The logopenic/phonological variant of primary progressive aphasia

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ABSTRACT

Objective: Primary progressive aphasia (PPA) is characterized by isolated decline in language functions. Semantic dementia and progressive nonfluent aphasia are accepted PPA variants. A "logopenic" variant (LPA) has also been proposed, but its cognitive and anatomic profile is less defined. The aim of this study was to establish the cognitive and anatomic features of LPA.

Methods: Six previously unreported LPA cases underwent extensive neuropsychological evaluation and an experimental study of phonological loop functions, including auditory and visual span tasks with digits, letters, and words. For each patient, a voxel-wise, automated analysis of MRI or SPECT data were conducted using SPM2.

Results: In LPA, speech rate was slow, with long word-finding pauses. Grammar and articulation were preserved, although phonological paraphasias could be present. Repetition and comprehension were impaired for sentences but preserved for single words, and naming was moderately affected. Investigation of phonological loop functions showed that patients were severely impaired in digit, letter, and word span tasks. Performance did not improve with pointing, was influenced by word length, and did not show the normal phonological similarity effect. Atrophy or decreased blood flow was consistently found in the posterior portion of the left superior and middle temporal gyri and inferior parietal lobule.

Conclusions: Logopenic progressive aphasia (LPA) is a distinctive variant of primary progressive aphasia. Cognitive and neuroimaging data indicate that a deficit in phonological loop functions may be the core mechanism underlying the LPA clinical syndrome. Recent studies suggest that Alzheimer disease may be the most common pathology underlying the LPA clinical syndrome.
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GLOSSARY

AD = Alzheimer disease; **BA** = Brodmann area; **CDR** = Clinical Dementia Rating; **CVLT-MS** = California Verbal Learning Test–Mental Status Edition; **ECD** = ethyl cysteinate dimer; **FWHM** = full-width at half-maximum; **GM** = gray matter; **LPA** = logopenic progressive aphasia; **MMSE** = Mini-Mental State Examination; **PNFA** = progressive nonfluent aphasia; **PPA** = primary progressive aphasia; **Rey-O** = Rey–Osterrieth; **SemD** = semantic dementia; **VBM** = voxel-based morphometry; **WAB** = Western Aphasia Battery; **WAIS-III** = Wechsler Adult Intelligence Scale, Third Edition.

Since Mesulam's original description of primary progressive aphasia (PPA) in 1982,[1] it has become clear that progressive isolated language disorders due to neurodegeneration are clinically heterogeneous. They are caused by patterns of localized cerebral dysfunction that do not necessarily match those affected "typically" by vascular strokes. Thus, the present-day distinction between progressive nonfluent aphasia (PNFA) and semantic dementia (SemD) may reflect an oversimplification of the clinical presentations of progressive aphasia.[2] In a recent study,[3] the term "logopenic"[4] was revived to label PPA patients who did not show the pattern

of language dysfunction typical of PNFA and SemD, respectively. Logopenic progressive aphasia (LPA) was characterized by slow speech, sentence repetition, and comprehension deficits, and relative sparing of motor speech, grammar, and single-word comprehension.[3] Significant atrophy was found in the left posterior temporoparietal region, rather than in the left frontoinsular or anterior temporal areas typically affected in PNFA and SemD, respectively. In agreement with the location of atrophy, it was hypothesized that a deficit in auditory verbal short-term memory could be the core mechanism in LPA.[3,5] Short-term memory is a limited-capacity system allowing the temporary storage and manipulation of information.[6] Baddeley[7] proposed a multicomponent model of verbal working memory comprising the central executive and the phonological loop. The phonological loop is a component of short-term memory that includes a "store," in which phonological memory traces are held over a period of few seconds, and an articulatory "rehearsal" process that refreshes them.

Despite the initial observation,[3] studies investigating the cognitive and anatomic mechanism in LPA are lacking, and even its existence is under debate. Here, we performed a detailed neuroimaging and cognitive study of six new cases of LPA, including an experimental assessment of phonological loop functions. We hypothesized that all patients would show phonological loop deficits and anatomic involvement of the left posterior temporoparietal region. Confirmation of this hypothesis would establish LPA as a recognizable, separate clinical variant of PPA with specific neuroimaging correlates.

METHODS **Subjects.** Six LPA patients (table 1) at the University of California, San Francisco Memory and Aging Center (n = 4) or at the Neurology Unit, San Raffaele Turro, Milan (n = 2), participated in the study. Patients were selected from a pool of LPA cases on the basis of their ability to participate in numerous testing sessions and the availability of a brain scan. They were all new cases, not included in our previous article.[3] Patients were evaluated by a team of experienced clinicians and underwent a baseline neurologic, neuropsychological, and language evaluation. LPA was diagnosed when patients did not meet criteria for SemD and PNFA because of the presence of slow, well-articulated and grammatic speech (thus excluding PNFA) and good single-word comprehension (thus excluding SemD).[3] Imaging findings were not used for

diagnosis. Informed consent was obtained, and the study was approved by each local ethics committee.

All patients had similar clinical histories with approximately 3 years of word-finding difficulties starting in their 50s. At the time of examination, three patients had mild calculation, writing, and verbal memory difficulties. None had visuospatial deficits. Anxiety, depression, and irritability were common. Two patients showed mild slowing of rapidly alternating movements in the right hand. Although extensive follow-up is still not available in most patients, clinical evolution was generally slow, with relative sparing of functional status 5 years after onset.

Cognitive assessment. *Neuropsychological assessment.* All patients underwent a comparable neuropsychological assessment, using language-specific tests of verbal long-term memory, verbal and visuospatial short-term memory, visuospatial abilities, and executive functions (table e-1 on the *Neurology*® Web site at www.neurology.org).

General language evaluation. Language and cognitive functions were assessed in each patient's native language with comparable measures. We tested fluency, single-word and sentence repetition, word–picture matching, sentence-to-picture matching, and confrontation naming using the Western Aphasia Battery,[8] the Boston Naming test,[9] and portions of Curtiss Yamada Comprehension Language Evaluation–Receptive[10] (cases 1–4), and with the Battery for the Analysis of the Aphasic Deficit[11] (cases 5 and 6). The Pyramid and Palm Trees Test pictures were used in all patients.[12] In the four US patients, the Motor Speech Evaluation was also administered.[13]

Experimental phonological loop assessment. The short-term memory model proposed by Baddeley[7] accounts for several effects that characterize the normal functioning of the phonological loop:

1. The phonological similarity effect: Sequences of items that sound similar (e.g., the letters *B* and *T*) are harder to remember compared with dissimilar sounding examples (e.g., the letters *W* and *Z*). The absence of this effect indicates a phonological store deficit.
2. The word length effect: Sequences of long words are harder to remember than sequences of shorter words because longer words take more time to rehearse and their trace fades more quickly.

The following testing procedures were applied to all patients to test for these effects.

Digit span tasks. Digit span tasks were administered under auditory/verbal, visual/verbal, and auditory/pointing conditions.[14] For each condition, patients were presented with a sequence of digits at a rate of one digit per second and were asked to recall the exact sequence immediately after presentation. Ten trials of each sequence length (i.e., one digit, two digits, etc.) were tested. Each correctly recalled trial was scored as 0.1, so the perfect score for any given sequence length would be 1. Span level was established when the patient recalled at least six trials at a given length.

For the auditory/verbal condition, stimuli were presented auditorily, and patients responded verbally. For the visual/verbal condition, each digit was presented sequentially in black font on a white background, and patients were required to reproduce the sequence verbally. For the auditory/pointing condition, stimuli were presented auditorily, and patients responded by pointing to the correct items within an array of single digits. The pointing condition excluded an articulation disorder.

Letter span tasks: Phonological similarity effect. Span levels for sequences of phonologically similar and dissimilar letters were

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, y/sex	56/F	60/F	56/F	63/M	57/F	61/F
Education, y	14	16	17	12	13	8
CDR total (0–3)	0.5	0.5	0.5	0.5	0.5	0.5
MMSE	22	25	17	22	16	28
Copy modified Rey-O figure (max = 17)	15	17	16	13	—	—
Copy Rey-O complex figure (max = 36)	—	—	—	—	12	32
WAIS-III no. digits forward	4	4	4	4	2	4
WAIS-III spatial span	4	7	4	7	—	—
Corsi span	—	—	—	—	2	5
CVLT 10-minute Delayed Free Recall	5	7	4	5		
Rey word list 15-minute Delayed Free Recall					0	14
WAIS-III no. digits backward	2	4	3	3	—	3
Trail Making	120	120	120	74	—	103
Spontaneous speech WAB (max = 20)	19	19	17	14	13	16
Motor Speech Evaluation (0–7 severity scale)						
Apraxia of speech	0	0	0	0	—	—
Dysarthria	0	0	0	0	—	—
Phonemic fluency	7	18	5	7	3	9
Semantic fluency	13	16	8	8	2	11
Confrontation naming, % correct	73	80	93	80	80	93
Word repetition, % correct	100	100	100	100	70	93
Sentence repetition, % correct	68	75	76	76	50	63
Single-word comprehension, % correct	95	100	98	98	90	100
Sentence comprehension, % correct	66	68	47	60	56	73
Pyramid and Palm Trees pictures, % correct	100	96	92	100	90	96

Table 1 Demographic, functional, and cognitive assessment for each patient (cases 1–4 from the United States, cases 5 and 6 from Italy)

Raw scores are reported for general cognitive assessment and percentage correct for language measures.
CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; Rey-O = Rey–Osterrieth; WAIS-III = Wechsler Adult Intelligence Scale, Third Edition; CVLT = California Verbal Learning Test; WAB = Western Aphasia Battery.

tested. The same procedures as for the digit span were adopted but tested only in the auditory/verbal and visual/verbal conditions. Two sets of letters, phonologically similar (e.g., B, C, D, G, P, and T for both languages) and phonologically dissimilar (e.g., F, K, Q, R, X, W, and Z), were used in both languages as previously described.[14] Ten sequences of letters, increasing in length and including letters from one set alone, were presented at a rate of one per second.

A group of 11 age- and education-matched normal controls (six Italian, five US) showed a significant effect of phonological similarity when tested with this material (mean phonologically similar: 6.00, mean phonologically dissimilar: 6.55; t test, $p < 0.05$).

Word span tasks: Word length effect. The auditory/verbal and visual/verbal conditions were tested. Two sets of two- or four-syllable words, matched by frequency, were used for each language.[14,15] For each set, 10 word sequences of increasing length were generated. No word was presented twice.

The same group of 11 controls showed a significant effect of word length (mean long word: 6.09, mean short word: 7.18; t test, $p < 0.01$).

Patients with a specific deficit in the phonological store are expected to show normal immediate recall of individual items,

defective span in both auditory/verbal and visual/verbal conditions with no improvement with pointing, and absence of phonological similarity. The word length effect should be preserved, unless the rehearsal is also affected.

Neuroimaging study. *Voxel-based morphometry analysis of MRI data (cases 1–4).* T1-weighted MRI scans were acquired using a 1.5-tesla Magnetom VISION system (Siemens Inc., Iselin, NJ) as previously described for cases 1–4.[3] Voxel-based morphometry (VBM) analysis was implemented in the SPM2 software package (The Wellcome Department of Imaging Neuroscience, London, UK) using standard procedures.[16] Images were normalized to an age-matched template, modulated, and spatially smoothed with a 12-mm full-width at half-maximum (FWHM) isotropic gaussian kernel.

Group analyses of gray matter (GM) and white matter (WM) images were used to compare patients with a control group of 40 age- and sex-matched healthy controls. Single-subject GM analyses were used to compare each patient with controls. Age, total intracranial volume, and sex were confounding variables. In the group analysis, significance was set at $p < 0.05$ corrected for multiple comparisons (family-wise error corrected). Because of the risk of false negatives in

Table 2 Digit, letter (similar and dissimilar), and word (short and long) span results

Sequence length, no. of items per sequence	Verbal response		Pointing	
	Digits		Digits	
	Auditory	Visual	Auditory	
1	1.0 (0)	1.0 (0)	1.0 (0)	
2	0.9 (0.2)	0.9 (0.2)	0.9 (0.1)	
3	0.7 (0.3)	0.6 (0.3)	0.7 (0.3)	
	Immediate verbal recall		Immediate verbal recall	
	Letters similar		Letters dissimilar	
	Auditory	Visual	Auditory	Visual
2	0.9 (0.2)	0.8 (0.3)	0.9 (0.2)	0.8 (0.3)
3	0.6 (0.2)	0.6 (0.2)	0.6 (0.3)	0.5 (0.1)
	Short words		Long words	
	Auditory	Visual	Auditory	Visual
1	1.0 (0)	1.0 (0)	1.0 (0.1)	1.0 (0.1)
2	0.8 (0.2)	0.9 (0.2)	0.1 (0.1)	0.6 (0.4)
3	0.6 (0.4)	0.6 (0.3)	—	—

Data are mean (SD) of correctly recalled trials (0.1 for each trial, 1.0 maximum).

single-subject and WM VBM analyses,[17] we report results of these analyses at $p < 0.001$, uncorrected for multiple comparisons.

99mTc-ethyl cysteinate dimer SPECT analysis (cases 5 and 6). 99mTc-ethyl cysteinate dimer SPECT imaging was used to detect regional hypoperfusion in the two Italian patients compared with 15 age-matched normal controls, using previously described procedures.[18]

Image preprocessing (spatial normalization to a standard Montreal Neurological Institute SPECT template and 12-mm FWHM smoothing) and statistical analysis were implemented in SPM99 using standard validated procedures.[19] Age and total global distribution of the tracer's uptake were entered as confounding variables. Single-subject analyses were performed by comparing each patient with the control group, with significance set at $p < 0.001$ uncorrected.

RESULTS Cognitive assessment. *Neuropsychological assessment.* Mini-Mental State Examination scores were abnormal in all patients, whereas the Clinical Dementia Rating was in the mild impairment range (0.5 in each patient) (table 1). The profile of neuropsychological and language impairment was compatible with an LPA diagnosis, as previously reported.[3] Visuospatial abilities and spatial working memory span were preserved with the exception of case 5, in whom they were mildly impaired. Conversely, most tests with a verbal component,

Figure 1 Pattern of gray matter atrophy or hypoperfusion in each patient compared with healthy controls
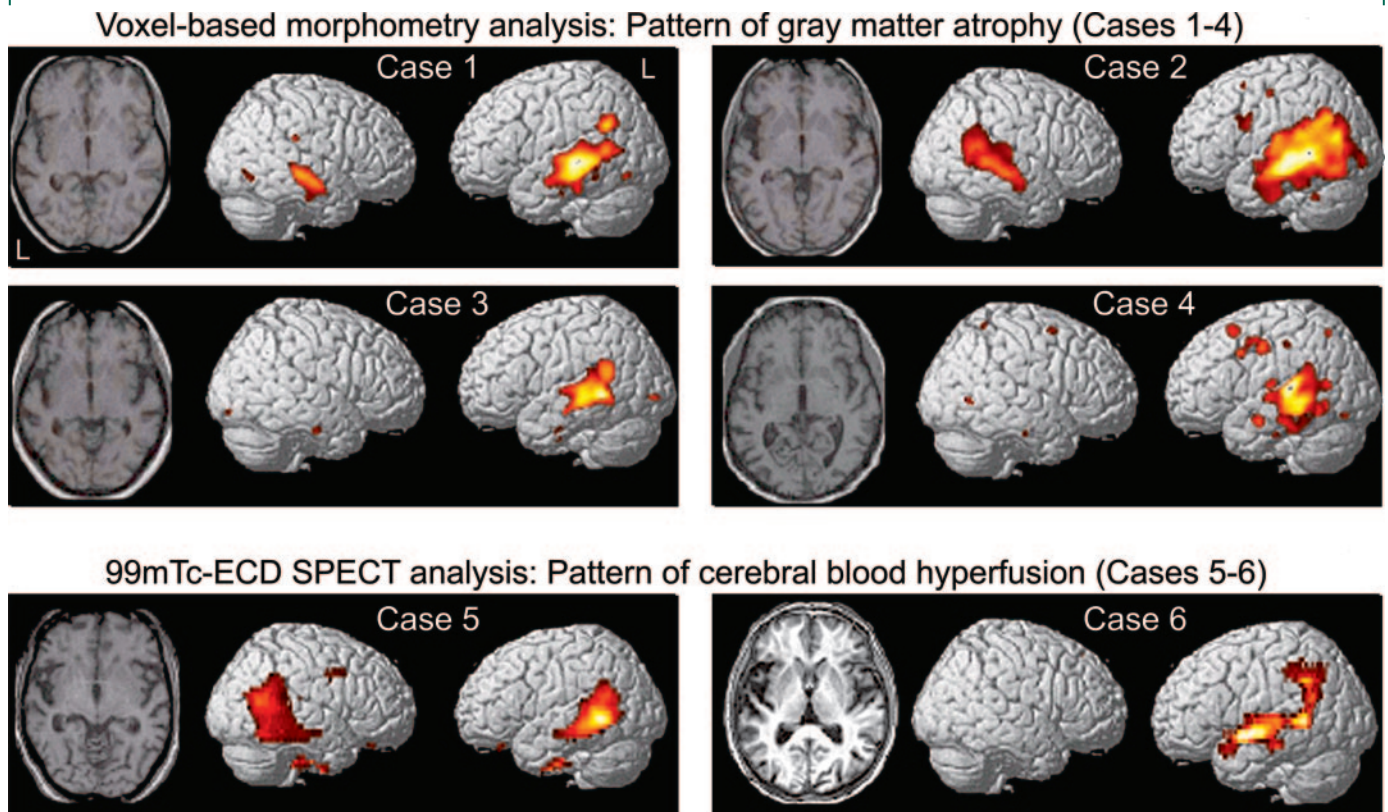
Representative axial sections of each original structural MRI are displayed in the left panel. Voxel-based morphometry and SPECT results are thresholded at $p < 0.005$ uncorrected for multiple comparisons and superimposed on the three-dimensional rendering of the Montreal Neurological Institute standard brain. ECD = ethyl cysteinate dimer.

Table 3 Results of the VBM gray matter group analysis (p < 0.05 FWE corrected for multiple comparisons) and SPECT single-subject analysis (p < 0.001 uncorrected)

Brain region (BA)	VBM: GM atrophy group analysis, cases 1–4				SPECT: hypoperfusion single-subject analysis, case 5				SPECT: hypoperfusion single-subject analysis, case 6			
	x	y	z	Z	x	y	z	Z	x	y	z	Z
L inferior parietal lobule (39/40)	−48	−58	32	4.9	−42	−50	−28	3.0*	−36	−42	36	3.8
									−54	−58	40	3.1
L superior temporal gyrus (22)	−58	−49	15	5.5	−58	−50	16	3.3				
	−62	−20	1	5.2					−60	−20	0	3.3
									−54	−4	−8	3.4
L middle temporal gyrus (21)	−55	−45	1	6.4	−52	−50	0	5.0+	−50	−48	0	3.5
	−65	−50	−8	5.6								
	−58	−63	11	5.1	−50	−54	20	3.2				
	−62	−16	−15	5.0								
L inferior temporal gyrus (20)	−62	−56	−14	4.9	−60	−52	−8	3.3				
	−52	−18	−29	4.7								
L posterior cingulum (26)					−8	−34	20	3.6				
R middle temporal gyrus (21)	68	−33	3	4.7	56	−44	0	3.1				
					48	−52	8	3.8				
R inferior temporal gyrus (20)	57	−17	−24	5.0								
R posterior cingulum (26)					−8	−34	20	3.6				

* p = 0.002 uncorrected for multiple comparisons.
+ p < 0.05 family-wise error (FWE) corrected for multiple comparisons in the SPECT single-subject analysis.
VBM = voxel-based morphometry; GM = gray matter; BA = Brodmann area.

such as the verbal short- and long-term memory tests, revealed deficits. Case 6 was the exception, showing normal performance in long-term verbal memory.

Language evaluation. Spontaneous speech production was characterized by slow, hesitant speech with word-finding pauses (see e-audio, table 2). Speech in response to a picture was characterized by decreased rate and occasional phonemic paraphasias and word-finding difficulty. Sentences were simple, but grammatically well formed and without omission of grammatic morphemes. Motor speech abilities were within normal limits, and no apraxia of speech or dysarthria was noted.

Comprehension was spared at the single-word level, and Pyramid and Palm Trees Pictures performance was mildly impaired in the two more advanced cases (cases 3 and 5), indicating that semantic memory was relatively preserved (table 1). Conversely, patients showed word-finding pauses in speech production and poor confrontation naming ability. Errors consisted mostly of complete anomia (no response) or phonemic paraphasias, suggesting a mixed mechanism of paraphasic and word-selection anomia.[20] Comprehension at the sentence level was impaired, but there was no evidence of a structural complexity effect.

A specific pattern of repetition difficulties was found in all patients. Single-word repetition was largely preserved, whereas sentence repetition was severely impaired, especially for low-probability sentences. The pattern of errors in sentence repetition suggested that patients were using a semantic rather than a phonological route.[21] For example, when asked to repeat "It looks as if nobody is around," one patient responded, "It looks like nobody is there."

Phonological loop assessment. *Digit span.* Patients performed normally on the immediate recall (repetition) of individual and pairs of digits but were severely impaired in sequences of more than three digits (table 2). Performance was unrelated to the modality of presentation (auditory or visual) or output (verbal or pointing).

Letter span: Phonological similarity effect. Span was three in both conditions (table 2). In contrast to normal subjects, phonologically dissimilar letters provided no benefit, either with auditory or with visual presentation.

Word span: Word length effect. Span was three for short words, but patients could repeat only one long word (table 2). This effect of word length was particularly evident in the auditory modality.

Neuroimaging study. *Analysis of gray matter atrophy or hypoperfusion.* A consistent pattern of GM atrophy (cases 1–4) or hypoperfusion (cases 5 and 6) was found

Figure 2 Pattern of white matter atrophy in the four US patients compared with controls
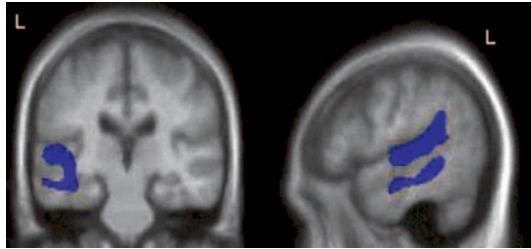
Voxel-based morphometry group analysis results are superimposed on the template image. Results are thresholded at $p < 0.005$ uncorrected for multiple comparisons. Peaks of white matter (WM) atrophy were located in the posterior portion of the left superior (most significant WM peaks: $x = -53$, $y = -40$, $z = 16$, $Z = 4.2$; $x = -49$, $y = -21$, $z = -1$, $Z = 3.9$) and middle ($x = -55$, $y = -40$, $z = -9$, $Z = 3.8$; $x = -55$, $y = -40$, $z = -9$, $Z = 3.6$) temporal gyri, and in the right posterior superior temporal gyrus ($x = 56$, $y = -33$, $z = 17$, $Z = 3.6$).

in the posterior portion of the left superior and middle temporal gyri and in the inferior parietal lobule (cases 1–4 and 6) (figure 1 and table 3). In three cases, damage spread from the posterior temporal areas to the inferior and/or more anterior temporal regions. The corresponding contralateral right posterior temporal region was involved in cases 1, 2, and 5. Case 5 alone showed hypoperfusion bilaterally in the posterior cingulum.

White matter atrophy. WM loss was observed in correspondence to GM atrophy in the posterior portion of left middle temporal and bilateral posterior superior temporal gyri (figure 2).

DISCUSSION We defined the neuropsychological and imaging features of the logopenic variant of PPA that in our experience represents 30% of all PPA cases. Our results suggested that the core cognitive deficit in LPA was a phonological loop disorder. Consistently, the imaging investigation showed involvement of GM and WM in the left posterior temporal and inferior parietal regions.

LPA is characterized by a decreased rate of spontaneous language production with frequent halts due to word-finding pauses. Phonemic paraphasias are common, but motor speech and grammar are spared. This pattern of language production is different from the fast output typical of early SemD patients, who usually fill word-finding pauses with circumlocutions and filler words. It is also distinct from the production deficit typical of PNFA, in which articulation deficits and agrammatism predominate.[22] LPA patients, therefore, show a pattern of "intermediate" fluency distinct from the fluent SemDs and the nonfluent PNFAs, raising the issue of how to label their language production. Fluency is a composite mea-

sure, defined by multiple features of spontaneous language production. The concept was introduced by Goodglass et al.[23] to describe language production in vascular aphasia. Within this framework, a patient with would be described as "nonfluent" if he or she exhibited slow, effortful production, with motor speech impairment, defective prosody, and omission of grammatic morphemes. Conversely, fluent aphasic production would be characterized by normal motor speech and production rate, spared grammar, and the presence of phonological and lexical errors. The features of LPA patients' spontaneous production do not easily fit within this dichotomy, because motor speech is unaffected and grammar is preserved, yet speech production is slowed and halting. LPA patients score as "fluent" on formal aphasia tests, which give more weight to articulation and grammar, but may be labeled as "nonfluent" by the clinician who is impressed by their slow and hesitant production at the bedside (see e-audio for example of spontaneous speech in case 2 two years after initial evaluation reported in table 1). We suggest that the label "nonfluent" should be reserved for patients who show the motor speech and grammar deficits typical of PNFA. The term *logopenic* (from the Greek: "lack of words") could instead be used to describe the slow language output typical of LPA. Given the phonological nature of this deficit, the term *phonological variant* could also be applied.

The disorder of language production in LPA affects sentence repetition severely, yet spares the repetition of single words. A phonological loop disorder had been proposed to underlie this symptom.[3] The performance of our patients on the experimental phonological loop battery seems to confirm this hypothesis. LPA patients have markedly reduced digit span but perform normally on single-digit repetition, indicating that their deficit cannot be attributed to defective speech perception. The abolition of the phonological similarity effect suggests that the store component of the phonological loop system is impaired.[5] The articulatory rehearsal process was less affected, as evinced by the lack of improvement when the response was made by pointing, and by the partially preserved word length effect, especially in the visual modality.

The phonological loop sustains comprehension by maintaining online incoming verbal information, thus allowing syntactic interpretation of word strings.[7] A capacity reduction in the system has been shown to interfere with the ability to process sentences.[24] Consistently, LPA patients showed sentence comprehension deficits, regardless of syntactic complexity, whereas single-word comprehension was spared.

LPA most closely resembles vascular conduction aphasia, a syndrome characterized by fluent speech and

defective repetition and comprehension of sentences.[25] Cases similar to LPA have been reported by Hillis et al.[26] as "progressive conduction aphasia" and also by other authors under other PPA-related labels.[27,28] Conduction aphasia has been hypothesized to be caused a lesion in the arcuate fasciculus,[29] although damage to posterior GM temporoparietal regions has been associated with persistent repetition disorders.[30,31] Consistently, our patients with LPA showed GM and WM atrophy within the same region.

Neuroimaging results in LPA showed atrophy or hypoperfusion in left posterior middle and superior temporal and inferior parietal regions, a pattern different from SemD and PNFA. This finding confirmed, at the single-subject level, across languages and across imaging modalities, a previous group study of 10 different LPA patients.[3] Both patient series showed similar location of damage, demonstrating that the LPA syndrome is associated with a typical and consistent pattern of anatomic impairment in the left posterior temporoparietal cortices. The previous association of these regions with the phonological store[5,31,32] strengthens our findings of a defective functioning of this component of auditory short-term memory in LPA.

Although the term *PPA* refers to a clinical syndrome and not to a specific pathologic substrate, it was generally accepted that most cases would show non-Alzheimer, frontotemporal lobar degeneration–type pathology at autopsy. However, recent articles have demonstrated that focal, atypical distribution of Alzheimer disease (AD) pathology is responsible for 20% to 30% of cases with various forms of PPA.[2,33-35] Retrospective PET and MRI studies[36,37] demonstrated in PPA patients with AD pathology a pattern of temporoparietal involvement similar to LPA. Furthermore, all US patients described in this article had cortical amyloid binding on PET scans using the Pittsburgh compound B tracer.[38] Taken together, all these findings suggest that AD could be the most frequent cause of LPA, whereas it may be less frequently responsible for the other PPA syndromes.

We have shown that LPA is a distinctive clinical variant of PPA, associated with a phonological loop disorder and with anatomic damage to the left posterior temporoparietal region. Future studies will establish whether AD is the most common pathology underlying LPA.

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