



Nosology of Primary Progressive Aphasia and the Neuropathology of Language

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Introduction

Primary progressive aphasia (PPA) is a major syndrome of frontotemporal lobar degeneration (FTLD) and accounts for nearly 25% of all FTLD cases [1]. Approximately 60% of PPA is associated with FTLD and the remaining 40% with the neuropathology of Alzheimer's disease (AD). Information on PPA prevalence is limited. One study from the UK suggests an approximate prevalence of 3–4/100,000, a level comparable to what has been reported for ALS [1]. The one common denominator for all PPA, whether caused by FTLD or AD, is the preferential degen-

eration of the language network, usually located in the left hemisphere of the brain. Current research on primary progressive aphasia is evolving in multiple directions. For one, the variety of the aphasic disturbances continues to fuel discussion on nomenclature and clinical classification. Second, the selective dissolution of individual language domains is offering new paradigms for exploring the functional anatomy of language, a pursuit that has already prompted modifications of classic models. Third, the multiplicity of the underlying degenerative diseases is generating new insights on the heterogeneity of dementias, the probabilistic relationship of syndrome to

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pathology, and the mechanisms of selective vulnerability. Fourth, there is lively interest in formulating personalized interventions aimed not only at the nature of the language disturbance but also at the biology of the underlying disease entity. These are some of the current trends that will be reviewed in this chapter. Given the constraints of space and the vast literature on PPA, the account will be selective and based predominantly on the PPA research programs at Northwestern University where a cohort of 235 PPA patients have been enrolled, 97 of whom have come to brain autopsy.

Diagnosis, Nomenclature, and Subtyping

The existence of progressive language disorders had been known for more than 100 years. Pick, Sérieux, Dejerine, Franceschi, and Rosenfeld were among the first to report such patients during the late nineteenth and early twentieth centuries [2–7]. However, this topic did not attract much, if any, attention during most of the twentieth century. The current resurgence of interest in this condition can be traced to the 1982 report of six patients who experienced a slowly progressive aphasia without other cognitive or behavioral impairments [8]. The syndrome was named “primary progressive aphasia,” and diagnostic criteria were formulated [9, 10]. The following decades witnessed a rapidly expanding literature on PPA and on overlapping entities designated progressive nonfluent aphasia (PNFA) and semantic dementia (SD) [11]. For a number of years, research on PNFA and SD developed in parallel to research on PPA. In 2011, an international group of investigators presented classification guidelines that incorporated PNFA and SD under the PPA umbrella [12]. This unitary approach stimulated rapid progress in this field.

Three features define PPA: (1) adult-onset and progressive impairment of language (not just speech), (2) absence of other consequential behavioral or cognitive deficits for approximately the first 2 years, and (3) neurodegenerative disease as the only cause of impairment [10]. These

criteria help to filter out patients where progressive aphasias arise in conjunction with equally prominent speech apraxia, behavioral disturbances, loss of memory for recent events, associative agnosias, or visuospatial deficits. In the course of diagnostic evaluation, patients may show subtle impairments in non-language tasks, especially those related to memory and executive function. Such abnormalities of test performance do not by themselves preclude a PPA diagnosis unless they are associated with limitations of daily life in the corresponding non-language domains.

Many neuropsychological tests require verbal responses and verbal instructions. The clinician needs to consider the influence of the aphasia on these aspects of performance. For example, a patient with PPA who cannot name a famous face is not necessarily prosopagnosic, a patient who cannot verbalize the nature of an object does not necessarily lack knowledge of the object, and a patient who cannot learn a word list is not necessarily amnesic. Conversely, patients who cannot produce words because of articulation deficits, those who cannot repeat language because of general working memory limitations, those who misname objects or faces they do not recognize, or those who have impoverished speech because of abulia or impaired executive function are not necessarily aphasic. As in the case of many other syndromes, the diagnosis of PPA relies on the judgment and experience of the clinician. While clear-cut cases do exist, there are also cases where the salience and primacy of the aphasia will generate debate, especially if the patient is examined a few years after symptom onset. In some patients, the aphasia will remain the only salient feature for over a decade [13]. Other patients, however, may first come to a specialty clinic at a time when the disease has progressed to encompass other cognitive domains. The term “PPA plus” (PPA+) can be used to designate such patients, based on the assumption that the disease had started as PPA, but that it had since spread beyond the language network [14].

In contrast to many other dementias, where the patient has little insight into the predicament, patients with PPA are usually the first to notice

and report the difficulty. At those stages of the disease, MRI and metabolic positron emission tomography (PET) scans may be negative. The absence of positive neurodiagnostic tests, combined with lack of recognition of these symptoms in general practice, may lead to unwarranted referrals to otolaryngologists or psychiatrists [15]. Patients and families often ask whether the diagnosis is PPA or AD. When AD biomarkers (such as amyloid and phospho-tau in cerebrospinal fluid [CSF] or amyloid PET scans) are positive, the clinician will have to explain that the patient has both PPA and AD, that PPA refers to the symptoms that bring the patient to the clinic, and that AD refers to the abnormal amyloid and tau proteins in the brain that attack the language centers. There was a time when PPA was underdiagnosed. There are now instances where it seems to be overdiagnosed, probably because language impairments can be so prominent during the office evaluation that other equally substantial cognitive and behavioral impairments become overlooked. This issue comes up most commonly in patients with prominent apraxia of speech or executive dysfunction who are also aphasic. We give these patient descriptive diagnoses such as “apraxia of speech with aphasia” or “aphasic frontal syndrome.”

Language impairment can encompass word retrieval, object naming, sentence construction, or language comprehension, either singly or in combination. Once the PPA diagnosis is established, the subtyping exercise can be initiated. At the time of writing, the 2011 guidelines dominate this process [12]. They help to classify PPA into nonfluent/agrammatic, logopenic, and semantic variants. Although this system has been immensely influential and is even frequently mandated during the review of manuscripts submitted for publication, it has widely recognized shortcomings [16–18]. For one, a strict adherence to the 2011 guidelines entails arduous assessment of nearly a dozen separate aspects of language. Second, even if the guidelines are strictly applied, approximately one-third of the patients will fail to be classified into any of the three variants. Third, there are certain feature clusters that allow the same patient to simultane-

ously fit the designation of both nonfluent/agrammatic and logopenic PPA. Yet another challenge is posed by the evolution over time, so that a patient who fits the logopenic subtype initially may fit criteria for one of the other two subtypes as the disease progresses.

The following modifications have helped us address some of these concerns [16]. (1) The relative preservation of both grammar and comprehension is made to be a core feature of the logopenic variant. This prevents the double assignment problem. (2) In contrast to the 2011 guidelines, repetition impairment is not considered an obligatory core feature of the logopenic variant. This practice reduces the number of unclassifiable patients. (3) Patients with combined impairments of grammar and word comprehension even early in the disease, and who would therefore remain unclassifiable by the 2011 guidelines, make up a fourth variant of “mixed” PPA. (4) The semantic variant is diagnosed when poor word comprehension is the principal feature. When additional and equally prominent impairments of object or face recognition (not just naming) are detected, a diagnosis of semantic dementia (SD) is made [11]. This recommendation is at odds with the 2011 guidelines, which would diagnose semantic PPA even in patients with significant face and object recognition impairment (i.e., visual associative agnosia). The justification for the distinction of PPA from SD is summarized in the section on the anatomy of language.

The modifications listed above lead to a classification method based on a template where the Y-axis represents worsening impairment in the grammaticality of sentence construction and the X-axis represents worsening impairment in single word comprehension [15]. Each of the four PPA subtypes will cluster within a different quadrant of this template. The *nonfluent/agrammatic* PPA patients, for example, will cluster in the upper left quadrant (impaired grammar but spared comprehension); the *semantic* PPA patients will cluster in the lower right quadrant (impaired comprehension but spared grammar); the *mixed* PPA patients will cluster in the lower left quadrant (combined impairments of grammar

and comprehension); and the *logopenic* PPA patients will cluster in the upper right quadrant (relatively spared grammar and comprehension). The logopenic group would have met the PPA criteria through impairments of word retrieval, naming, and spelling. Specific tests for assessing grammaticality of sentence construction and word comprehension and their normative values have been reported [15]. As patterns of agrammatism vary greatly from language to language, considerable attention is being directed to the adaptation of grammar tests for languages other than English [19].

Some logopenic patients maintain fluency as they circumvent word finding failures through circumlocution; others pause after word retrieval failures and produce halting nonfluent speech that appears similar to what is seen in patients with nonfluent/agrammatic PPA. Word finding impairments and paraphasias may make it impossible to gauge a sentence grammaticality. The delineation of logopenic from agrammatic PPA can thus be quite challenging [17]. Quantitative analyses of speech samples show that the nonfluent/agrammatic patients make word finding pauses that are longer before verbs, whereas logopenic patients make pauses that are longer before nouns [20]. Furthermore, patients with nonfluent/agrammatic PPA display a preferential impairment of verb rather than object naming, whereas the converse may be seen in logopenic PPA [21]. When research objectives necessitate such distinctions, these features may help to establish a quantitative differentiation of nonfluent/agrammatic from logopenic forms of PPA. Subtyping need not become an end unto itself. For purposes of both research and treatment, the emphasis could also be on single parameters, such as grammar or naming, across all subjects and regardless of subtype.

The 2011 guidelines did not prescribe acronyms for the three variants. At present, *non-fluent variant* (nfvPPA), *logopenic variant* (lvPPA), and *semantic variant* (svPPA) are the most popular choices. Alternative acronyms such as naPPA, agPPA, PPA-NFV, LPA, and PPA-SV have also been used, albeit more rarely [22–25]. The “nfv” prefix is particularly problematic because it appears to overlook grammar, which is the single

most characteristic impairment of this subtype. The choice of “nfv” was probably based on experience derived from stroke aphasia where low fluency can be used as a proxy for agrammatism. In PPA, grammar and fluency can be dissociated, especially in logopenic patients where long word finding pauses diminish fluency but without grammatical impairment [26]. Based on these considerations and also in order to underscore the primacy of the PPA diagnosis, we have used the alternative acronyms of PPA-G, PPA-L, PPA-S and PPA-M for the nonfluent/agrammatic, logopenic, semantic and mixed variants, respectively. It may take another collective international effort to determine whether the 2011 consensus guidelines should be modified along the lines listed above and whether the acronyms can be harmonized.

Clinical progression patterns vary by subtype and are likely to reflect the differential anatomical trajectories of disease spread. In PPA-S, the spread of atrophy from the anterior temporal lobe to orbitofrontal, insular, or contralateral temporal lobe can lead to the additional face and object recognition impairments of SD, and to the behavioral abnormalities seen in behavioral variant frontotemporal dementia (bvFTD). In PPA-G, spread of atrophy from the inferior frontal gyrus (IFG) to other premotor and frontal cortices can lead to the abnormalities seen in apraxia of speech, corticobasal syndrome, supranuclear ophthalmoplegia, and frontal-type executive dysfunction. In PPA-L, spread of atrophy from the temporoparietal junction (TPJ) to surrounding cortices can lead to additional impairments of explicit memory and constructions. For all subtypes, the spread of atrophy tends to be more pronounced in the left hemisphere, and there are substantial interindividual differences in the speed and trajectory of progression [27].

Contributions to the Anatomy of Language

The classic Wernicke-Lichtheim-Geschwind model of language revolved around two epicenters, namely Broca’s area in the inferior frontal gyrus (IFG) and Wernicke’s area in the temporo-

parietal junction (TPJ), a region that can be said to encompass parts of the inferior parietal lobule and the posterior segments of the superior and middle temporal gyri [28] (Fig. 1). The former has been linked to fluency and grammar and the latter to language comprehension. The literature of the past 150 years displays greater agreement on the location and function of Broca's area than of Wernicke's area [28]. These two epicenters are connected through the arcuate fasciculus, which is thought to play a critical role in language repetition [29]. This basic model has undergone major revisions through investigations with functional imaging, event-related potentials, and sophisticated neuropsychological assessments [30–32].

Each of these approaches has advantages and disadvantages. Cerebrovascular lesions cause sudden and irreversible destruction of the core lesion site. However, the damage usually extends into deep white matter. The exact contribution of the damaged cortical region to the ensuing language impairment is therefore difficult to specify. Functional mapping approaches based on MRI and electrical recordings, on the other hand, can reveal activity confined to the cerebral cortex but cannot differentiate areas that are critical for a function from those that have collateral participatory roles.

Investigations based on focal cortical atrophy can circumvent some of these shortcomings. Regions where the magnitude of cortical thinning correlates with the magnitude of impairment can be said to have critical (rather than participatory) roles in maintaining the integrity of that function. Consequently, PPA has offered new tools for investigating the cortical anatomy of the language network without the deep white matter problem of stroke or the collateral activation dilemma of functional brain mapping. Nonetheless, clinicoanatomical correlations in PPA are not without caveats. For one, the slow evolution of the lesion is likely to trigger compensatory plasticity that may complicate the interpretation of correlations. Second, even areas of peak atrophy may contain residual neurons that could sustain some functionality of that region [33]. Third, each neuropathologic entity

may trigger a different pattern of cortical injury. For example, the neurofibrillary tangles of AD have a predilection for deep cortical layers whereas the opposite is the case for Pick's disease.

Despite these potential complications, clinico-anatomical investigations on PPA have generated new insights into the functional anatomy of language. Each PPA variant is associated with a characteristic location of peak atrophy, for instance, Broca's area (IFG) in PPA-G, Wernicke's area (TPJ) in PPA-L, and the anterior half of the temporal lobe (ATL) in PPA-S [34–36]. The anatomical correlate of PPA-G is in keeping with prevailing models of language, which give Broca's area a critical role in the maintenance of fluency and grammar [37]. The relationships in PPA-L and PPA-S, however, are in conflict with classic aphasiology and also with most contemporary models of language. For one, traditional models of language exclude the ATL. For example, an influential review published at the height of twentieth-century aphasiology states that the probability that a lesion would impair comprehension is “very high in or near the first temporal gyrus, and fades out with different gradients (varying among individuals) toward the poles. And by the time it gets to any pole (occipital, temporal, or frontal) the probability is essentially zero” [38]. Research on PPA-S has contradicted this statement by showing that damage to the left ATL, including the temporal pole and anterior fusiform gyrus, causes severe impairments of word comprehension. Based on this finding, a proposal has been made that this region should be considered a core component of the language network [28].

This proposal has generated considerable debate. The disagreement revolves around the alternative characterization of ATL as an amodal hub for all semantic knowledge, verbal and non-verbal. Consequently, ATL damage should cause more than a language impairment (i.e., aphasia) and should give rise to a universal loss of semantic knowledge not only for words but also for faces and objects [39]. Based on this point of view, the syndrome of ATL damage was designated semantic dementia (SD), a syndrome

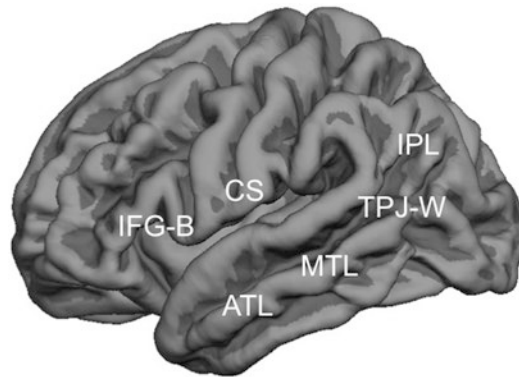


Fig. 1 Major components of the left hemisphere language network – ATL: The acronym ATL will be used to refer to the anterior third of the temporal lobe including the temporal pole; CS (the central sulcus) is shown as a reference point, IFG-B (the inferior frontal gyrus) contains Broca's area, IPL (inferior parietal) lobule, MTL (the middle third of the temporal lobe), TPJ-W (the temporoparietal junction) contains the posterior third of the temporal lobe and the immediately adjacent parts of the inferior parietal lobule. Although the exact site of Wernicke's area remains ambiguous, it is usually considered to be located within the TPJ-W and adjacent parts of the MTL

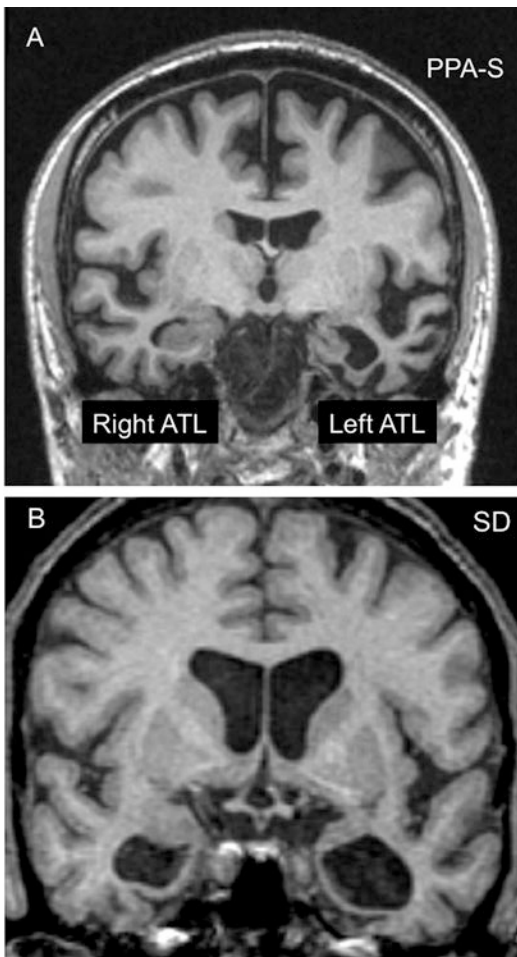


Fig. 2 PPA-S versus SD. Figure 2a shows the MRI scan of a right-handed man with symptom onset at the age of 59. On examination, 7 years later, the clinical pattern was PPA-S and atrophy was much more prominent in the left anterior temporal lobe (ATL). At that time, he had severe word comprehension impairments but no difficulty with non-verbal object recognition either in testing or in everyday life. In comparison, Fig. 2b shows the MRI scan of a right-handed man with symptom onset at the age of 65. Three years later, at his initial visit, ATL atrophy was bilateral. He had prominent word comprehension and object recognition impairments. This combination led to a subsequent diagnosis of semantic dementia (SD)

defined by the combination of semantic aphasia (word comprehension deficit) with visual associative agnosia (loss of face and object recognition) [11, 39]. Such patients would not fit the diagnostic criteria for PPA since the aphasia would no longer constitute the dominant feature.

The disagreement on the nature of the syndrome caused by ATL damage can be resolved by considering the influence of hemispheric specialization [28, 40, 41]. Clinical observations and specially designed experimental tasks show that PPA-S is a selective aphasic syndrome of the left anterior temporal lobe, whereas the SD syndrome reflects a wider deficit with a more bilateral anatomical substrate [42–45]. The patients with left ATL damage may not be able to name objects and faces but are generally cognizant of their identity and nature [46]. It should be pointed out, however, that many PPA-S patients may also have minor atrophy in the right anterior temporal lobe, and that further spread of neurodegeneration within the right hemisphere may lead some, but not all, to eventually develop the additional face and object recognition deficits of SD. It is not surprising, therefore, that some authors have considered PPA-S and SD to be the two sides of the same coin [40, 41]. The question is whether syndromic designations should be based on clinical presentation at disease onset, as we advocate, or based on possible progression trajectories (Fig. 2). When ATL atrophy is predominantly right-sided, the patient may present with one of three syndromes, SD, non-aphasic associative agnosia, or bvFTD [47, 48].

Exactly how the left ATL contributes to word comprehension is a topic of active investigation. Resting state functional imaging experiments show that the left ATL has left-sided asymmetric functional connectivity patterns that support its inclusion within the language network [49]. In our cohort, all right-handed patients with severe word comprehension impairment have also had substantial left ATL atrophy extending all the way into the pole. However, some patients with such a location of atrophy may have severe anomia in the absence of word comprehension impairment. In these patients, the distinctive comprehension impairment of PPA-S emerges as

the atrophy extends posteriorly from the anterior tip of the left temporal lobe into adjacent parts of the middle portion of the temporal lobe (MTL), especially the middle temporal gyrus (MTG) [28]. In keeping with this observation, functional MRI studies in PPA and clinicoanatomical correlations in stroke have shown that the connectivity of the mid-to-posterior parts of the MTG with ATL and other parts of the language network may have important roles in sustaining word comprehension [50, 51]. In our experience, isolated atrophy of the middle parts of the temporal lobe in PPA has not been associated with impairment of this function [28]. Damage to the left ATL may therefore be necessary but not always sufficient for word recognition impairment. Posterior expansion of damage into the middle parts of the temporal lobe may also be required.

Patients with PPA-S have severe naming impairments principally because they do not understand the meaning of the word that denotes the object they are asked to name [46]. The impairment initially undermines the comprehension of a word at its specific level of meaning (does the word denote a strawberry or a cherry) but later generalizes to the generic meaning of the word (does the word denote a fruit or an animal) [52]. Based on these observations in PPA-S, the left ATL can be conceptualized as a transmodal region of cortex where sensory word form information is linked to the multimodal associations that collectively encode the meaning of the word [28, 53]. Word recognition at a specific level of meaning requires more extensive associative elaboration and would therefore be more vulnerable to early stages of neurodegeneration.

Another unexpected outcome of research on PPA was the finding that patients with the logopenic variant have normal single word comprehension despite peak atrophy sites that encompass Wernicke's area as defined above. In fact, regression analyses in 73 PPA patients showed no correlation between atrophy in Wernicke's area and impairment of word comprehension [28, 54]. In addition to clinicoanatomical correlations in PPA-L, which have shown that severe cortical degeneration of Wernicke's area does not impair single word comprehension, investiga-

tions on PPA-S have shown that an intact Wernicke's area is not sufficient to sustain word comprehension if the ATL is damaged. The body of work on PPA therefore leads to the conclusion that the cortex of Wernicke's area is neither necessary nor sufficient for word comprehension. This conclusion can be reconciled with classic aphasiology by keeping in mind that nearly all reports linking Wernicke's area to word comprehension are based on cerebrovascular lesions. Such lesions include not only the cortex of Wernicke's area but also deep white matter axons, such as those in the middle longitudinal fasciculus [55], that are likely to carry projections of otherwise intact distal posterior and contralateral cortices. The resultant additional cortical disconnections may explain why stroke in Wernicke's *region* impairs word comprehension while neurodegeneration in Wernicke's *cortex* does not [54].

The large-scale network model posits that each network node mediates critical (or essential) as well as ancillary (or sustaining) functions related to its principal cognitive domain [56, 57]. While damage to a given node may not cause fixed impairments of its ancillary functionalities, the overall computational flexibility of the network for mediating that task may be compromised. These principles apply to the role of Wernicke's area in language comprehension. For example, agrammatic and logopenic PPA patients whose atrophy encompasses Wernicke's area but not the ATL, and who have normal word comprehension in standard tests and daily life, display abnormally prolonged semantic interference effects and loss of the N400 semantic incongruence potential [52, 58]. Furthermore, functional magnetic resonance imaging (fMRI) investigations using synonym identification tasks revealed activations not only in the anterior temporal lobe but also in regions overlapping Wernicke's area [59, 60]. The cerebral cortex within Wernicke's area therefore serves an ancillary role in word comprehension. Multiple lines of evidence show that Wernicke's area plays a critical role in language repetition, a finding that is in keeping with observations in stroke aphasia [54]. This area is important for language repetition presumably because it links phonologic

word form codes to their articulatory sequences [61–63].

An additional contribution of PPA to the anatomy of language comes through the discovery of the aslant tract, a pathway that connects the core language network with dorsal premotor cortex and appears to play a major role in sustaining fluency [64]. Patients with PPA may also show patterns of aphasia that have not been observed in other settings. For example, some patients may show a preferential inability to name objects orally but not in writing and fail to understand words they hear but not those they read [65]. These patients do not fit the pattern seen in pure word deafness because they are anomie and they do not fit the pattern of auditory agnosia because they can match objects to their characteristic sounds. Investigations on this small group of patients have helped to explore the functionality of a putative “auditory word form area” that sits at the confluence of modality-specific pathways for word comprehension and language repetition.

The totality of these investigations on PPA depicts a large-scale language network built upon the interactive functionalities of dorsal and ventral (rather than anterior and posterior) streams of processing [31]. The dorsal route mediates phonological encoding, repetition, articulatory programming, fluency, word retrieval and also the sequencing of morphemes and words into grammatically correct sentences. The ventral route mediates the lexicosemantic processes of object naming and word comprehension. Word finding in speech is a joint function of both routes and therefore the most common presenting complaint in PPA.

Asymmetry of Neuropathology and Genetics

In our group of 97 consecutive autopsies, the primary neuropathology was FTLT with tauopathy (FTLT-tau) in 29%, FTLT with transactive response DNA-binding protein 43 (FTLT-TDP) in 25%, and AD in 44%. All three major neuropathologic forms of FTLT-tau (Pick's disease,

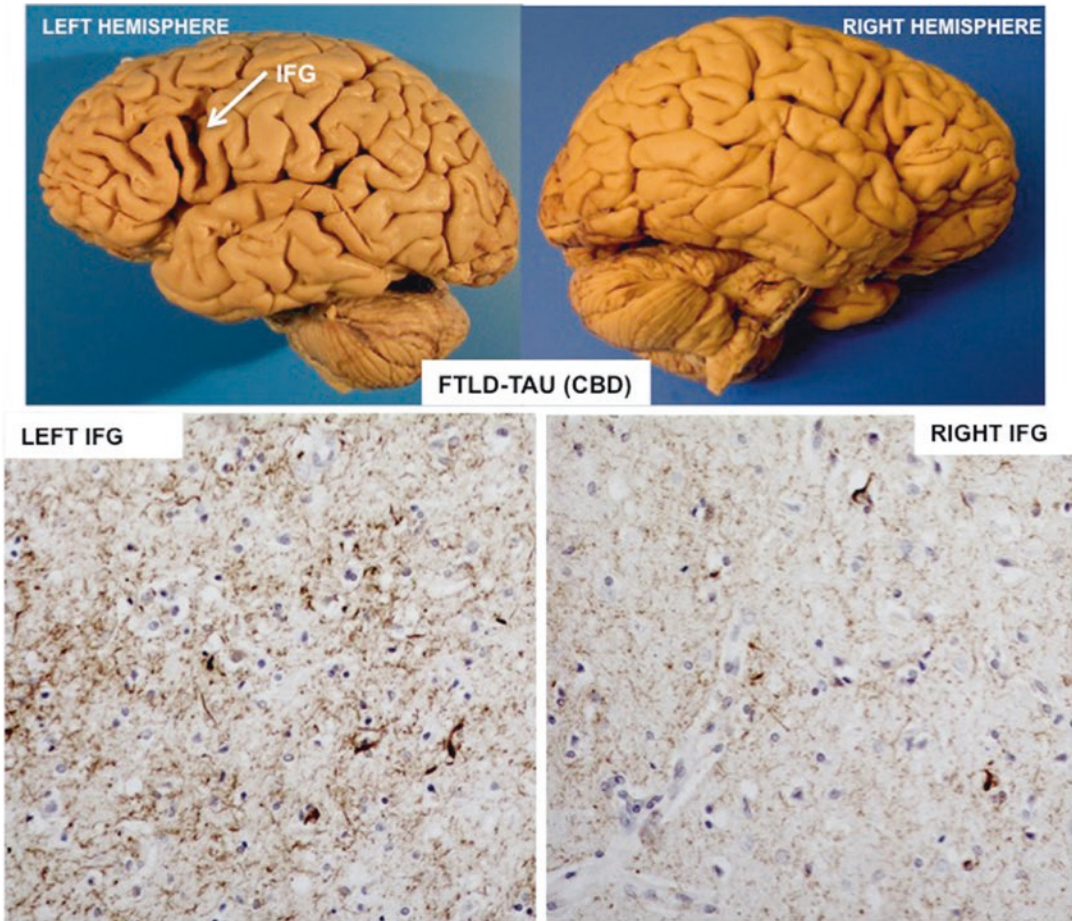


Fig. 3 Asymmetry of neurodegeneration. Postmortem examination of a right-handed woman with symptom onset at the age of 72 and findings of agrammatic PPA with prominent word finding impairments. Death occurred 6 years later. The primary neuropathology was found to be FTLD-tau of the CBD type. The top figures show the pro-

found asymmetry of atrophy. There is an almost cystic area of atrophy around the left inferior frontal gyrus (IFG) but no comparable atrophy of the right. The photomicrographs at the bottom, based on phosphotau immunostaining in the same patient, show the tauopathy to be more intense in the left IFG than in the right

corticobasal degeneration [CBD], progressive supranuclear palsy [PSP]), and all three major forms of FTLD-TDP (types A, B and C) were represented. There were some disease-specific preferential patterns of atrophy. For example, AD almost always led to peak atrophy that included the temporoparietal junction; TDP-C almost always led to severe anterior temporal atrophy; Pick’s disease routinely caused combined atrophy of anterior temporal and prefrontal cortex; and PSP and CBD tended to be associated with surprisingly modest cortical atrophy, usually in dorsal premotor or inferior frontal cortex. The

one common denominator of nearly all cases is the leftward asymmetry of the atrophy (Figs. 3 and 4). What is surprising is that the asymmetry is almost always maintained up to the time of death. The initial predilection of the language-dominant left hemisphere is therefore not a random event at disease onset but a core biological feature of the syndrome.

There was nearly equal representation of males and females in our autopsy cohort. Age of onset varied from 41 to 80 with a mean of 61 ± 8 years. Survival from symptom onset to death varied from 2 to 23 years with a mean of

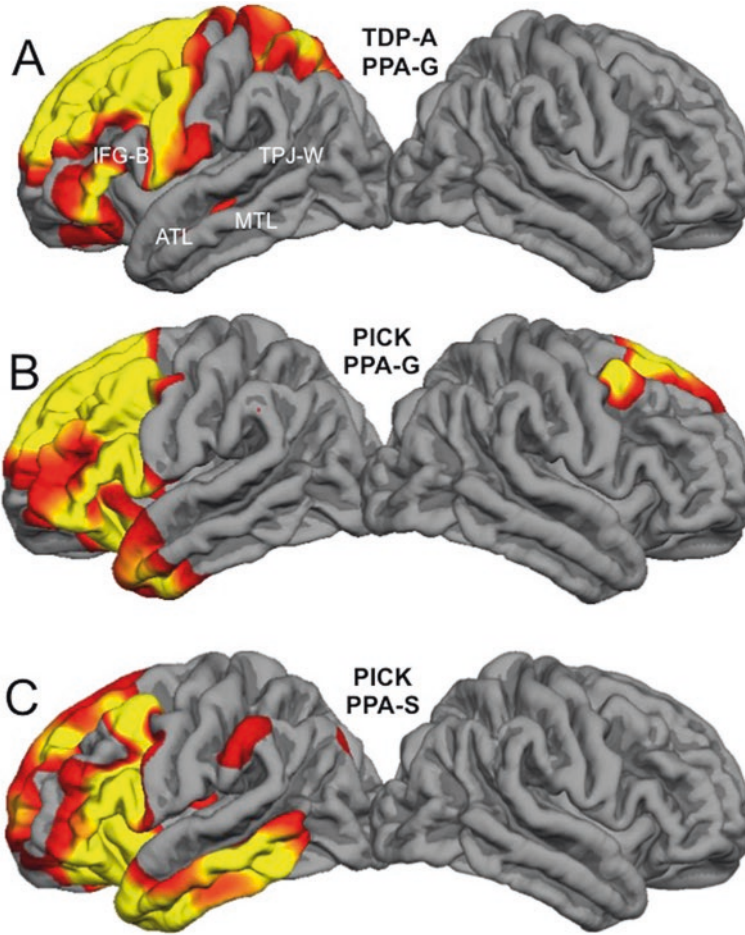


Fig. 4 Correspondences of pathology, atrophy, and syndrome. Quantitative MRI morphometry in three right-handed patients who had come to postmortem brain autopsy. Areas of significant cortical thinning compared to controls are shown in red and yellow. (a) Onset of PPA-G was at the age of 65. The scan was obtained 2 years after onset. At postmortem, the primary pathology was FTLD-TDP type A. (b) Onset of PP-G was at the age of 57. The scan was obtained 5 years after onset. At postmortem, the primary pathology was Pick's disease. (c) Onset

of PPA-S was at the age of 62. The scan was obtained 5 years after onset. At postmortem, the primary pathology was Pick's disease. Despite the differences in neuropathology and clinical syndrome, the one common denominator is the profound leftward asymmetry of atrophy. Abbreviations: ATL anterior third of the temporal lobe, IFG-B inferior frontal gyrus where Broca's area is located, MTL middle third of the temporal lobe, TPJ-W temporo-parietal junction where Wernicke's area is located

9.69 ± 3.93 . Survival tended to be the longest for those with AD (10.8 ± 4.4) and FTLD-TDP type C (12.4 ± 2.6) and shortest for those with FTLD-TDP types A and B (5.8 ± 2.2). In keeping with these different rates of progression, FTLD-TDP aggregates extracted from subjects with type A pathology were shown to be more cytotoxic than aggregates from subjects with type C pathology [66].

The relationship of PPA variants to the underlying neuropathologic entity is probabilistic rather than absolute [67]. Autopsy data show that the vast majority of PPA-S cases have had TDP-C pathology but approximately 20% have had Pick's disease; the majority of PPA-G cases have had FTLD-tau (all types) but approximately 30% have had FTLD-TDP or AD; the majority of PPA-L cases have had AD but 30% have shown

FTLD-tau or FTLD-TDP. Figure 4 illustrates the clinicopathologic heterogeneity of PPA, namely that the same neuropathologic entity can cause more than one aphasic variant and that the same PPA variant may be caused by more than one neuropathologic entity. As shown in Fig. 4a and b, FTLD-TDP type A and Pick's disease cause nearly identical peak atrophy patterns that extend into the frontal components of the language network known to underlie grammar and fluency, giving rise to the concordant syndrome of PPA-G. Figure 4b and c raise challenging questions. They show atrophy patterns in two different patients with Pick's disease at autopsy, one with PPA-G (Fig. 4b), the other with PPA-S (Fig. 4c). As explained in the section on the anatomy of language, the semantic aphasia associated with Fig. 4c could be attributed to the posterior expansion of atrophy from ATL into more middle sections of the temporal lobe. However, it is difficult to understand why the patient in Fig. 4c was not also agrammatic since the frontal atrophy is nearly as extensive as in the other two cases with PPA-G. Perhaps this discrepancy can be blamed on vagaries of cortical morphometry performed on single subjects or, alternatively, on individual variations in the functional anatomy of the language network.

During life, cortical thinning (i.e., atrophy) and hypometabolism are the two most conspicuous markers of asymmetric neurodegeneration. Considerable progress has been made in exploring the potential cellular substrates of the asymmetrical atrophy (Fig. 3). For example, neurofibrillary tangles (NFT) (but not the amyloid plaques) of AD, tauopathy of CBD/PSP, Pick bodies, abnormal TDP-43 deposits of FTLD-TDP, activated microglia, and the extent of neuronal atrophy/loss tend to be more prominent in the left hemisphere than in the right hemisphere and also more prominent in language-related than other cortical areas of the left hemisphere [68–73]. In one left-handed PPA patient with documented right hemisphere language dominance and FTLD-TDP neuropathology, cortical atrophy and neurodegeneration markers were more prominent in the right hemisphere [74]. In at least some PPA patients with AD neuropathology, NFT may be

more numerous in the language-related cortices of the left hemisphere than in the medial temporal areas, a distribution that deviates from the Braak and Braak pattern of neuropathology and underlies the atypical preservation of episodic memory in these patients [71, 73].

Quantitative investigations have also looked into the concordance of PPA subtypes with regional variations of neurodegeneration markers. A study of four right-handed PPA patients with FTLD-TDP type A neuropathology showed that the two patients with PPA-G displayed the highest density of TDP-43 precipitates in the frontal components of the language network, whereas the two with PPA-L displayed the highest density of precipitates in the temporoparietal components of the language network [69]. The cellular pathology in PPA can therefore asymmetrically target parts of the language-dominant hemisphere in a way that also mirrors the anatomical predilection patterns of the specific PPA variant. In the future, it would be useful to conduct similar analyses based on synaptic density. Some patients, especially those with PPA-G and FTLD-tau, may have no detectable cortical atrophy in the initial years of disease. These patients display abnormalities of functional connectivity, suggesting that physiological perturbations of the language network may precede atrophy [75]. In this group of patients, the neurodegeneration may be particularly prominent in subcortical white matter [76]. It is important to keep in mind that the identity of the disease marker that shows the best correlation with clinical dysfunction can change over time. Inclusions are likely to reflect leading indicators and would be expected to show the best correlation with clinical patterns in early disease stages, whereas neuronal death is likely to represent a trailing indicator more closely aligned with clinical patterns late in the disease.

In our autopsy cohort of 97 cases, a third of TDP-A cases had granulin (*GRN*) mutations. No other disease-causing mutations were encountered. Other studies have also shown that mutations in the *GRN* gene constitute the most common genetic correlate of familial PPA [77]. In such *GRN* families, some members may have PPA and others bvFTD [78, 79]. Rarely, all

affected members of a *GRN* family will have PPA [80]. Even then, the type of aphasia may differ from one sibling to another and there is considerable heterogeneity of PPA subtypes associated with *GRN* mutations [81, 82]. The literature also contains rare associations of PPA with mutations in the presenilin (*PSEN1*), tau (*MAPT*), and *C9orf72* genes [83–85]. The most common clinical variants associated with dominantly inherited diseases are PPA-G and PPA-L, but rare cases of PPA-S have been reported [82]. The cellular neuropathology is FTLD-TDP type A in *GRN* mutations, FTLD-TDP type B in *C9orf72* mutations, and any one of the major FTLD-tau types in *MAPT* mutations. FTLD-TDP type C is very rarely, if ever, associated with known disease-causing mutations [86–88].

The heterogeneity of phenotypes encountered within *GRN* families shows that molecular underpinnings alone are not sufficient to account for the patterns of selective vulnerability and their clinical manifestation. The biological mechanisms underlying the selective and asymmetric involvement of the language-dominant hemisphere in PPA remain to be elucidated. One line of investigation has focused on the significantly higher frequency of learning disabilities, including dyslexia, in PPA patients and their first-degree relatives compared to control populations and patients with other dementias [89–91]. Follow-up research has replicated this association and raised the possibility that it may be peculiar to PPA-L [92]. Some families of PPA probands have strikingly high prevalence of developmental dyslexia in siblings or children [89]. We saw one family where seven of nine siblings of a PPA patient had findings indicative of developmental dyslexia [93]. As a group, the dyslexic siblings in this family had decreased functional connectivity within the language network although none had any findings of PPA. These observations led to the speculation that at least some cases of PPA could be arising on a developmentally or genetically based vulnerability of the left hemisphere language network. In some family members, this vulnerability would interfere with the acquisition of language and lead to dyslexia, while in others, it would make the language

network a locus of least resistance for the effects of an independently arising neurodegenerative process, leading to PPA [33]. So far, linkage studies addressing this hypothesis have not detected an association between PPA and known dyslexia genes [77]. Given the polygenic nature of dyslexia, negative results may reflect an insufficient number of cases.

Therapeutic Interventions

The heterogeneity of PPA highlights the need to individualize therapeutic approaches. Interventions in individual patients should target the underlying disease as well as the symptom complex. The former step requires the use of in vivo biomarkers. There are excellent CSF and PET biomarkers for detecting PPA patients with AD neuropathology and blood-based biomarkers may be on the horizon. However, current tau ligands for PET do not yet offer reliable identification of non-AD tauopathies associated with CBD, PSP, and Pick's disease [94]. When such biomarkers become available, they will enable the identification of PPA patients with FTLD-tau and, by exclusion, those with FTLD-TDP. The goal of these diagnostic investigations is to prescribe approved medications (e.g., cholinesterase inhibitors if AD) and to channel the patient to relevant disease-specific clinical trials. Although clinical examination is rarely sufficient to specify the underlying disease entity, we have found that prominent single word comprehension deficits that arise as the most salient feature of PPA are never associated with AD. The presence of this feature may therefore be used to forego AD biomarker testing.

The nonpharmacologic interventions aimed at the language impairment include speech therapy and brain stimulation modalities such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) [95]. Promising effects have been reported following left hemisphere tDTS in PPA-S [96]. If confirmed, this may well be the first time that brain stimulation will be shown to have therapeutic effects in an FTLD syndrome. Evidence for the effectiveness

of speech-language therapy in PPA is emerging [97–99]. Utilization of this intervention modality is low in part due to the misconception that speech-language therapy is not appropriate for neurodegenerative syndromes where worsening is inevitable [100, 101]. An additional barrier is the lack of familiarity of speech-language pathologists with neurodegenerative conditions. Speech-language therapy in PPA requires personalization to fit the pattern of impairment and its evolution over time. For example, there are patients with modality-selective impairments of naming and word comprehension who could benefit from treatments emphasizing the relatively spared channels of language processing [65]. Additional questions to be resolved in the course of speech-language therapy include the relative usefulness of multicomponent, impairment-based, or compensatory approaches and the comparative benefits of group, dyadic, or patient-only approaches [102]. In each case, ecologically meaningful and statistically robust outcome measures will need to be devised.

Recent developments in telemedicine raise the possibility of delivering speech-language therapy in the home of the individual living with PPA [103, 104]. Communication Bridge, for example, is a two-arm, randomized control trial of speech-language intervention delivered through video chat for individuals with PPA [104]. The experimental arm uses a client-informed, dyadic approach for individuals with PPA and their communication partner. Impairment-based exercises using personalized stimuli and compensatory strategies are utilized to address real-world communication difficulties. The trial includes an individually tailored web application with native practice exercises and education materials that participants rehearse between treatment sessions. To evaluate whether treatment gains are relevant to the daily functions of the participant, outcomes are measured using a communication confidence rating scale and goal attainment scores. This method allows the targeting of individualized goals of high relevance to participants. In the future, transcranial stimulation could be combined with speech-language therapy to attain even more effective benefits [95].

Conclusions

Despite its relative rarity, PPA has led to conceptual advances in understanding the heterogeneity of dementia, the principles of selective brain vulnerability, and the neuroanatomy of the language network. PPA was arguably the first entity to show that there is more to dementia than memory loss, that the same clinical syndrome can be caused by multiple neuropathologies, that the same neuropathology can cause multiple syndromes, and that the relationship of syndrome to neuropathology is probabilistic rather than deterministic. Future work on PPA is likely to shed new light on the anatomical tropisms of neurodegenerative diseases and on the internal architecture of the language network.

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