ARTICLE

Familial language network vulnerability in primary progressive aphasia

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Abstract

Objective
To investigate evidence of the potential role of early cortical vulnerability in the development of primary progressive aphasia (PPA).

Method
A woman with a diagnosis of PPA and her 9 adult siblings, 7 with developmental language disabilities, underwent neuropsychological testing, structural MRI, and resting-state fMRI. Whole-exome sequencing was conducted for genes associated with dyslexia or with neurodegenerative dementia.

Results
The siblings demonstrated lower verbal than nonverbal cognitive test scores in a developmental dyslexia pattern. On structural MRI, although the siblings did not differ from controls in total brain volume, the left hemisphere language area volume was significantly smaller than the right. Furthermore, cortical connectivity between the left superior temporal area, previously identified as the region of peak atrophy in the proband early in the course of illness, and adjacent language network components, including the planum temporale, was decreased in the siblings. No distinctive genetic signatures were identified.

Conclusion
This report further supports the hypothesis that at least some cases of PPA may be based on a familial language network vulnerability that interferes with the acquisition of language in some members and that makes the language network a locus of least resistance to the effects of an independently late-arising neurodegenerative disease in others. This association offers a conceptual model to explain why identical neurodegenerative diseases may selectively target the language network in some individuals while targeting networks that regulate memory or behavior in others. The genetic basis for this vulnerability remains to be determined.

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Glossary

FD = frame displacement; **FTLD** = frontotemporal lobar degeneration; **MINT** = Multilingual Naming Test; **MNI** = Montreal Neurological Institute; **MoCA** = Montreal Cognitive Assessment; **PPA** = primary progressive aphasia; **PRI** = Perceptual Reasoning Index; **PSTC^{R}** = perisylvian cortex; **ROI** = region of interest; **ROIp** = peak ROI; **STG** = superior temporal gyrus; **VCI** = Verbal Comprehension Index; **WASI-II** = Wechsler Abbreviated Scale of Intelligence, Second Edition; **WRAT-4** = Wide Range Achievement Test–Fourth Edition.

Primary progressive aphasia (PPA) has several clinical subtypes and can be caused by numerous neuropathologic entities, including Alzheimer disease, frontotemporal lobar degeneration (FTLD) with transactive DNA-binding protein 43, FTLD with tauopathy,[1] and less common diseases.[2] The common denominator for all subtypes and all neuropathologic correlates is the asymmetric neurodegeneration of the language dominant (usually left) hemisphere. This asymmetry is maintained throughout the course of the disease and is detectable at postmortem examination.[1,3,4] Underpinnings of the predilection for the left hemisphere are poorly understood. One approach has focused on the high incidence of learning disability, including dyslexia, in patients with PPA and their first-degree relatives.[5–7] One study suggested that learning disabilities are more common in patients with the logopenic form of PPA, presumed likely to be associated with Alzheimer neuropathology, than in those with the agrammatic or semantic forms, more likely to be caused by FTLD.[8] From our earlier work, it was hypothesized that families with PPA and dyslexia harbor a genetic or developmental vulnerability of the language network manifested as a learning disability in some and as a locus of least resistance for the effects of independently arising neurodegeneration in others.[9] Indirect support for the locus of least resistance hypothesis comes from 2 cases of congenital left hemicranial hypoplasia[10] and 1 case of surgical removal of a left temporal abscess at 11 years of age.[5] None of the 3 cases had a known language disorder during early adulthood but developed PPA in their 60s within the context of progressive neurodegeneration.

Not all persons with PPA have a personal or family history of learning disability, but in some families, the frequency of dyslexia is striking. Thus, in 1 of the 23 families reported previously, all 3 children of the proband and both grandchildren were dyslexic; in another, both children and all 3 siblings were dyslexic; and in a third family, all 5 siblings had such a history.[6] This information was historical and obtained through clinical interviews of the patients rather than direct testing of affected individuals. Here, we report a family in which the proband with PPA and her 9 siblings, 7 of whom had language-based early learning disabilities, were systematically studied with neuropsychological testing, structural and functional neuroimaging, and whole-exome sequencing.

Methods

A 58-year-old, right-handed woman diagnosed with mild logopenic PPA and her 9 siblings (age range 48 to 61 years at time of test), all right-handed, and mother participated in Northwestern University's PPA Research Program and the Clinical Core of the Alzheimer's Disease Center at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease. The research evaluations for the proband and family included a comprehensive neuropsychological battery, quantitative structural and functional brain imaging, and a blood draw for genetic research.

Study protocol approvals, registrations, and patient consents

All participants gave informed consent for research protocols approved by the Northwestern Institutional Review Board.

The siblings were administered the neuropsychological battery of the Uniform Data Set[11] of the Alzheimer Disease Centers program at the National Institute on Aging, including the Montreal Cognitive Assessment (MoCA),[12] a cognitive screening test sensitive to early signs of cognitive decline in early neurodegenerative disease, and the Multilingual Naming Test (MINT).[13] The MINT is an abbreviated test of naming, a rudimentary language skill affected in many different forms of aphasia. They were also administered the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II)[14] and the Wide Range Achievement Test–Fourth Edition (WRAT-4).[15] The WASI-II yields a Verbal Comprehension Index (VCI) score and a Perceptual Reasoning Index (PRI) score. The VCI is a composite of scores on 2 subtests of fundamental language processes (vocabulary, similarities), and the PRI is a composite of scores on 2 subtests of nonverbal cognitive abilities, namely constructions and deductive reasoning (block design and matrix reasoning, respectively). The WRAT-4 is commonly used to assess achievement in basic academic skills of reading, spelling, and arithmetic computation.

The practice of diagnosing dyslexia and other learning disabilities early in the course of elementary education has emerged only in the last generation. In the present family, members were not formally diagnosed and instead reported histories of what they labeled dyslexia and other problems acquiring language-based academic skills such as spelling and writing prose. To capture their experiences in a systematic manner, the proband and siblings also completed a survey of 10 symptoms of early language-based learning problems and were interviewed in detail about their histories and the extent to which symptoms affected their lives in childhood and in adulthood. Dyslexia and other language-based academic

difficulties were rated as absent if the sibling reported no early difficulty with reading, spelling, math, or speech development; no need for tutoring; and no residual symptoms in adulthood. In those in whom symptoms were present, experiences ranged from early evidence of language difficulties in speech, reading, and spelling, which then resolved with age, to persistent difficulties that prevented the pursuit of higher education or more current language-based activities such as reading for pleasure.

For structural MRI, T1-weighted 3D magnetization-prepared rapid gradient echo sequences (repetition time 2,300 milliseconds, echo time 2.91 milliseconds, inversion time 900 milliseconds, flip angle 9°, field of view 256 mm) at a slice thickness of 1.0 mm were acquired on a 3T Siemens TIM Trio (Munich, Germany) using a 12-channel birdcage head coil at Northwestern University's Center for Translational Imaging. MRIs were processed with FreeSurfer (version 5.1.0, surfer.nmr.mgh.harvard.edu/).[16] Topologic surface errors were corrected by manual intervention iteratively until completely resolved.[17] Estimates of cortical gray matter volume were extracted from the subject native space for each hemisphere. The volumetric estimates were adjusted for head size using the estimated total intracranial volume calculated from the unbiased within-participant template.[18]

fMRI scans were obtained with a Siemens Trio 3T scanner using a T2-weighted echo planar sequence (voxel size 3 × 1.7 × 1.7 mm^3, repetition time 2,800 milliseconds, echo time 20 milliseconds, flip angle 80°) while participants were instructed to remain awake with eyes open for 10 minutes. fMRI volumes were preprocessed with the DPARSFA 4.3 toolbox in SPM12 including only cortical gray matter. fMRI volumes were corrected for slice timing, realigned, coregistered to the structural images, and warped into Montreal Neurological Institute (MNI) space. The resulting volumes were overlaid on normalized T1 images for each participant to confirm accurate alignment. Misalignments were manually corrected. Nuisance covariates, including the 6 affine motion parameters, global signal, white matter signal, and CSF signal, were regressed out of each time series. Volumes were checked for frame displacement (FD) according to Power et al.[19] Two siblings (7 and 9, table 1) with images with FD > 0.5 mm affecting 50% to 100% of volumes were not included in the analysis. In the 7 who were included, bad volumes were removed when FD affected <50% of them. The volumes were then smoothed with a 6-mm kernel.

The center of peak atrophy (p) for the proband at her initial visit was used to generate a 10-mm spherical region of interest (ROI; MNI coordinates −63, −27, 11) within the left superior temporal gyrus (STG) for whole-brain connectivity analysis to determine whether there was selective vulnerability within the language network in the siblings with dyslexia. This region, located in the posterior aspect of STG, is known to be involved in auditory phonologic processing,[20] a fundamental skill believed to be deficient in individuals with developmental dyslexia.[21] For comparison, we also measured connectivity within a nonlanguage dorsal attention network ROI in the intraparietal sulcus[22] using a 10-mm seed (MNI coordinates: x = ±23, y = −58, z = 53).

Whole-brain resting-state functional connectivity maps were created for the siblings and controls using the proband's ROIp as a seed with the REST-plus tool kit in MATLAB (MathWorks, Natick, MA). The hemodynamic time series from all voxels included in the ROI were averaged and correlated with the individual time series from all other voxels in the brain. The Pearson correlation coefficients were then normalized with Fisher z transformation, yielding a whole-brain functional connectivity map for each participant. The whole-brain connectivity map from the siblings was then compared to that of controls, resulting in 2-sample t maps. These t maps were thresholded at $p < 0.0001$ (uncorrected for multiple comparisons), revealing areas throughout the cortex that showed decreased connectivity with the relevant spherical ROI compared to a healthy control sample.

Whole-exome sequencing was conducted on deidentified DNA samples to screen known genes associated with dyslexia or with neurodegenerative brain diseases that cause dementia. Whole-exome regions were captured with the SeqCap EZ Human Exome Kit version 3.0 (Roche, Basel, Switzerland) and sequenced on an Illumina HiSeq2500 (San Diego, CA) at the UCLA Neuroscience Genomics Core (semel.ucla.edu/ungc). Sequence reads were mapped to the GRCh37/hg19 reference genome and variants joint-called according to Genome Analysis Toolkit Best Practices recommendations.[23] Ingenuity Variant Analysis (Qiagen, Venlo, Netherlands) was used for variant annotation and filtering. Candidate variants were confirmed by Sanger sequencing. The hexanucleotide repeat of *C9orf72* was screened using both fluorescent and repeat-primed PCR, as previously described.[24]

Data availability

All data that support our conclusions are reported in this article, and there are no other relevant data available.

Results

At her first research visit, the 58-year-old proband had reported a 2-year history of increasing word-finding difficulty, causing her to stop work as a teacher. She had 20 years of education and no early learning difficulties. The initial examination was consistent with a root diagnosis of PPA[25] and with the logopenic subtype,[26] marked by reduced speech fluency, normal grammar and single-word comprehension, and mildly impaired repetition of phrases and sentences, as determined by a subtyping template developed previously.[27] Nonlanguage test scores were at least average for age (table 1).

Image analysis at the initial visit showed a highly focal region of atrophy in the posterior aspects of the left STG (figure 1A).

Table 1 Dyslexia family proband: 58-year-old woman with PPA and no history of dyslexia at 3 time points, 2 years apart

Age at test, y	58	60	62
Symptom duration, by report, y	2	4	6
Language measures scores, n			
WAB information content (10)[a]	9	9	8
WAB fluency and grammar (10)	9	9	6
WAB yes/no (60)	60	60	60
WAB sequential commands (80)	80	80	78
WAB repetition (100)	68	54	46
WAB animal fluency (20)	17	7	2
WAB AQ (100)	88.9	85.8	63.6
WAB rep 66 (66)	35	24	20
BNT (60)	55	38	4
PPVT (36)	36	36	36
PPT words (52)	52	51	
PPT pictures (52)	52	49	49
Lexical fluency F, total words per minute	16	3	4
PALPA spelling exceptional words (10)	10	10	5
NAT canonical/noncanonical (15/15)	15/14	15/14	14/11
Nonlanguage measures scores			
MMSE (30)	28	18	8
Digit span forward	4	3	0
Digit span backward	3	3	2
Trail Making Part A time, s	31	48	137
Trail Making Part B time, s	88	173	300
3W3S copy shapes/words (15/15)	15/15	15/15	15/15
3W3S delay shapes/words (15/15)	15/15	15/10	14/3
3W3S recognition shapes/words (10/10)	10/10	10/10	10/10
Benton facial recognition (54)	46	46	44
Visual verbal sorts/shifts (20/10)[44]	18/8	18/8	19/9
ADLQ total percent (<33%–mild)	15.5	32.1	47.4
FBI negative/disinhibition (36/36)	6/1	14/2	14/1
CDR sum of boxes	1	3.5	5
CDR global	0.5	0.5	1
CDR behavior	0	0	0.5
CDR language	0.5	1	1

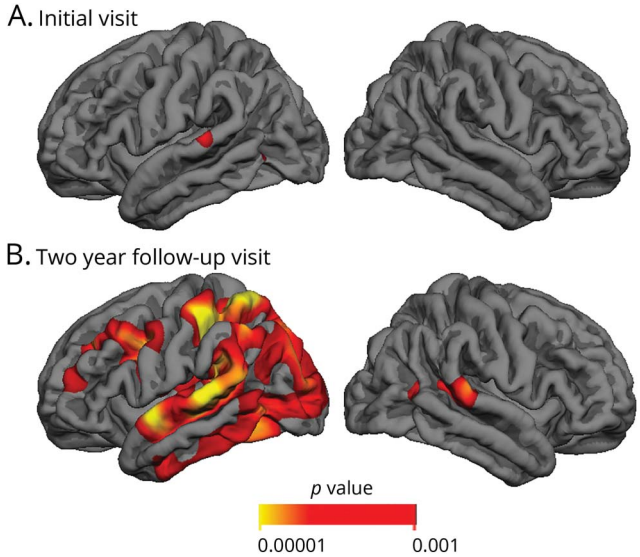
Abbreviations: ADLQ = Activities of Daily Living Questionnaire[40]; AQ = Aphasia Quotient; BNT = Boston Naming Test[34]; CDR = Clinical Dementia Rating scale[42,43]; FBI = Frontal Behavior Inventory[41]; MMSE = Mini Mental State Examination[39]; NAT = Northwestern Anagram Test[38]; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia[37]; PPA = primary progressive aphasia; PPT = Pyramids and Palm Trees[36]; PPVT Peabody Picture Vocabulary Test[35]; 3W3S = Three Words–Three Shapes; WAB = Western Aphasia Battery[33]; WAB Rep 66 = subset of most difficulty repetition subtest items WASI-II VCI = Wechsler Abbreviated Scale of Intelligence Verbal Comprehension Index.
[a] Numbers in parentheses after each test name represent the total possible raw score on that test.

Over 4 years, as was anticipated in PPA, language test scores declined while other test scores remained normal, as did her level of functioning in routine activities of daily living (table 1). A repeat MRI scan 2 years later (figure 1B) showed more extensive involvement of the left cerebral hemisphere, localized primarily to the perisylvian region, and focal atrophy in the right hemisphere localized to the poster aspects of the STG, homologous to the area identified in the left hemisphere at initial visit.

The patient's mother, 85 years of age and cognitively healthy at the time of study, did not report early learning difficulties and worked as a medical professional until her retirement. Three of her own 10 siblings reportedly had symptoms of early learning difficulties. Her deceased spouse, the proband's father, reportedly had early difficulty with math but was a successful teacher. At 70 years of age, he had complained to his spouse, "I am losing my words" and died of "a dementia" at 86 years of age. No further information was available about her father, although the reported history raises suspicion that he may also have had a language-prominent dementia.

Table 2 shows scores on the MoCA and MINT, scaled scores on the WASI-II,[14] standard scores on the WRAT-4,[15] and number of early and persistent symptoms of language-based learning disability endorsed by each sibling. The cutoff score for normal cognition on the MoCA is 26, and 2 siblings' scores fell below that level. Sibling 8, with the lowest MoCA score (24 of 30), lost points on language-dependent items, including sentence repetition, similarities, and delayed word recall but had normal recognition. MINT scores were all normal for age and education according to tables available online from the National Alzheimer Coordinating Center (alz.washington.edu/WEB/UDS3means.pdf).

Figure 1 Cortical atrophy in proband with primary progressive aphasia compared to controls



Colored regions show significant cortical thinning in the proband compared to controls (A) at baseline and (B) at the 2-year follow-up. False discovery rate was set at 0.05. Heat map shows significance level for each region.

WASI-II VCI scores for the siblings ranged from 85 (psychometrically considered to lie in the low-average range) to 120 (superior range), with an average of 105 (SD 13.16), solidly in the average range of a normal distribution. In contrast, PRI scores ranged from 115 (high-average range) to 142 (very superior range), with an average of 128.11 (SD 11.15), the psychometrically superior range. The discrepancy between VCI and PRI scores was an average of 29.60 points (SD 17.45), with all but 2 siblings showing higher PRI than VCI scores. On average, in this age group, a VCI-PRI discrepancy of <10 points is not considered statistically significant, but a discrepancy from 16 to 45 points, as determined in the siblings, even those with no early history, is unlikely to occur by chance, well beyond the $p = 0.05$ level.[14] Despite their early learning difficulties, however, all siblings' current standard scores on the WRAT-4 were at least in the average range on tests of single word oral reading, spelling, and arithmetic achievement. Nevertheless, standard WRAT-4 scores were significantly lower than the scaled scores on the nonverbal tests of the WASI, indicating a discrepancy between reading achievement and capacity.

Seven of the 9 siblings could be labeled as having early language-based learning disabilities, including dyslexia. Table 2 shows the number of symptoms of early dyslexia or other language-based difficulties endorsed by each sibling as present in childhood and in adulthood. For some, symptoms were prohibitive in elementary school but then seem to have been overcome by adulthood as in sibling 3 (table 1). Several siblings held managerial or other positions with high levels of responsibility. Hobbies emphasized nonverbal skills and talents such as home construction, the arts, and physical sports. Many spoke proudly of their strong people skills.

Vertex-wise thickness analyses across the cortex were used to compare the 9 siblings to 13 controls of similar age and level of education (mean controls demographics: age 56 ± 3.24 years, education 16 ± 2.6 years) and no history of early learning disability. No difference was detected. Hemispheric asymmetry of language-relevant areas was assessed with a previously described perisylvian cortex ($PSTC^R$) ROI.[28] The asymmetry index was calculated as (left $PSTC^R_{volume}$ − right $PSTC^R_{volume}$)/whole $cortex_{volume}$) and was compared to zero with the use of t tests. In this analysis, the siblings showed significant within-group asymmetry (asymmetry ratio −0.006 ± 0.003; $p = 0.007$), indicating smaller left hemisphere $PSTC^R$ ROI volume than right (left hemisphere 104.7 ± 6.1 cm^3, right hemisphere 108.1 ± 5.2 cm^3). The asymmetry index for controls was not significant (asymmetry ratio −0.004 ± 0.007; $p > 0.05$).

Seven of the 9 siblings (all but siblings 7 and 9 in table 2) had MRI data usable for resting-state fMRI analysis. Comparison between these siblings and 7 healthy controls (mean age 57.25

Table 2 Demographics, test scores, and language learning disability history in siblings with PPA

Participant	SIB 1	SIB 2	SIB 3	SIB 4	SIB 5	SIB 6	SIB 7	SIB 8	SIB 9
Dyslexia/ LD lang	Present	Present	Present	Absent	Absent	Present	Present	Present	Present
Sx Child (10)[a]	3	6	1	NA	NA	7	10	9	1
Sx Adult (10)[a]	0	3	1	NA	NA	0	7	4	1
Early Sx	Speaking, reading	Reading, "dyslexia"	Spelling	NA	NA	Spelling, reading, grammar	Dyslexia Dx	Dyslexia	Writing
MoCA total (30)	27	27	25	30	29	28	30	24	29
MINT (32)	31	32	29	30	28	32	31	30	32
WASI-II VCI[b]	108	100	108	99	90	120	109	85	126
WASI-II PRI	138	145	130	115	125	118	142	120	120
PRI-VCI	30	45	22	16	35	−2	33	35	−6
WRAT-4[c] Reading	108	113	109	116	106	116	102	92	105
WRAT-4 Spe	112	102	98	109	102	104	94	88	109
WRAT-4 Math	116	127	117	120	110	104	108	94	111

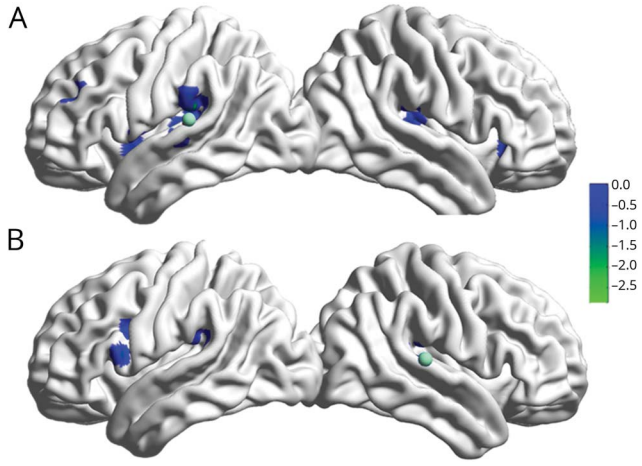
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; Dx = diagnosis; LD lang = language-based developmental learning disability/difficult; MINT = Multilingual Naming Test; MoCA = Montreal Cognitive Assessment; NA = not applicable; PPA = primary progressive aphasia; PRI = Perceptual Reasoning Index; SIB = sibling; Sx = symptoms of dyslexia and other language-related difficulties reported in childhood (Child) and adulthood (Adult); VCI = Verbal Comprehension Index; WASI-II = Wechsler Abbreviated Scale of Intelligence, Second Edition; WRAT-4 = Wide Range Achievement Test–Fourth Edition; WRAT-4 Math = WRAT-4 Mathematics subtest standard score; WRAT-4 Read = WRAT-4 Word Reading subtest standard score; WRAT-4 Spe = WRAT-4 Spelling subtest standard score.
Tables for means and SD on subtests of the UDS 3.0 neuropsychological battery can be found at: alz.washington.edu/WEB/UDS3means.pdf.
[a] Numbers in parentheses represent total number of symptoms surveyed.
[b] Scaled scores are reported (mean 100, SD 15).
[c] Standard scores are reported (mean 100, SD 15).

± 3.62 years, mean education 16 ± 3 years) showed that the siblings with PPA had decreased connectivity between the left superior temporal cortex ROIp and left hemisphere language regions and regions in the right hemisphere (figure 2). Because there was a trend toward an older average age for siblings compared to controls, age was entered as a covariate. Areas with decreased connectivity with the left ROIp in the siblings include the STG, auditory cortex, insula, planum temporale, supramarginal gyrus, inferior frontal gyrus pars opercularis, and middle frontal gyrus on the left side and the STG and insula on the right. Areas with decreased connectivity with the right hemisphere homologous ROIp in the siblings with PPA compared with controls included pars opercularis of inferior frontal gyrus, insula, and supramarginal gyrus on the left side. There was no significant decrease in connectivity between a homologous right hemisphere seed and homologous language network regions on the right. Maps were thresholded at $p < 0.0001$, uncorrected.

Connectivity of the left ROIp was also analyzed separately within controls and within siblings with PPA. Figure 3A shows regions of connectivity with the left ROIp in the controls, which included the posterior STG, posterior middle temporal gyrus, insula, planum temporale, and pars opercularis of inferior frontal gyrus on the left side and the posterior STG, insula, and planum temporale on the right. Although we did not do quantitative comparisons, a similar analysis in the siblings with PPA (figure 3B) showed that connectivity with these regions was reduced especially on the left. Of note, there were no differences between the siblings with PPA and controls in the connectivity of the right or left attention network ROI, confirming specificity of the above findings to the perisylvian cortex.

Exome sequencing was performed in 8 affected (proband, 5 cases of severe dyslexia, and 2 cases of mild dyslexia) and 3 unaffected (mother, 2 siblings) family members. A total of 101,884 variants were identified within the targeted exomes. First, we focused on the most common frontotemporal demential and Alzheimer disease genes (*GRN*, *MAPT*, *TARDBP*, *FUS*, *APP*, *PSEN1*, and *PSEN2)* for which no known pathogenic variants were observed; a *C9orf72* repeat

Figure 2 Language network connectivity in siblings of proband with PPA



Functional connectivity maps comparing 7 siblings with primary progressive aphasia (PPA) and 7 healthy controls ($p < 0.0001$, uncorrected). (A) Areas with decreased connectivity with the left region of interest centered at the peak area of atrophy in the proband (ROIp) in the siblings. (B) Areas with decreased connectivity with the right hemisphere homologous ROIp in the siblings with PPA compared with controls. Heat map scale depicts *z* values.

expansion was also excluded. After filtering out variants with low quality, we focused on protein-changing variants that were present in all dyslexic cases and had minor allele frequencies up to 20% in the gnomAD database (gnomad.broadinstitute.org) because that corresponds to the estimated frequency (15%–20%) of language-based learning disability in the general population. None of the shared candidate variants segregated perfectly with the dyslexia phenotype in this family; they were also observed in relatives with no reports of language disability. We also looked at rare (minor allele frequency <1%), predicted damaging protein-changing variants within brain expressed genes that were observed only in the case with PPA, but we found no compelling candidate variant.

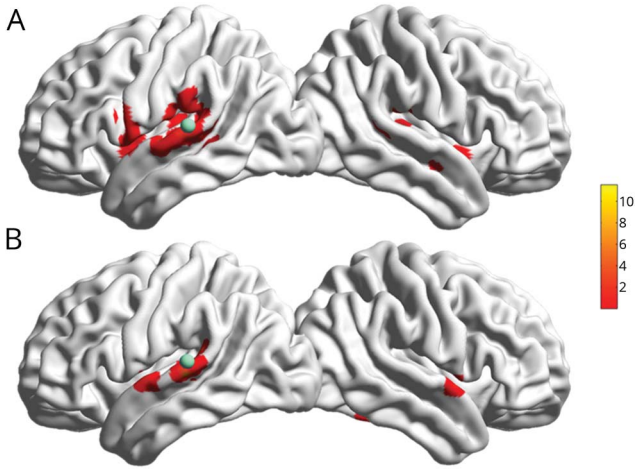
Discussion

This article reports the family of a proband with PPA with a strong prevalence of developmental language-based difficulties, including dyslexia. Although the proband lacked a history of early language disability, 7 of her 9 siblings reported early, in some cases persistent, symptoms of difficulties with reading, spelling, writing, and grammar. All but 2 of the siblings displayed a unique neuropsychological signature marked by a highly significant discrepancy between scores on neuropsychological tests of verbal and nonverbal abilities, with the former significantly lower than the latter. Structural MRI showed no differences between the siblings and controls in brain volume. However, within the siblings, the left hemisphere was smaller than the right hemisphere in the language areas, a difference not seen in controls. Resting-state analysis comparing the siblings to controls revealed decreased connectivity between a left hemisphere STG seed, chosen to overlap the area of greatest atrophy in the proband at an early disease stage, and other regions of the language network in the left hemisphere and, perhaps to a lesser extent, in homologous regions in the right cerebral hemisphere. In contrast, connectivity within a dorsal frontoparietal attention network was similar to that in controls. Finally, none of the known genes associated with dyslexia showed an association with members of this family, nor were there any of the known mutations associated with neurodegenerative diseases of the FTLD or Alzheimer type.

Functional imaging studies in children with dyslexia have shown reduced activation in regions including the left middle frontal gyrus and inferior parietal lobule, right superior frontal and middle temporal gyri, and right inferior parietal lobule.[29] Thus, the siblings in the family reported here also showed reduced connectivity in these areas, consistent with their early language-based learning difficulties.

The prevalence of dyslexia in children has been estimated at anywhere from 5% to 17%.[30] In the family reported in the present study, the patient herself did not have a history of learning disabilities. However, an astonishing 7 of her 9 siblings (77%) reported early struggles with language-based subjects such as reading, spelling, and writing. In some cases, the difficulties persisted into adulthood, but all siblings had achieved success in their careers, which tended to be non–language skill oriented. It is of interest also that on formal academic achievement tests of reading, spelling, and arithmetic, none of the

Figure 3 Resting-state fMRI maps showing connectivity with the left hemisphere seed for 7 controls and 7 siblings with PPA



Colored regions show areas with connectivity with the left region of interest centered at the peak area of atrophy in the proband (ROIp; green sphere) in each group. (A) In controls, areas of connectivity include posterior superior temporal gyrus (STG), posterior middle temporal gyrus, insula, planum temporale, and pars opercularis of the inferior frontal gyrus on the left side and the posterior STG, insula, and planum temporale on the right. (B) In the siblings with primary progressive aphasia (PPA), connectivity with the above areas is diminished compared with controls. Maps were thresholded at $p < 0.0001$, uncorrected. Heat map scale depicts *t* values.

siblings had abnormal scores at the time of testing. In a review of their index scores on the WASI-II, it is apparent that these individuals possess some above-average talents in many cognitive areas that perhaps permitted them to overcome or compensate for their early language-based difficulties. Furthermore, although adult reading achievement test scores were within the normal range, they were nevertheless lower than the nonverbal WASI-II scores, further highlighting the discrepancies between non–language- and language-based cognitive abilities.

This unique family adds to the growing evidence that at least some cases of PPA arise on a background of a familial vulnerability of the language network. Although the siblings with dyslexia had no area of significant regional atrophy within the left hemisphere language network, they did have overall smaller left than right cortical volume. They also had decreased resting-state connectivity within the perisylvian cortex on the left, including the planum temporale, an area of particular relevance to language dominance and dyslexia.[31]

These findings are in keeping with the hypothesis that some cases of PPA reflect a congenital vulnerability of the language network. In some individuals, the vulnerability interferes with the development of language (as in the 7 siblings of this family). In others (as in the proband), compensatory events of neuroplasticity allowed the normal development of language. However, the vulnerability reemerges in adulthood as a locus of least resistance for the effects of an independently arising neurodegenerative disease. This may explain why the proband developed PPA rather than another form of dementia in response to her neurodegenerative disease. An early report of late-onset hemiparkinsonism in 4 men with congenital hemiatrophy on the same side as the hemiatrophy[32] has established that this mechanism is plausible. In the current family, the absence of significant genetic correlates may simply reflect the small sample size. A larger number of families such as the one reported here may offer the statistical power needed to detect potential genetic correlates of this selective vulnerability. Progress in this area would also lead to new discoveries on the molecular basis of brain asymmetry and the language network.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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