patients met inclusion criteria for PPA. Speech-language testing was employed to address the symptoms and signs specified in the most current clinical criteria for PPA (Gorno-Tempini *et al*., 2011). Language and neuropsychological testing, and not neuroimaging, were the sole criteria for classification of patients into PPA subtypes as previously described (Gorno-Tempini *et al*., 2004).

Statistical analyses for demographics, cognitive, speech and language evaluation

Demographic characteristics, cognitive, speech and language measures were examined using histograms, quantile-quantile plots and the Shapiro-Wilks test for normality. Differences in these measures across the three groups were analysed using ANOVA and analysis of covariance (ANCOVA) while adjusting for age. Non-normally distributed measures were compared using ANOVA or ANCOVA accompanied by a permutation-based technique. Categorical variables were compared using tests of proportions. Fisher's exact tests were performed to compare learning disability frequency and hand preference among the three variants. Finally, Chi-square and Fisher's analyses were performed to compare expected versus observed rates of non-right-handedness. Statistical significance was examined based on the 0.05 significance level cut-off. In addition to reporting average scores across the PPA variants, we also reported standardized effect sizes as *t*-values and Cohen's d. The effect sizes of categorical variables are reported based on chi-square test statistic values. The analyses were executed using SPSS 20.0 software and R program for Scientific Computing (available at www.r-project.org).

Neuroimaging

Study population

We set up group comparisons to identify the pattern of atrophy in each PPA variant choosing the healthy control group from a larger cohort matched for demographics (age, gender, hand preference, and scanner type).

Image acquisition

Subjects underwent structural MRI obtaining sequences previously described on either a 1.5 T (Gorno-Tempini *et al*., 2004), 3 T (Bettcher *et al*., 2012) or 4 T scanner (Zhang *et al*., 2011). MRI scans were acquired within 1 year of each University of California San Francisco visit and in each case the first available image was used for the analysis. Healthy controls were recruited from the University of California San Francisco Memory and Aging Center healthy ageing cohort, a collection of participants with normal neurological exam, MRI scans without clinically evident strokes, and without cognitive deficits or diagnosis of major psychiatric disease.

Image processing

Image analysis was performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) developed in the Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, running in MATLAB R2012a (Mathworks).

Voxel-based morphometry

All structural T_1 images were processed using the VBM8 Toolbox implemented in SPM8. The images were segmented into grey matter, white matter and CSF based on an adaptive maximum, a posterior technique (Rajapakse *et al*., 1997) that takes into account intensity inhomogeneity and other local variations of intensity. This segmentation approach also uses partial volume estimation with a simplified mixed model of two tissue types (Tohka *et al*., 2004). The images were then registered to the Montreal Neurological Institute (MNI) space through an affine and a non-linear deformation. The non-linear deformation parameters were calculated with the high dimensional Diffeomorphic anatomical registration through exponentiated lie algorithm and the predefined templates with the Diffeomorphic anatomical registration through exponentiated lie toolbox (Ashburner, 2007). The images were modulated by multiplying the voxel values by the Jacobian determinant derived from the spatial normalization to ensure that relative volumes of grey matter were preserved. Finally, the images were smoothed with a full-width at half-maximum Gaussian kernel filter of $10 \times 10 \times 10$ mm in order to render the data more normally distributed and to compensate for inexact spatial normalization.

Statistical analysis

Data were analysed in the general linear regression model in SPM8. Each PPA variant group was compared with their relative group of controls matched for age, gender, handedness, scanner and sample size. We compared patients with logopenic variant PPA ($n = 24$; age = 64 ± 9 years; 11 males; 20 right-handed) versus healthy controls ($n = 24$; age = 65 ± 7 years; 11 males; 19 right-handed), non-fluent variant PPA ($n = 40$; age = 68 ± 7 years; 14 males; 38 right-handed) versus healthy controls ($n = 40$; age = 67 ± 6 years; 15 males; 39 right-handed) and semantic variant PPA ($n = 58$; age = 63 ± 7 years; 31 males; 43 right-handed) versus healthy controls ($n = 58$ age = 62 ± 5 years; 31 males; 43 right-handed). All statistical analyses were performed by covarying out age, gender, handedness, scanner and total intracranial volume. Corrections for multiple comparisons were performed by controlling the family-wise error rate at $P < 0.001$.

Results

Demographics

Among the three variants of PPA, the patient groups did not differ statistically in terms of gender, race or education. The group with semantic variant PPA differed by age at first visit ($t = -4.17$, d = 0.70; $P = 0.001$), years from first symptom ($t = 4.45$, d = 0.56; $P < 0.001$), Clinical Dementia Rating Scale total score ($t = 3.52$, d = 0.64; $P = 0.001$) and Clinical Dementia Rating Scale Box score ($t = 4.17$, d = 0.6; $P < 0.001$). The cohort with non-fluent variant PPA differed on the Mini-Mental State Examination ($t = -3.93$, d = 0.85; $P = 0.001$). The cohort with logopenic variant PPA had greater *APOE4* allelic frequency [χ^2 (2) = 7.64, $P = 0.02$] (Table 1).

Cognitive, speech and language measures

Within the three variants of PPA, the groups showed significant differences in the expected directions for the following tasks: Boston naming test ($t = -12.55$, d = 1.19; $P < 0.001$), apraxia of speech ($t = -7.94$, d = 1.74; $P < 0.001$), dysarthria ($t = -5.34$, d = 1.16; $P < 0.001$), western aphasia battery fluency ($t = 5.19$, d = 1.02; $P < 0.001$), semantic fluency ($t = -2.39$, d = 0.53; $P = 0.008$), western aphasia battery repetition ($t = -2.01$, d = 0.41; $P = 0.047$), western aphasia battery auditory word comprehension ($t = -3.11$, d = 0.76; $P = 0.002$), irregular word reading ($t = -3.52$, d = 0.70; $P = 0.001$), modified trails ($t = 5.83$, d = 0.78; $P < 0.001$), digit span backwards ($t = 6.67$, d = 1.33; $P < 0.001$), and Benson delay ($t = -5.31$, d = 1.15; $P < 0.001$). In tests where differences did not reach statistical significance, the means and medians were in the expected direction for the following tasks: western aphasia battery sequential commands, phonemic fluency, Regular word reading, pseudo-word reading, Benson copy, visual object and space perception battery and calculation (Table 2).

Neuroimaging

Voxel-based morphology regions of atrophy were consistent with previous reports: logopenic variant PPA having greatest involvement in the posterior temporal and inferior parietal regions extending anteriorly to the temporal pole; non-fluent variant PPA the inferior frontal and premotor regions centred on the pars opercularis extending dorsally; and semantic variant PPA attacking the left temporal pole affecting the fusiform, inferior and middle temporal gyri extending to across the entire medial temporal gyrus and the anterior part of the superior temporal gyrus (Fig. 1 and Table 3).

Language learning disability

Across the entire PPA cohort 16/189 (8%) patients displayed a past medical history of language learning disability. Thirteen had a personal history of dyslexia, one also had a history of stuttering. Of the three patients without clear histories of dyslexia, two endorsed speech delays and one had a history of stuttering since childhood.

Among the PPA subtypes, history of learning disability was significantly greater in the logopenic variant ($n = 12/48$, 25%; 10/12 were dyslexic) relative to semantic variant PPA [$n = 3/90$ 3%; χ^2 (1, $n = 138$) = 15.17, $P < 0.001$] and non-fluent variant PPA cohort [$n = 1/51$ 2%; χ^2 (1, $n = 99$) = 11.51, $P \leqslant 0.001$] (Fig. 2). The observed counts were not significantly different when comparing semantic variant with non-fluent variant PPA.

Hand preference

Across the entire PPA cohort 24/198 (12%) patients were non-right-handed. Using the estimate of 10% of people being non-right handed in the general population, in semantic variant PPA, non-right-handedness ($n = 17/96$, 18%) was significantly higher when compared with the expected counts from the general population [χ^2 (1, $n = 96$) = 6.34, $P = 0.01$]. In semantic variant PPA, the non-right-handed population was comprised of five ambidextrous/mixed-handed, one forced right and 11 left handed individuals. In patients with the logopenic variant ($n = 5/48$, 10%), observed counts were not significantly different than for the general population. In logopenic variant PPA, the non-right-handed population was comprised of one ambidextrous/mixed-handed, one forced right, and three left-handed individuals. Likewise, in

Table 1 Demographics of the PPA cohort

Diagnostic group Mean ± SD (*n*)	All patients with PPA (*n* = 198)	Patients with logopenic variant PPA (*n* = 48)	Patients with non-fluent variant PPA (*n* = 54)	Patients with semantic variant PPA (*n* = 96)
Age at first visit (years)	66.1 ± 8.3 (198)	66.7 ± 9.4 (48)	69.2 ± 7.5 (54)	63.9 ± 7.6 (96)[a]
Years from first symptom	4.5 ± 2.9 (197)	3.8 ± 2.2 (48)	3.4 ± 1.9 (54)	5.4 ± 3.4 (95)[a]
Gender % female	52.5% (198)	52.1% (48)	61.1% (54)	47.9% (96)
Race % Caucasian	95% (186)	100% (47)	95.8% (48)	91.2% (91)
Education (years)	15.8 ± 3.2 (192)	15.9 ± 3.6 (47)	15.7 ± 3 (52)	15.8 ± 3.1 (93)
Mini-Mental State Examination at first visit (30)	21.9 ± 7 (168)	19.6 ± 7.1 (40)	24.8 ± 5 (49)[a]	21.2 ± 7.6 (79)
Clinical Dementia Rating total score	0.71 ± 0.53 (141)	0.58 ± 0.23 (26)	0.52 ± 0.42 (41)	0.86 ± 0.62 (74)[a]
Clinical Dementia Rating Box score	3.7 ± 3.1 (141)	3.0 ± 1.6 (26)	2.4 ± 2.1 (41)	4.7 ± 3.7 (74)[a]
Apoe4 allelic frequency	14.5% (117)	25% (20)[a]	7.1% (35)	15% (62)

SD = standard deviation; [a]$P < 0.05$ between total cohorts logopenic variant versus non-fluent variant versus semantic variant PPA.

Table 2 Language and neuropsychological battery of the PPA cohort

Diagnostic group mean ± SD (*n*)	Logopenic variant PPA (*n* = 48)	Non-fluent variant PPA (*n* = 54)	Semantic variant PPA (*n* = 93)
Boston naming test abbreviated (15)	9.2 ± 4.5 (37)	11.7 ± 2.8 (49)	4.3 ± 3.7 (73)[a]
Apraxia of speech (7)	0.75 ± 1.9 (20)	2.7 ± 2.2 (41)[a]	0.0 ± 0.0 (61)
Dysarthria (7)	0.6 ± 2.1 (20)	2.3 ± 2.8 (41)[a]	0.0 ± 0.0 (61)
WAB sequential commands (80)	64.2 ± 15.3 (21)	69.5 ± 11.9 (42)	69.7 ± 16.6 (55)
WAB fluency (10)	8.0 ± 2.0 (21)	6.3 ± 3 (40)[a]	8.7 ± 1.4 (61)
Phonemic fluency	6.4 ± 3.9 (36)	4.6 ± 2.7 (47)	7.2 ± 4.2 (67)
Semantic fluency	6.7 ± 5.0 (36)	9.3 ± 4.9 (47)[a]	7.3 ± 5.3 (70)
WAB repetition (100)	70.7 ± 17.5 (20)	78.7 ± 19.6 (38)	85.8 ± 13.9 (57)[a]
WAB auditory word comprehension (60)	57.1 ± 7.1 (21)	58 ± 6.4 (42)	50.0 ± 13.4 (61)[a]
Regular word reading % correct	96.1 ± 5.2 (20)	94.6 ± 9.38 (28)	92.9 ± 10.3 (56)
Irregular word reading % correct	90.4 ± 8.6 (20)	87.3 ± 17.5 (28)	73.2 ± 22.0 (56)[a]
Pseudo-word reading % correct	75.8 ± 21.3 (18)	72.0 ± 27.3 (21)	79.6 ± 21.25 (40)
Modified trails number of lines/min	6.7 ± 6.3(30)	9.7 ± 8.5 (42)	18.3 ± 12.9 (64)[a]
Digit span backwards (9)	3.2 ± 1.0 (35)	3 ± 1.2 (46)	4.6 ± 1.2 (69)[a]
Benson copy (17)	13.0 ± 4.4 (37)	14.1 ± 2.2 (47)	15.3 ± 1.8 (74)
Benson delay (17)	4.8 ± 3.5 (37)	8.9 ± 3.6 (47)[a]	6.7 ± 4.5 (73)
VOSP number location (10)	6.6 ± 2.9 (28)	8.3 ± 1.9 (42)	9.1 ± 1.2 (54)
Calculations (5)	3.0 ± 1.1 (35)	4.1 ± 1.1 (49)	4.5 ± 0.79 (72)

SD = standard deviation; VOSP = Visual Object and Space Perception; WAB = Western Aphasia Battery.
[a]$P < 0.05$ between total cohorts logopenic variant versus non-fluent variant versus semantic variant.

non-fluent variant PPA ($n = 2/54$, 4%), there was no significant difference compared with the general population, but this analysis was not sufficiently powered to detect differences (estimated power to detect the difference is 56%, we would need a total of 95 non-fluent variant PPA subjects to have sufficient power at 80%). In non-fluent variant PPA, both non-right-handed subjects were left-handed. Between semantic variant and non-fluent variant PPA, handedness rates were significantly different [χ^2 (1, $n = 150$) = 6.12, $P = 0.019$] (Fig. 3).

An independent sample of 35 patients with semantic variant PPA from the Mayo Clinic, Jacksonville, 34 with recorded hand preference, revealed a similarly elevated proportion of non-right-handedness ($n = 6/34$, 18%). Of these six non-right-handed individuals, two were ambidextrous/mixed-handed, one was forced-right and three were left-handed.

Within-group analyses of logopenic variant and semantic variant primary progressive aphasia

Materials and methods

Study population

We performed within-group comparisons to investigate whether the presence of learning disability or non-right-handedness was associated with differences in demographic, cognitive and neuroimaging features.

Statistical analyses for demographics and cognitive, speech, and language findings within groups

The same statistical analyses were performed as described earlier.

Table 3 Coordinates of voxel-based morphometry analysis in logopenic variant, non-fluent variant and semantic variant PPA

Regions	*t*-score	Peak level family-wise error correction	*x*	*y* (mm)	*z*
Logopenic variant PPA					
Temporal mid left	11.95	0.000	−56	−52	10
Occipital middle left	9.84	0.000	−27	−84	31
Temporal superior left	8.96	0.000	−62	−43	22
Supramarginal left	8.80	0.000	−56	−45	28
Temporal inferior left	7.84	0.000	−60	−21	−27
Non-fluent variant PPA					
Caudate left	9.68	0.000	−11	17	−5
Putamen left	9.65	0.000	−24	3	6
Precentral left	8.39	0.000	−44	8	36
Frontal inferior tri left	7.38	0.000	−47	23	19
Insula left	7.13	0.000	−44	18	1
Supplementary motor area 1	7.56	0.000	−6	8	49
Semantic variant PPA					
Fusiform left	15.34	0.000	−32	−10	−35
Parahippocampal left	15.23	0.000	−26	−6	−27
Temporal pole superior left	14.74	0.000	−30	9	−29
Middle temporal gyrus left	5.98	0.003	−56	−25	−8
Fusiform right	9.84	0.000	30	−8	−39
Parahippocampal right	6.96	0.000	41	3	−20
Middle temporal gyrus right	6.50	0.000	54	−1	−21
Inferior temporal gyrus right	5.22	0.007	59	−29	−26

Neuroimaging

Voxel-based morphometry of logopenic variant primary progressive aphasia

Study population

Of the 12 patients identified with a learning disability and logopenic variant PPA, six had available imaging. Of the 38 patients who were non-learning disabled with logopenic variant PPA, 18 had available imaging. We compared patterns of brain atrophy between logopenic variant patients with and without history of learning disability using two different groups of healthy controls matched for age, gender, handedness, scan and sample size.

Statistical analysis

ANCOVA comparisons were performed on learning disabled patients with logopenic variant PPA ($n = 6$; age = 56 ± 6 years; one male; five right-handed) versus healthy controls ($n = 12$; age = 57 ± 6 years; two males; 10 right-handed) and non-learning disabled patients with logopenic variant PPA ($n = 18$; age = 67 ± 9 years; 10 males; 15 right-handed) versus healthy controls ($n = 36$; age = 66 ± 8 years; 20 males; 30 right-handed). All statistical comparisons were co-varied for age, gender, handedness, scanner and total intracranial volume. Corrections for multiple comparisons were performed by controlling the family-wise error rate at $P < 0.001$.

Voxel-based morphometry of semantic variant primary progressive aphasia

Study population

Of the 79 right-handed patients with semantic variant PPA, 43 had available imaging. Of the 17 non-right-handed patients with semantic variant PPA, 15 had available imaging. We compared patterns of brain atrophy between the respective semantic variant PPA cohorts against separate control groups matched for age, gender, handedness, scanner and sample size.

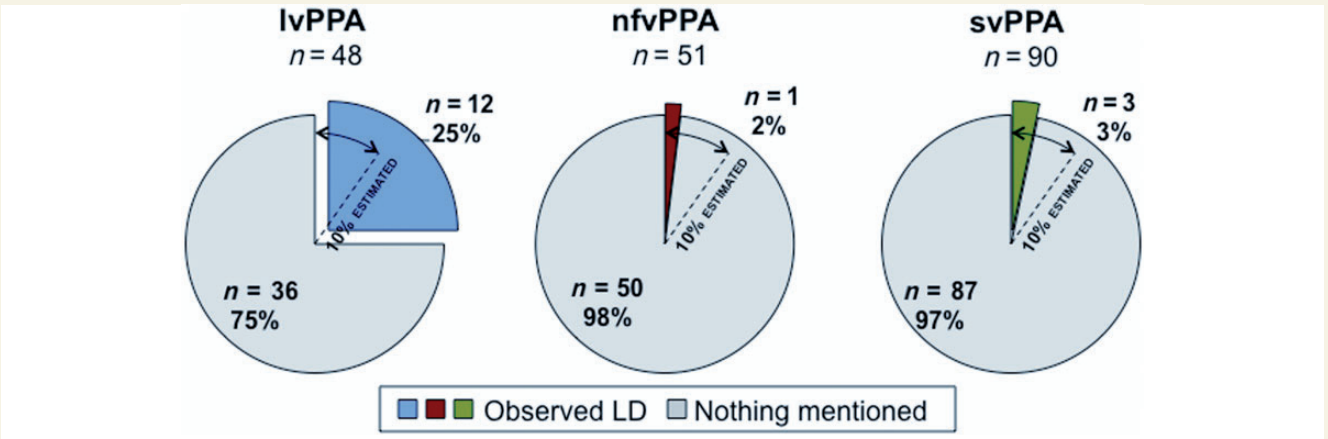

Figure 2 Distribution of learning disability in PPA. Estimated rates of dyslexia are 5–10% of the general population, the dashed line above represents the demarcation for an estimated 10% rate. LD = learning disability; lvPPA = logopenic variant PPA; nfvPPA = non-fluent variant PPA; svPPA = semantic variant PPA.

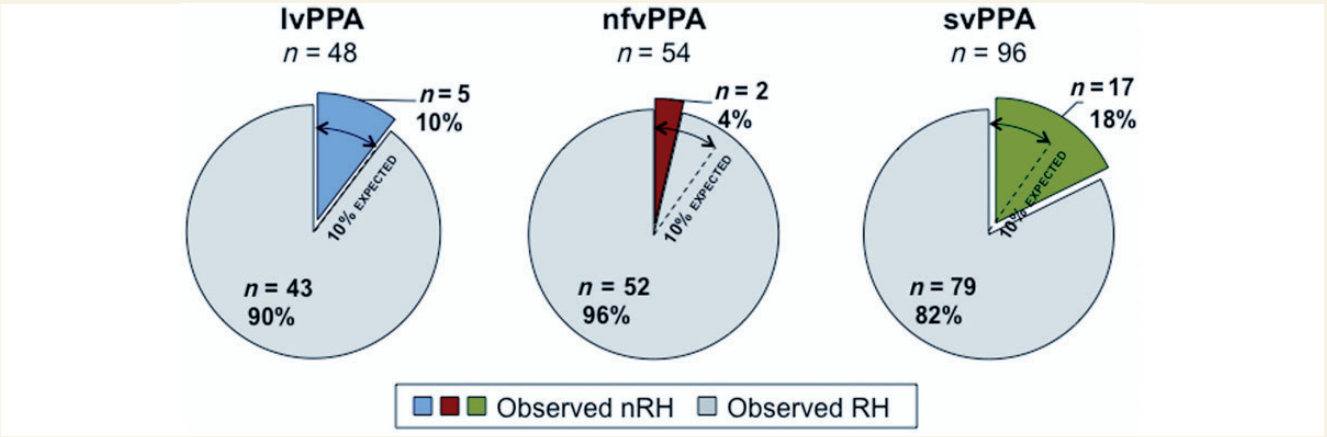

Figure 3 Distribution of hand preference in PPA. Expected rates of non-right-handedness are 8–10% of the general population, the dashed line above represents the demarcation for an expected 10% rate. lvPPA = logopenic variant PPA; nfvPPA = non-fluent variant PPA; nRH = non-right-handed; RH = right-handed; svPPA = semantic variant PPA.

Statistical analysis

ANCOVA comparisons were performed on right-handed patients with semantic variant PPA ($n = 43$; age = 62 ± 6 years; 22 males) versus right-handed healthy controls ($n = 50$; age = 61 ± 4 years; 27 males) and non-right-handed patients with semantic variant PPA ($n = 15$; age = 66 ± 7 years; nine males) versus non-right-handed healthy controls ($n = 18$; age = 64 ± 6 years; 11 males). All statistical comparisons were co-varied for age, gender, handedness, scanner and total intracranial volume. Corrections for multiple comparisons were performed by controlling the family-wise error rate at $P < 0.001$.

Results

Learning disability versus non-learning disability logopenic variant primary progressive aphasia

Demographics

The average age at first visit was 62.4 years ($n = 12$) for learning disabled patients with logopenic variant PPA, whereas non-learning disabled patients with logopenic variant were older at 68.1 years ($n = 36$; $t = 1.87$, d = 0.6; $P = 0.038$; median ages were 62 and 70, respectively). The average Mini-Mental State Examination score was five points higher at time of presentation in the learning disabled logopenic variant cohort compared with the non-learning disabled logopenic variant cohort (23.7, $n = 10$ versus 18.3, $n = 30$; $t = 1.77$, d = 0.93; $P = 0.03$) (Table 4).

Cognitive, speech and language measures

The learning disabled logopenic variant group performed better on the Boston Naming Test ($t = -2.59$, d = 0.92; $P = 0.02$) (Table 3).

Neuroimaging

The learning disabled logopenic variant cohort showed a pattern of significant left hemisphere brain atrophy centred on posterior portions of the middle and superior temporal gyri extending into the supramarginal and angular gyri. The non-learning disabled logopenic variant group displayed a pattern of atrophy that was considerably larger extending anteriorly towards the temporal pole, dorsally into the inferior temporal gyrus, and posteriorly as far back as the inferior parietal lobule (Fig. 4 and Table 5).

Semantic variant primary progressive aphasia: right-handed versus non-right-handed

Demographics

Within the semantic variant PPA group, there were no statistically significant differences between right-handed and non-right-handed cohorts (Table 6).

Cognition, speech and language

Across all tests, Benson delay was the only measure to show differences within semantic variant PPA groups with the non-right-handed patients performing much worse than their right-handed counterparts ($t = -2.19$, d = 0.67; $P = 0.03$) (Table 6).

Neuroimaging

Whole brain voxel-based morphometry analyses show similar pattern of atrophy in the semantic variant PPA handedness subgroups involving the anterior temporal lobe.

Brain asymmetry analysis of healthy controls and semantic variant primary progressive aphasia

Materials and methods

Study population

To investigate if handedness plays a role as marker of neural organization and brain development as function of asymmetry,

Table 4 Demographics, language, and neuropsychological battery within logopenic variant PPA

Diagnostic group mean ± SD (*n*)	Logopenic variant PPA (*n* = 48)	
	Non-learning disabled (*n* = 36)	Learning disabled (*n* = 12)
Age at first visit (years)	68.1 ± 8.9 (36)	62.4 ± 10 (12)[a]
Years from first symptom	3.9 ± 2.2 (36)	3.4 ± 2.3 (12)
Gender % female	50.7% (36)	58.3% (12)
Race % Caucasian	100% (35)	100% (12)
Education (years)	16 ± 3.1 (35)	15.5 ± 4.7 (12)
Mini-Mental State Examination at first visit (30)	18.3 ± 7.5 (30)	23.7 ± 3.4 (10)[a]
Clinical Dementia Rating total	0.6 ± 0.25 (21)	0.5 ± 0.0 (5)
Clinical Dementia Rating Box score	3.1 ± 1.7 (21)	2.5 ± 0.6 (5)
Apoe4 allelic frequency	25% (14)	25% (6)
Boston Naming Test abbreviated (15)	8.3 ± 4.6 (28)	12 ± 3.4 (9)[a]
Apraxia of speech (7)	0.54 ± 2 (13)	1.1 ± 2 (7)
Dysarthria (7)	0.69 ± 2.5 (13)	0.42 ± 1.1 (7)
WAB sequential commands (80)	64.4 ± 16.8 (14)	63.9 ± 12.9 (7)
WAB fluency (10)	7.9 ± 2.3 (14)	8.3 ± 1.6 (7)
Phonemic fluency	5.7 ± 2.7 (27)	8.4 ± 5.9 (9)
Semantic fluency	6.1 ± 5 (27)	8.6 ± 5.1 (9)
WAB repetition (100)	68.1 ± 20.1 (14)	76.8 ± 7.2 (6)
WAB auditory word comprehension (60)	56.3 ± 8.4 (14)	58.7 ± 3 (7)
Regular word reading % correct	96.1 ± 6 (14)	96.1 ± 3.3 (6)
Irregular word reading % correct	88.3 ± 9.4 (14)	95.3 ± 3.4 (6)
Pseudo-word reading % correct	80.3 ± 21.4 (13)	64.2 ± 18.1 (5)
Modified trails number of lines/min	6.4 ± 5.9 (23)	7.6 ± 8.1 (7)
Digit span backwards (9)	3.3 ± 1 (26)	2.8 ± 1.2 (9)
Benson copy (17)	12.8 ± 4.5 (28)	13.7 ± 4.2 (9)
Benson delay (17)	4.4 ± 3.1 (28)	5.9 ± 4.5 (9)
VOSP number location (10)	6.1 ± 3 (20)	8.0 ± 2.8 (8)
Calculations (5)	3.0 ± 1 (26)	3.0 ± 1.3 (9)

VOSP = Visual Object and Space Perception; WAB = Western Aphasia Battery.
[a]$P < 0.05$ within logopenic variant PPA cohort with and without learning disability.

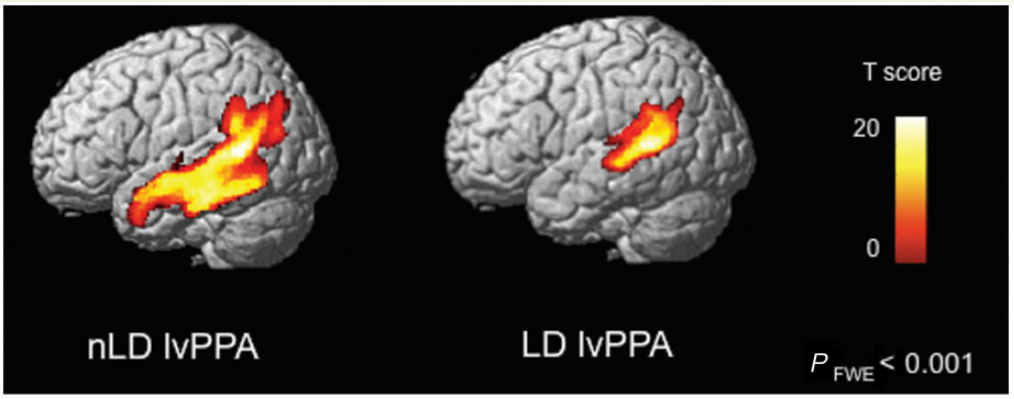

Figure 4 Pattern of atrophy in learning disability and non-learning disability in patients with logopenic variant PPA versus controls. Statistical parametric maps show patterns of grey matter atrophy in non-learning disabled ($n = 18$) and learning disabled ($n = 6$) patients with logopenic variant PPA (lvPPA) compared with their relative healthy control groups matched for age, gender, handedness, scan and sample size. Voxel-based morphometry results are thresholded at a family-wise error rate of $P < 0.001$. LD = learning disabled; nLD = non-learning disabled.

we performed voxel-based analyses of asymmetry in 18 right-handed and 18 non-right-handed healthy controls and in 45 right-handed and 15 non-right-handed patients with semantic variant PPA.

Table 5 Coordinate results for voxel-based morphometry analysis of logopenic variant PPA with and without learning disability

Regions	*t* score	Peak level family-wise error correction	*x*	*y* (mm)	*z*
Logopenic variant PPA without learning disability					
Temporal mid left	9.45	0.000	−56	−52	10
Temporal inferior left	8.18	0.000	−62	−34	20
Occipital mid left	7.49	0.000	−50	−72	18
Angular left	7.03	0.000	−47	−72	28
Supramarginal left	6.99	0.000	−56	−45	28
Logopenic variant PPA with learning disability					
Temporal mid left	8.50	0.000	−57	−54	12

Neuroimaging

Voxel-based morphometry

We followed previously suggested methods to create asymmetry maps in our healthy control population (Watkins *et al.*, 2001). T_1 images were segmented into grey matter, white matter, and CSF in SPM8 as described above and then registered to the MNI space using the symmetric templates. Grey matter asymmetry images were created by subtracting the mirror images from the original. We thereby obtained images revealing differences in grey matter between the two hemispheres (Fig. 5B). Finally the images were smoothed with a full-width at half-maximum Gaussian kernel filter of 10 × 10 × 10 mm.

Statistical analysis

We used one sample *t*-tests co-varying for age and gender to identify areas of significant grey matter asymmetry in both non-right-handed healthy controls ($n = 18$; age = 64 ± 5 years; 12 male), and right-handed ($n = 18$; age = 64 ± 6 years; 11 male). Corrections for multiple comparisons were performed by controlling the family-wise error rate at $P < 0.05$.

Table 6 Demographics, language and neuropsychological battery within semantic variant PPA

Diagnostic group mean ± SD (*n*)	Semantic variant PPA (*n* = 96)	
	Right-handed (79)	Non-right-handed (17)
Age at first visit (years)	63.5 ± 7.6 (79)	65.7 ± 7.5 (17)
Years from first symptom	5.4 ± 3.6 (79)	5.1 ± 2.7 (16)
Gender % female	50.6% (79)	35.3% (17)
Race % Caucasian	90.5% (74)	94.1% (17)
Education (years)	15.6 ± 3.1 (76)	16.6 ± 3 (17)
Mini-Mental State Examination at first visit (30)	21 ± 7.7 (63)	21.8 ± 7.3 (16)
Clinical Dementia Rating total	0.87 ± 0.66 (60)	0.86 ± 0.41 (14)
Clinical Dementia Rating Box score	4.7 ± 3.9 (60)	4.3 ± 2.1 (14)
Apoe4 allelic frequency	16.3% (49)	11.5% (13)
Boston Naming Test abbreviated (15)	4.4 ± 3.7 (57)	4 ± 3.7 (16)
Apraxia of speech (7)	0.0 ± 0.0 (47)	0.0 ± 0.0 (14)
Dysarthria (7)	0.0 ± 0.0 (47)	0.0 ± 0.0 (14)
WAB sequential commands (80)	69.2 ± 18.1 (42)	71.5 ± 11.1 (13)
WAB fluency (10)	8.6 ± 1.5 (47)	9.1 ± 0.83 (14)
Phonemic fluency	6.9 ± 4.5 (53)	8.2 ± 3.1 (14)
Semantic fluency	7.3 ± 5.5 (56)	7.1 ± 4.7 (14)
WAB repetition (100)	86.5 ± 12.9 (43)	83.9 ± 17 (14)
WAB auditory word comprehension (60)	48.9 ± 13.7 (47)	53.7 ± 12 (14)
Regular word reading % correct	92.8 ± 11.0 (42)	93.2 ± 8.1 (14)
Irregular word reading % correct	72.9 ± 23.2 (42)	74.0 ± 19.1 (14)
Pseudo-word reading % correct	78.4 ± 22.8 (29)	82.7 ± 17.1 (11)
Modified trails number of lines/min	18.2 ± 13.3 (49)	18.8 ± 11.7 (15)
Digit span backwards (9)	4.6 ± 1.1 (54)	4.5 ± 1.4 (15)
Benson copy (17)	15.5 ± 1.3 (59)	14.7 ± 3 (15)
Benson delay (17)	7.3 ± 4.5 (58)	4.5 ± 3.7 (15)[a]
VOSP number location (10)	9.2 ± 1.2 (42)	8.8 ± 1.4 (12)
Calculations (5)	4.5 ± 0.8 (57)	4.5 ± 0.5 (15)

SD = standard deviation; VOSP = Visual Object and Space Perception; WAB = Western Aphasia Battery.
[a]$P < 0.05$ within semantic variant PPA cohort right-handed versus non-right-handed.

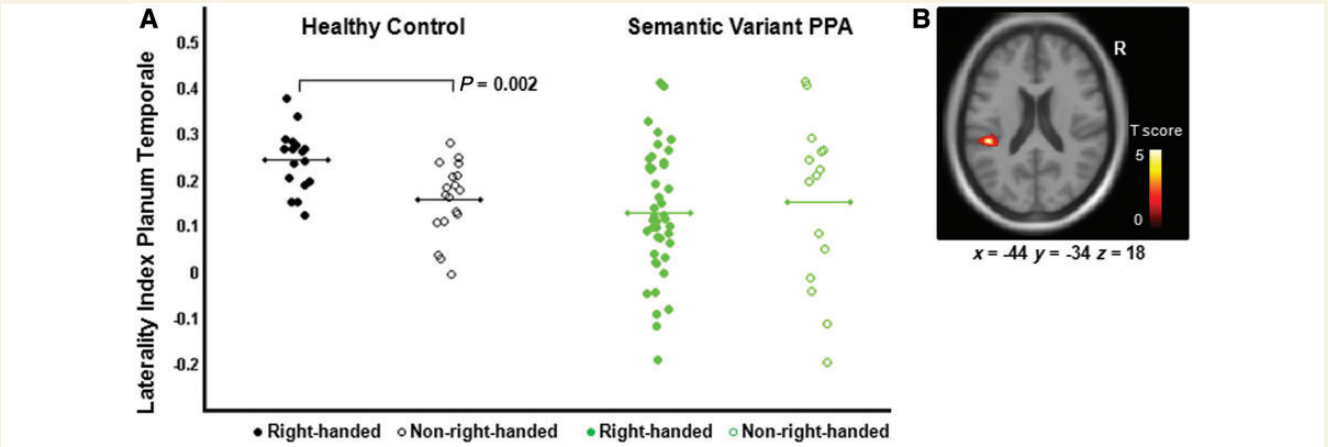

Figure 5 Planum temporale volumes and laterality index distribution in right-handed and non-right-handed healthy controls and right-handed and non-right-handed patients with semantic variant PPA. (**A**) Laterality index of planum temporale for each cohort. The laterality index between right-handed healthy controls and non-right-handed healthy controls showed a significant difference ($P = 0.002$), whereas there was no difference between right-handed patients with semantic variant PPA and non-right-handed patients with semantic variant PPA. (**B**) Statistical parametric maps show grey matter leftward asymmetries in the area of the superior temporal gyrus correspondent to the planum temporale ($x = -44$; $y = -34$; $z = 18$) in right-handed healthy controls with a family-wise error rate threshold of $P < 0.05$.

We calculated the left volume by extracting the voxels' intensity from the modulated and normalized grey matter images relative to the mask of the significant planum temporale cluster. We did the same for the right hemisphere after flipping the cluster. The difference between left and right (laterality index) was calculated as

$$\text{laterality index} = (\text{left} - \text{right})/(\text{left} + \text{right})$$

We obtained planum temporale volumes and laterality indices for each healthy control and patient with semantic variant PPA. Because ANCOVA (accompanied by permutation based techniques) inferred a significant interaction [$F(1,90) = 3.91$, $P = 0.05$] between handedness and the disease status (semantic variant PPA versus healthy controls), we performed subsequent analysis comparing laterality index in right-handed healthy controls ($n = 18$; age = 64 ± 6 years; 11 males) to non-right-handed healthy controls ($n = 18$; age = 64 ± 5 years; 12 males) and right-handed patients with semantic variant PPA ($n = 43$; age = 62 ± 6 years; 22 males) to non-right-handed patients with semantic variant PPA ($n = 15$; age = 66 ± 7 years; nine males).

Results

We found a significant difference in the laterality index between right-handed and non-right-handed healthy controls [$F(1,34) = 12.6$, $P = 0.002$] and no difference between right-handed and non-right-handed semantic variant PPA (Fig. 5A). To investigate the interaction of hand preference and disease, we compared healthy controls with semantic variant PPA with the same hand preference and compared healthy controls and semantic variant PPA without the same hand preference. There was significant difference in laterality index between right-handed healthy controls and right-handed semantic variant PPA [$F(1,59) = 11.7$, $P = 0.001$], and between right-handed healthy controls and non-right-handed semantic variant PPA [$F(1,31) = 3.95$, $P = 0.05$]. No significant difference was found in laterality index between non-right-handed healthy controls and non-right-handed semantic variant PPA in non-right-handed or between right-handed semantic variant PPA and non-right handed healthy controls.

Discussion

Recent findings suggest that neurodevelopmental factors contribute to disease susceptibility in some patients with neurodegenerative disorders. We studied the prevalence of learning disability and hand preference in each of the three main PPA variants and discovered that language-related learning disabilities were common only in patients with a progressive phonological deficit and left posterior temporoparietal atrophy—the logopenic variant of PPA. Conversely, left-handedness was more frequent only in patients with semantic memory deficits and bilateral anterior temporal atrophy consistent with semantic variant PPA. Individuals with nonfluent variant PPA had neither learning disability nor a greater frequency of left-handedness. These findings suggest that the distribution of developmental factors among neurodegenerative disease subtypes reflects distinctive disease vulnerabilities as a consequence of variations in underlying brain structure and function.

Hand preference and reading ability represent early neurodevelopmental milestones and likely predate the occurrence of neurodegenerative disease. Rogalski *et al*. (2008) showed that PPA is associated with increased frequency of learning disabilities; however, as we now know that each PPA variant is most frequently caused by different neurodegenerative conditions, we sought to investigate the prevalence of learning disability in each PPA subtype. Our study of a large, well-characterized group of PPA patients divided into three PPA variants based on current criteria,

showed that history of learning disability was most frequent in logopenic variant PPA, which is most often caused by Alzheimer's disease. The most commonly described form of dyslexia and logopenic variant PPA share similar cognitive (phonological) and anatomical (posterior temporoparietal) substrates, thus suggesting susceptibility of the same neural network. Consistent with the presence of a neurodevelopmental locus of greater disease vulnerability, logopenic variant PPA patients with learning disability showed a younger age of onset, greater global preservation of cognition, and atrophy centred directly over brain areas implicated in the pathogenesis of developmental dyslexia (Horwitz *et al*., 1998; Darki *et al*., 2012; Richlan *et al*., 2012). It could be surmized that the altered pattern of connectivity within the language network in dyslexia (Horwitz *et al*., 1998; Darki *et al*., 2012; Richlan *et al*., 2012) might interfere with intersynaptic transmission of pathological proteins in Alzheimer's disease (Liu *et al*., 2012; Nussbaum *et al*., 2012), thus potentially explaining the more focal language presentation. Together, these findings in logopenic variant PPA associated with learning disability raise the possibility that it represents a different form of logopenic variant PPA resulting from the vulnerability of people with Alzheimer's disease to particular neurodevelopmental factors. Further in-depth analysis of patients' genetic profiles, developmental brain structures and functional activities are needed to clarify this point.

We also looked at hand preference as a proxy for underlying structural and functional brain differences in the PPA cohort. We observed non-right-handed rates at nearly twice the general population estimates in the semantic variant PPA variant alone, suggesting that non-right-handed status might be associated with underlying vulnerability to this FTLD with abnormal TARDBP-specific disorder. The non-right-handed and right-handed semantic variant PPA cohorts were no different in their performance in cognitive tests or in their pattern of atrophy, suggesting that they might be a homogenous population despite their obvious difference in handedness. Given the known relationships between lateralization and hand preference, our data raise the question of whether increased hemispheric structural symmetry might subserve developmental vulnerability to FTLD with abnormal TARDBP. To test this assertion, we performed an analysis of brain symmetry, which reveals in the entire semantic variant PPA population a trend towards planum temporale symmetry, raising the possibility that our observation of increased non-right-handedness is a reflection of an underlying vulnerability associated with a more symmetrical brain structure.

The non-fluent variant PPA cohort appears to be the most uniform of the three variants, displaying both a relative dearth of learning disability and non-right-handedness. With a larger cohort, we may be able to investigate the few examples of patients with non-fluent variant PPA that are non-right-handed or have a history of learning disability; however, at this time, mechanisms underlying our findings in this cohort remain speculative. Nevertheless, extending the logic of specific structural and functional vulnerabilities (applied to logopenic variant PPA and semantic variant PPA) to the non-fluent variant PPA cohort, we should consider that functional language lateralization displays three distinct canonical patterns. More than 95% of right-handed individuals display left-lateralized language activity, whereas non-right-handed individuals show a wider variety of lateralization patterns: left-lateralized in 60–78% of non-right-handed individuals, bilateralized in 14–30% and right-lateralized in 8–10% of non-right-handed individuals (Geschwind *et al*., 2002; Szaflarski *et al*., 2002). Accordingly, language lateralization is ipsilateral to dominant motor hand control in almost all right-handed individuals. Conversely, ipsilateral language lateralization and dominant motor hand control is the least common presentation in the non-right-handed, occurring only when language is completely right-lateralized. Thus it could be hypothesized that a pattern of ipsilateral hand and language dominance may be associated with susceptibility to this FTLD with abnormal tau motor speech disorder. In this case, the relative absence of non-right-handedness might suggest a potential protective effect of non-right-handed functional lateralization as opposed to a direct propensity of this condition to selectively affect right-handed individuals.

Limitations of this study stem from the retrospective nature of data collection. Whereas it is standard for our clinical assessments to query for these conditions, it is possible that the findings presented here under-represent the true prevalence of non-right-handedness and learning disability. Should this study reflect a systematic bias, we would expect the bias to affect all three PPA groups equally, thus limiting concerns relative to the current approach. Our findings were replicated in an independent semantic variant PPA cohort, lending support to the validity of our findings and the collection methods behind them.

Concerns have also been raised in the research community as to the reliability of making correct diagnoses of PPA. A recent review suggested that non-fluent variant PPA and semantic variant PPA diagnoses were relatively easy to detect but that patients with logopenic variant PPA were harder to distinguish from an undifferentiated cohort (Sajjadi *et al*., 2012). This difficulty in detecting logopenic variant PPA, however, is not universal (Mesulam *et al*., 2008; Leyton *et al*., 2011; Rohrer *et al*., 2012).

Regarding the analysis of planum temporale volumes and laterality indices in our semantic variant PPA population, we cannot rule out the possibility that the atrophy patterns extend beyond the regions shown in our voxel-based morphometry analysis of this cohort (Fig. 1) and into the region of the planum temporale. However, even if atrophy is affecting this region, the results of our laterality index analysis in patients with semantic variant PPA suggest some very exciting possibilities regarding an interaction between lateralization and pathophysiology. As already shown, we find a statistical difference in laterality index between right-handed healthy controls and right-handed patients with semantic variant PPA, but not between non-right-handed healthy controls and non-right-handed patients with semantic variant PPA. Supposing that previous to disease, right-handed patients with semantic variant PPA came from a random sample of right-handed healthy controls, and similarly non-right-handed patients with semantic variant PPA from a random sample of non-right-handed healthy controls, our laterality index results suggest one of two potentials. Either the effects of semantic variant PPA pathogenesis on our right-handed cohort are different than its effects on our non-right-handed cohort, or the assumption that the right-handed patients with semantic variant PPA are a random sample of right-handed healthy controls is incorrect. This second

possibility, that right-handed patients with semantic variant PPA before developing the disease came from a non-random sample of right-handed healthy controls, is supported by the observation that the laterality index in non-right-handed healthy controls and right-handed patients with semantic variant PPA are similar. This raises the possibility that the right-handed semantic variant PPA group came from a subpopulation within a larger right-handed cohort with brain symmetry similar to that of non-right-handed populations. To further support this hypothesis, we do not see any particular differences in our voxel-based morphometry analyses of right-handed versus non-right-handed semantic variant PPA cohorts, nor do we elicit any differences when comparing them on neuropsychological testing. These findings warrant further investigation.

This study suggests that neurodevelopmental signatures impart differential trajectories toward specific neurodegenerative diseases presenting as variants of PPA. In the future, these and other signatures may afford opportunities to predict and prospectively study disease vulnerability in a range of disease types (Alzheimer's disease, FTLD with abnormal tau pathology, and FTLD with abnormal TARDBP) at their earliest stages, many decades before clinical symptoms arise, providing the greatest opportunities for disease prevention and early treatment.

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