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Primary progressive aphasia: a model for neurodegenerative disease

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Abstract

Purpose of review—Knowledge on primary progressive aphasia (PPA) has expanded rapidly in the past few decades. Clinical characteristics, neuroimaging correlates, and neuropathological features of PPA are better delineated. This facilitates scientific studies on the disease pathophysiology and allows speech and language therapy to be more precisely targeted. This review article begins with a summary of the current understanding of PPA and discusses how PPA can serve as a model to promote scientific discovery in neurodegenerative diseases.

Recent findings—Studies on the different variants of PPA have demonstrated the high compatibility between clinical presentations and neuroimaging features, and in turn, enhances the understanding of speech and language neuroanatomy. In addition to the traditional approach of lesion-based or voxel-based mapping, scientists have also adopted functional connectivity and network topology approaches that permits a more multidimensional understanding of neuroanatomy. As a result, pharmacological and cognitive therapeutic strategies can now be better targeted towards specific pathological/molecular and cognitive subtypes.

Summary—Recent scientific advancement in PPA potentiates it to be an optimal model for studying brain network vulnerability, neurodevelopment influences and the effects of nonpharmacological intervention in neurodegenerative diseases.

Keywords

frontotemporal dementia; neurodegenerative disease; neuroimaging; neuropathology; primary progressive aphasia

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Primary progressive aphasia (PPA) is a clinical syndrome characterized by speech and language impairment caused by neurodegeneration of language networks. In 1892, Pick [1] reported the case of a 71-year-old man who presented with nonsensical speech, anomia, dyslexia, dysgraphia, personality changes, and memory impairment. Apart from a few reports of Gogi aphasia in Japan in the 1940s [2], discussion of neurodegenerative aphasia remained dormant until the 1970s when British investigators published several cases with progressive semantic loss, semantic dementia [3,4], and Mesulam and colleagues first introduced the term PPA [5]. In 1996, Grossman *et al.* [6] also introduced the term progressive nonfluent aphasia to describe patients with progressive loss of speech fluency. PPA was initially described as a unitary syndrome with anomia as main symptom but this view did not explain the spectrum of presentations described. Furthermore, many patients did not show the typical features of semantic or nonfluent presentations; it was later clarified that most of these patients have a third PPA subtype, named the logopenic variant of PPA [7]. In 2011, an international group of experts introduced a common framework in which PPA was classified into three different variants, based on specific cognitive and neuroimaging features: semantic (svPPA), nonfluent/agrammatic (nfvPPA), and logopenic variants (lvPPA) [8]. Recent clinicopathological studies demonstrated that each variant is associated with different probabilities of neuropathological changes and, rarely, genetic mutations. Table 1 presents the 2011 PPA classification, including the diagnostic algorithm allowing for three diagnostic levels: clinical, imaging-supported, and definite diagnosis.

This article focuses on describing the updated clinical and neuroimaging features of the three main PPA variants. We then summarize pathological and genetic findings and finally discuss the role of PPA in furthering the scientific understanding of neurodegenerative diseases.

SEMANTIC VARIANT PRIMARY PROGRESSIVE APHASIA

The first three cases of this syndrome were described by Warrington [3] in 1975. Patients suffered from loss of word and object knowledge, and deficits were typically most severe for low frequency and low familiarity items [8]. Symptoms included poor performance in confrontational naming, single word comprehension, and object and face identification tasks. Later work by Snowden *et al.* [4] and Hodges *et al.* [10] further demonstrated that semantic loss also leads to surface dyslexia, a disorder in which patients can read pseudowords but not exceptionally spelled words. Typical reading errors include ‘regularization’ errors in irregular words, such as ‘yacht’ or ‘island’ are pronounced as ‘yachdt’ and ‘is-land’ [10]. SvPPA patients often produce semantic paraphasias and tend to substitute specific, subordinate (in the semantic hierarchies) words with generalized terms, such as replacing ‘screwdriver’ with ‘thing’ and ‘panther’ with ‘animal.’ For a decade, it was unclear whether semantic dementia and ‘fluent PPA’ were different entities [11]. In 2004, Gorno-Tempini *et al.* [7,8] included semantic dementia as one of the three PPA variants and the term semantic variant PPA (svPPA) was later adopted by the international workgroup. This new classification of svPPA includes the key classic features of semantic dementia, such as anomia and word comprehension deficits. Supporting diagnostic features include

surface dyslexia or dysgraphia, impairment in object or face knowledge, and relatively spared repetition and speech production abilities [8]. Further reports described deficits in different categories of objects and stimuli modalities, such as famous faces [12], voices [12], nonverbal environmental sounds [13], smells [14], and taste stimuli [15], sometimes in relation to greater right ATL damage. In general, the hallmark feature of this disorder is an inability to identify the meaning of stimuli despite preserved perception. As svPPA progresses, behavioural symptoms including lack of empathy, changes in personality, disinhibition, mental inflexibility, and compulsive behaviours commonly occur [16].

In addition to different clinical symptoms, the three main PPA variants show distinct neuroimaging features [8]. The different patterns of neuroanatomical changes in each subtype are determined by the selective vulnerability of certain brain networks to the neurodegenerative disorders that cause neuronal damage [8,17]. Damage to the ATL in svPPA is identified as atrophy on volumetric brain imaging (MRI) or as hypometabolism on fluorodeoxyglucose (FDG)-PET (Fig. 1). The ATL damage is most often greater in the left hemisphere, which is consistent with naming, word comprehension, and reading difficulties [10,18], but in roughly 30% of svPPA cases, atrophy is more severe in the right ATL [19,20]. Individuals with greater right ATL atrophy present initially with difficulty identifying familiar people, recognizing facial expressions, and with behavioural abnormalities, such as loss of empathy and compulsive, repetitive behaviours [19–21]. Structural connectivity analysis demonstrated severe damage to ventral white matter tracts, typically the anterior portion of the inferior longitudinal fasciculi (ILF) and uncinata fasciculi [22,23] (Fig. 2). Task-free fMRI studies show that focal ATL damage causes decreased functional connectivity and functional changes in a widespread semantic network including modality-specific primary and association cortices [24,25]. Magnetoencephalography (MEG) study shows hyposynchrony of alpha and beta frequencies in the left temporoparietal junction, also suggesting that functional disruption areas expand beyond atrophic regions [26].

SvPPA is most often associated with frontotemporal lobar degeneration-TAR DNA-binding protein 43 (FTLD-TDP 43) type C disorder [27]. Consistently, recent molecular PET imaging show that amyloid deposition is uncommon in svPPA especially under 60 years of age [28] and CSF abeta and tau studies are usually negative [29]. [¹⁸F]AV1451 PET designed to specifically target tau shows ATL binding in svPPA, raising concerns regarding the specificity of this ligand to tau [30].

As the disease progresses, anatomical damage extends to connected brain regions in the posterior temporal lobes, contralaterally to the initially less involved ATL and anteriorly to orbitofrontal regions [20]. Consistently semantic and language impairments become more generalized, although islands of fluency might remain and can be useful for differential diagnosis later in the disease course. Typically, patients develop more prominent behavioural symptoms, whereas motor functions are usually spared until the final stages, unless svPPA is associated with motor neuron disease [31].

NONFLUENT/AGRAMMATIC VARIANT PRIMARY PROGRESSIVE APHASIA

Key features of the nonfluent/agrammatic variant PPA (nfvPPA) are effortful speech and/or agrammatism with relatively spared semantic knowledge and single word comprehension [8]. Neuroimaging changes occur in a cortical–subcortical network anchored to left posterior frontoinsula region and the disorder is most often associated with FTL spectrum of the tau subtype (Fig. 1). The cardinal clinical feature in nfvPPA is a motor speech impairment consistent with apraxia of speech (AOS) and often with dysarthria [7,8]. Dysarthria is usually a mixed type with both hypophonic and spastic features [32]. Motor speech planning difficulties cause inconsistent speech sound errors and prosody distortions, sometimes referred to as phonetic and prosodic AOS [33]. Motor speech and phoneme selection impairments also cause speech sound substitution, transposition, insertions, and deletions [32,34]. AOS is most frequently elicited when performing multiple repetition of multisyllabic words with initial consonant clusters and various place of articulation, such as ‘artillery’ or ‘catastrophe’ (i.e. repeating ‘artillery’ in rapid succession five times) [32]. Motor speech deficits are almost universally the most salient feature in nfvPPA; when they appear to be isolated from other language symptoms, the term primary progressive apraxia of speech (PPAOS) has been adopted [33]. Agrammatism, the other important feature in nfvPPA, mostly manifests as decreased mean length of utterance and simplified grammar in oral and written speech [35]. Omission of grammatical morphemes, incorrect usage of inflection morphology and inaccurate word order in spontaneous speech also can occur. NfvPPA patients produce fewer verbs than nouns as well as fewer function words (e.g. prepositions, pronouns, conjunction etc.) than content words [35,36]. Language testing shows that syntactically complex sentences, such as passive sentences and embedded and object-relative clauses are particularly challenging to produce and understand [37]. When grammatical deficits are most prominent, the term agrammatic PPA (AgPPA) has been used [38]. Patients with AgPPA often show a prominent dysexecutive syndrome, such as working memory, planning, and sequencing deficits [39].

The site of most consistent brain damage in nfvPPA (epicenter) is in the pars opercularis of left inferior frontal gyrus (IFG) and premotor cortex, and atrophy can extend to connected cortical and subcortical regions, such as anterior insula, prefrontal regions, supplementary motor complex, basal ganglia, and supramarginal gyrus [40,41]. This network has been named the speech production network (SPN) (Fig. 3) [40]. Differential involvement of specific nodes and connections within this network probably explain the clinical variability within a nonfluent-spectrum disorder, such as pure motoric (premotor cortex), agrammatic (prefrontal), or even dynamic (medial frontal) type of communication disorders [7,41,42,43,44]. In fact, nfvPPA patients with early mutism have cortical volume loss across the entire SPN network [45]. Few studies show significant white matter microstructural damage in the frontal aslant tracts, the fasciculus that connects inferior frontal regions with supplementary motor complex [46,47], frontostriatal, superior longitudinal, and arcuate fasciculi in nfvPPA [43,48] (Fig. 2). White matter integrity in the intrafrontal tracts correlates with the severity of motor speech symptoms [40,47], whereas syntactic processing performance is associated with the integrity of the arcuate and superior longitudinal fasciculi [22,40]. The finding of early white matter damage in nfvPPA is consistent with

clinicopathology studies showing FTLD-tau as the most frequent cause of nfvPPA spectrum disorder [49,50]. Task-free fMRI studies in nfvPPA reveal decreased intrinsic functional connectivity within the SPN along with altered network topology [44■], whereas activation fMRI shows decreased recruitment of the frontotemporal syntax network [51]. MEG indicates significant hyposynchrony of alpha and beta frequencies within the left IFG in nfvPPA [26]. Molecular PET studies showed that amyloid positivity is also rare in nfvPPA patients less than 60 years of age [28■,52■], whereas [18^F]AV1451 and [18^F]THK5351 PET studies show mild binding in grey matter and white matter within the SPN with unclear specificity to tau [30■,53■].

As disease progresses, patients often exhibit motor symptoms, such as parkinsonism and dystonia, orofacial or limb apraxia, frontal lobe dysfunctions, or mood disorders [54]. Clinically, most cases eventually fulfill the diagnostic criteria for progressive supranuclear palsy or corticobasal syndrome [54,55]. Longitudinal neuroimaging shows that atrophy progresses along the predetermined, functionally and structurally connected SPN, supporting the theory of transsynaptic spread of toxic misfolded proteins in neurodegenerative disorders [40,44■]. Longitudinal case series of patients with relatively isolated motor speech deficits, or PPAOS, show that they eventually develop various degrees of aphasic symptoms, suggesting that, in most cases, PPAOS might be an early presentation within a nfvPPA spectrum rather than a separate entity [56]. Pathological studies seem to confirm this hypothesis, as both nfvPPA and PPAOS are mostly caused by FTLD-tau disorder [49,50,56].

LOGOPENIC VARIANT PRIMARY PROGRESSIVE APHASIA

The key clinical feature of lvPPA feature is wordfinding difficulty with pauses in spontaneous speech in the context of spared motor speech and grammatical production [8]. The core cognitive deficit in lvPPA is a phonology and auditory verbal short-term memory disorder [57,58]. These deficits manifest as word-finding pauses, phonological paraphasias in confrontation naming (especially for long words), and difficulty in repeating long, unfamiliar sentences or string of words or digits. The differential diagnosis between nfvPPA and lvPPA is more challenging, as both exhibit varying degrees of impairments in speech fluency and sentence comprehension. In nfvPPA, these deficits are because of motor speech and grammatical problems whereas in lvPPA they are likely secondary to auditory verbal short-term memory deficits [57]. Unlike the effortful pauses in nfvPPA, lvPPA pauses are largely caused by word-finding difficulties, therefore, these patients have islands of fluent speech in between pauses, false starts, and hesitations [35]. Sounds errors in lvPPA are largely phonemic (i.e. existing phonemes being inserted, deleted, or substituted into words) and not phonetic (i.e. errors that produces distorted nonexisting phonetics) in nature [59■]. Individuals with lvPPA struggle with confrontational naming tasks though to a lesser degree than svPPA individuals [60]. Other features of lvPPA include dyscalculia and ideomotor apraxia [61,62]. Although PPA patients, by definition, do not complain of nonlanguage symptoms, neuropsychological tests assessing visuospatial, memory and executive functions often show differential impairments and can help differentiate lvPPA from nfvPPA [63■, 64].

The left inferior parietal lobule (IPL), left posterior temporal lobe and left temporoparietal junction (TPJ) are consistently involved in lvPPA, as demonstrated on volumetric MRI analysis and FDG-PET [49,65] (Fig. 1). Naming difficulties in lvPPA correlate with left middle temporal gyrus atrophy [66], whereas repetition deficits correlate with temporoparietal junction damage [67]. White matter damage in lvPPA is less severe than in nfvPPA and involves left dorsal parietal white matter tracts that connect frontal and posterior temporal regions [22] (Fig. 2). Task-free functional MRI suggest reduced connectivity over the left temporal language and ‘working memory’ network [68]. A portion of these networks is included in the default mode network, the circuit vulnerable to Alzheimer’s disease [71] supporting clinic-pathological and biomarker studies showing that this syndrome is an atypical Alzheimer’s disease variant [49,69]. Indeed, cerebrospinal fluid (CSF) analysis shows a pattern consistent with Alzheimer’s disease [70]. Molecular PET studies also confirmed the presence of amyloid deposition in about 90% of lvPPA patients [28■,52■,71]. Whereas amyloid deposition is diffuse in lvPPA, [¹⁸F]AV1451 binding is high and located in the atrophied language regions [30■]. A MEG study shows hyposynchrony of high-frequency oscillation bands within the left posterior temporal and occipital cortices but hypersynchrony of low-frequency bands within bilateral frontal and parietal cortices [26].

lvPPA often progress to a global aphasia, with episodic memory impairment, dysexecutive, and visuospatial dysfunction [57,63■,72], resembling the clinical picture of early-onset Alzheimer’s disease patient [65]. Although limb apraxia is common, severe extrapyramidal symptoms, such as dystonia and parkinsonism usually occur later than in nfvPPA. Anxiety, irritability, agitation, and depression have been reported in lvPPA, whereas frank disinhibition and lack of empathy are rare [73]. Longitudinal neuroimaging studies showed progression of grey matter atrophy within the language and default mode networks [72].

PRIMARY PROGRESSIVE APHASIA WITH ATYPICAL PRESENTATIONS

The current clinical classification accurately groups most PPA patients, but cases with mixed or unclassifiable clinical presentations occur, ranging around 6% in one recent large meta-analysis [28■]. The diagnosis of some of the unclassifiable cases sometimes become evident as their disease progresses [8]. A genetic mutation should be considered in ‘atypical’ PPA, as mixed presentations have been reported in cases with autosomal dominant genetic mutations [74].

Generally, less than one-third of PPA cases have a positive family history of FTL spectrum disorders with less than 10% of cases fulfilling an autosomal dominant inheritance pattern [75] and nfvPPA shows the highest heritability (20–30% having family history). In contrast, only 10–20% of svPPA and lvPPA individuals have a positive family history of FTL spectrum disorders [75]. NfvPPA has been reported to be associated with *MAPT*, *GRN*, *C9ORF72*, *TARDBP*, *SQSTM1*, *TBK1*, and *CHCHD10* gene mutations [76■]. In the few cases in which svPPA was associated with a genetic mutation, these individuals were found to have *MAPT*, *C9ORF72*, *TARDBP*, *TBK1*, *TREM 2*, or *CHCHD10* mutations [76■]. *APP* and *GRN* mutations were also recently discovered in a few lvPPA cases [77■,78]. Despite often having Alzheimer’s disease neuropathology, patients show variable allele frequency of apolipoprotein e4 allele across different lvPPA cohorts, usually intermediate between

amnesic Alzheimer's disease and FTD-spectrum disorders [79], suggesting the possibility of multiple risk factors.

PRIMARY PROGRESSIVE APHASIA AS A MODEL TO STUDY THE NEUROANATOMY OF SPEECH AND LANGUAGE FUNCTIONS

The distribution of atrophy in PPA is unique and differs from patterns found in stroke aphasia, allowing the study of novel brain–behaviour correlations and providing valuable perspectives for understanding the neural basis of speech and language function in the brain [80]. For instance, the functions of the ATL have largely been delineated through studying svPPA [10,18]. The gradual, variable nature of the degeneration of grey and white matter structures in PPA also allowed understanding of the contribution of different anatomical components of speech and language symptomatology. For instance, the association between the degree of damage in the Aslant tract with severity of specific motor speech deficits pointed towards a specific role of this white matter structure in articulatory functions [35,46,47].

Cross-linguistic studies in PPA offer an interesting prospective to the study of language organization in the brain. Studies show unique symptoms in different languages. Japanese speaking svPPA individuals show characteristics of Gogi aphasia, with more severe deficits in kanji (logographic) than kana (alphabetic) script, because kanji strongly relies on semantic knowledge [2]. On the other hand, Italian is a language with a mainly shallow orthography (i.e. mainly composed of regular words) in which stress assignment is arbitrary. Therefore, Italian svPPA would not show surface dyslexia and only show stress assignment errors while reading [e.g. pronouncing 'ma'cchina' (nonword) instead of 'macchina' (car)] [81]. Deep dyslexia is instead noted in Chinese-speaking svPPA individuals, likely because Chinese is a logographic language that heavily relies on ATL-supported lexical–semantic memory [82]. The unique characteristics of different languages can thus provide interesting perspectives regarding the development, plasticity and cognitive reserve of specific language networks depending on different linguistic context.

PRIMARY PROGRESSIVE APHASIA AS A MODEL OF STUDYING NETWORK SUSCEPTIBILITY TO PATHOGENIC PROTEINS

Three decades of PPA research have demonstrated that by applying the knowledge of basic cognitive and imaging neuroscience to the study of neurodegenerative disease, we can identify specific clinical phenotypes and accurately map these phenotypes to specific brain networks [7]. As each brain network has a selective vulnerability to specific toxic proteins, clinicoanatomical phenotyping improves the prediction of in-vivo neuropathological changes [83]. By combining evidence from clinical, neuroanatomical, genetic, and biomarker studies, we can correctly identify underlying Alzheimer's disease from FTLT disorder in PPA premortally. Differentiation between FTLT-subtype disorder is also quite accurate, though slightly less reliable because of the lack of in-vivo biomarkers, such as molecular PET or CSF. Albeit the current PPA consensus classification has greatly increased our ability to predict underlying neuropathology, such prediction will never be perfect, as the selective

vulnerability is relative and not absolute. In-vivo pathological prediction is crucial in neurodegenerative diseases because therapeutic pharmacological strategies are, or soon will be, directed towards decreasing or clearing toxic molecules, such as amyloid, tau or TDP.

Different autopsy studies show that the prevalence of FTLN-TDP-43 type C (TDP-C) disorder ranges between 73 and 83% in clinically diagnosed svPPA [28,49]. The prevalence of TDP-C disorder is higher when svPPA cases are diagnosed prospectively and followed longitudinally [49]. The remaining cases usually have FTLN-tau, including Pick's disease and globular glial tauopathies (GGT), or, more rarely, Alzheimer's disease [49]. Consistent with the selective vulnerability theory, nfvPPA shows a very different pattern of pathological changes compared with svPPA, mainly caused by FTLN-tau deposition [49]. In one prospectively diagnosed cohort with 25 nfvPPA patients, nfvPPA was most commonly associated with FTLN-tau disorder (88%), with 72% being four-repeat tauopathies (4Rtau), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), and 16% having threerepeat tauopathies (3R-tau), such as Pick's disease [49]. A small portion of nfvPPA cases was found to have FTLN-TDP-43 type A or B disorder, likely because of GRN or C9ORF72 mutations [49]. Sporadic lvPPA clinical syndrome is associated with Alzheimer's disease biomarkers and Alzheimer's disease pathological changes in about 85–90% of cases [28,49,52]. Therefore, recent Alzheimer's disease diagnostic criteria include lvPPA as an atypical earlyonset variant of Alzheimer's disease [84]. Other causes are Pick's disease (3R tauopathy) or TDP-43 type A disorder, the latter associated with GRN mutations [28,78]. A few lvPPA cases also reported Lewy body disorder in isolation or as co-disorder with Alzheimer's disease [85]. Interestingly, coexisting disorders or biomarkers discordant with the clinical syndrome are more common than predicted in PPA (and FTD), especially in older individuals [28,52]. These studies are very relevant to clinical trials. For instance, given that FTLN-4 repeat (4R) tauopathies are rarely associated with svPPA, svPPA patients should not be considered for clinical trials that target 4R tau that are instead appropriate for nfvPPA.

In-vitro and animal studies have demonstrated that toxic proteins including amyloid, tau, and TDP43 spread transneuronally through connected networks in a prion-like manner [86–88]. Neuroimaging studies in PPA support these findings by showing network-specific damage in each variant. Given the extensive available knowledge on the anatomy and physiology of the speech and language networks, PPA is an ideal model to investigate the intricate relationship between protein deposition patterns and network susceptibility in neurodegenerative diseases. Neurodevelopmental disorders are increasingly associated with neurodegenerative diseases and might contribute to network vulnerability [89,90]. Notably, developmental dyslexia seems overrepresented in PPA, with one study indicating greater association in lvPPA [89,90]. Moreover, nonright handedness dominance is found to be more common in svPPA, at nearly twice the prevalence of the general population [89]. Thus, PPA can potentially be an optimal model to study the neurodevelopment influences in neurodegenerative diseases.

PRIMARY PROGRESSIVE APHASIA AS A MODEL FOR TARGETED SPEECH AND LANGUAGE REHABILITATION STRATEGIES IN NEURODEGENERATIVE DISEASES

There is increasing evidence supporting the effectiveness of targeted speech and language rehabilitation therapy in PPA, with or without the addition of noninvasive brain stimulation. In nfvPPA, motor speech impairment and agrammatism showed positive effects to structured oral reading tasks training and video-implemented script training for aphasia (VISTA) therapy [91,92]. When coupled with language therapies, transcranial direct current stimulation (tDCS) has demonstrated improvements in various speech and language performances in all variants of PPA [93,94,95]. Lexical retrieval treatments are one of the most widely explored nonpharmacological therapies in PPA [96]. To maximize its therapeutic effects, it is crucial to build on spared language abilities, such as phonological and autobiographical memory processes in svPPA and semantic memory abilities in lvPPA [96]. A recent study shows that intensive naming therapy is associated with increased bilateral activation in functional MRI after treatment [97]. PPA served as a model to show that targeted cognitive therapy can be useful in improving and delaying progression of cognitive symptoms in neurodegenerative disorders.

CONCLUSION

PPA is emerging as a model for understanding the link between clinical, neuroimaging and neurobiological vulnerability in focal neurodegenerative disorders. Research in PPA shows that a multidisciplinary, precision medicine approach is the best strategy towards finding effective pharmacological and cognitive therapies for neurodegenerative diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- of special interest

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KEY POINTS

- PPA can be largely divided into three variants or subtypes, semantic, nonfluent, and logopenic, each with distinct functional neuroanatomy, underlying proteinopathies and clinical characteristics.
- Premortem neuropathological prediction of PPA can be highly accurate by combining the clinical, neuroanatomical, genetic, and biomarker evidence.
- PPA provides additional valuable perspectives for understanding the neural basis of speech and language.
- PPA is an ideal model to study the link between clinical, neuroimaging, and neurobiological vulnerability in focal neurodegenerative disorders.

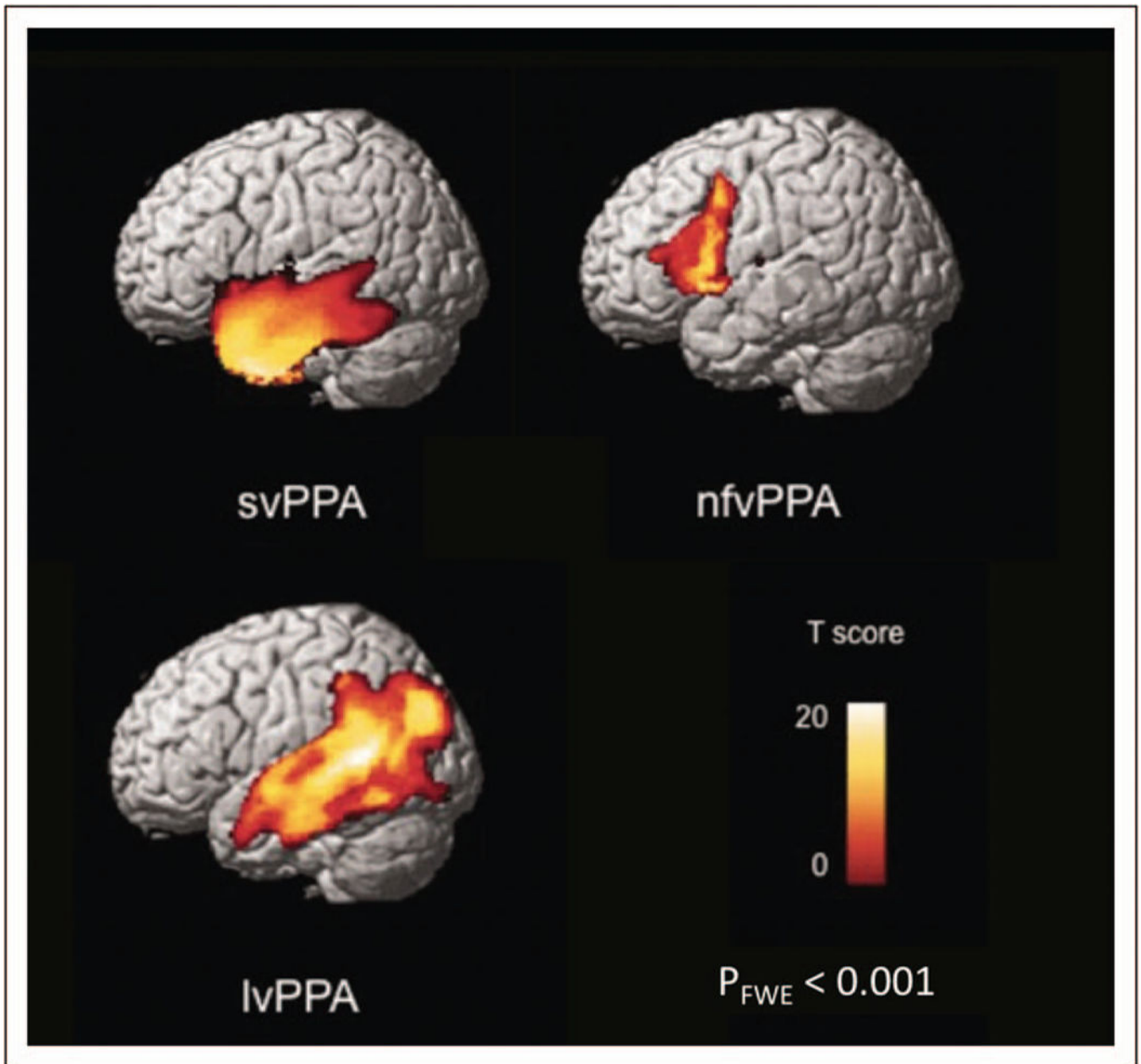


FIGURE 1.

Grey matter atrophy patterns in patients with three main primary progressive aphasia variants versus controls. Presented here are statistical parametric maps that depict the grey matter atrophy patterns in semantic variant PPA (svPPA, $n = 58$), nonfluent/agrammatic variant PPA (nfvPPA, $n = 40$), and logopenic variant PPA (lvPPA, $n = 24$) compared with control groups that are matched for age, sex, scanner and sample size. Voxel-based morphometry results thresholded are set at a family-wise error rate of $P < 0.001$. FWE, familywise error rate; PPA, primary progressive aphasia. Reproduced with permission from [88].

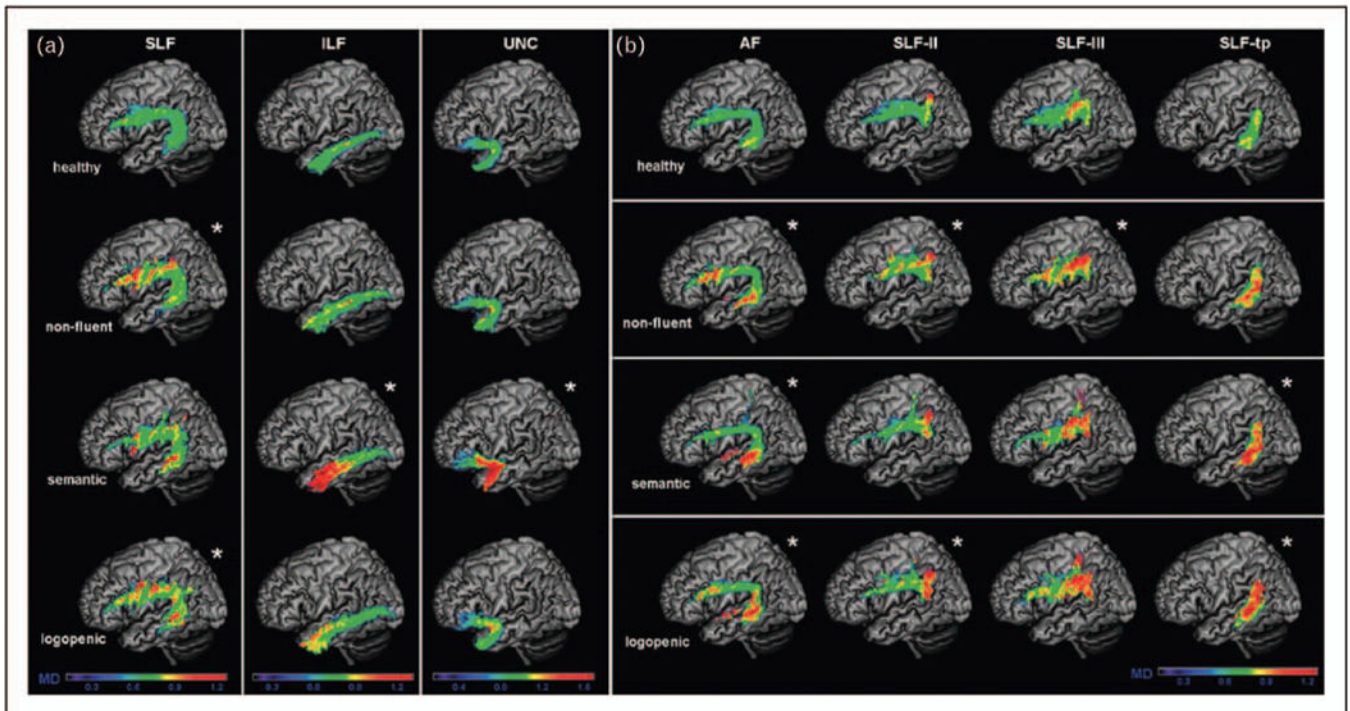
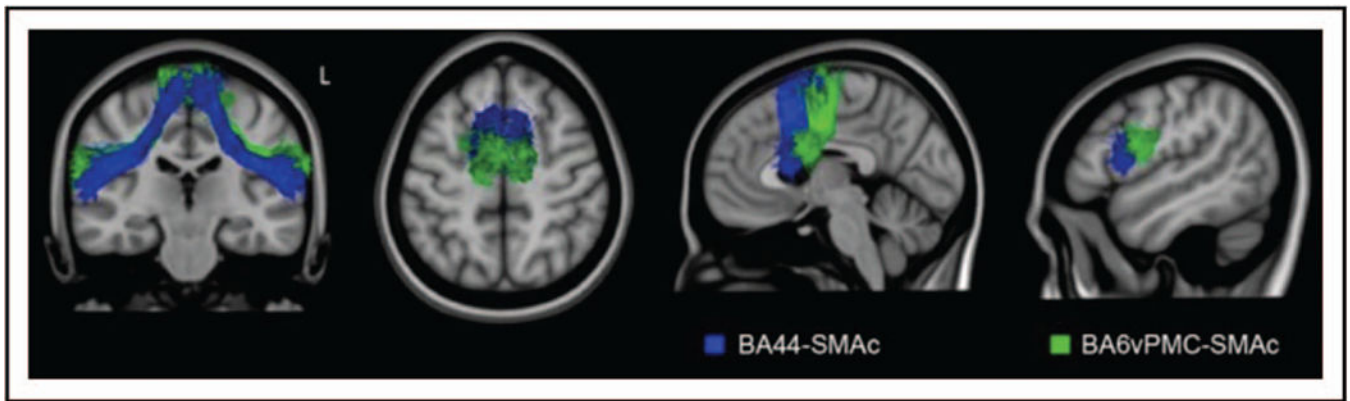


FIGURE 2.

White matter damage in the three main primary progressive aphasia variants versus controls. (a) The average mean diffusivity values for left superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UNC) in all three PPA variants when compared with healthy controls on a standard MNI (Montreal Neurological Institute of McGill University Health Centre) brain template. The asterisk symbol (*) indicates statistical difference from normal controls with P value less than 0.05. The colour bar represents the average mean diffusivity values, ranging from low (violet-blue) to high values (yellow-red). Mean diffusivity is measured in $10^{-3} \text{ mm}^2 \text{ s}^{-1}$. (b) The average mean diffusivity values for arcuate fasciculus (AF), frontoangular SLF (SLF-II), frontosupramarginal SLF (SLF-III), and temporoparietal SLF (SLF-tp) in all three PPA variants when compared with healthy controls on a standard MNI (Montreal Neurological Institute of McGill University Health Centre) brain template. The asterisk (*) indicates statistical difference from normal controls with P value less than 0.05. The colour bar represents the average mean diffusivity values, ranging from low (violet-blue) to high values (yellow-red). Mean diffusivity is measured in $10^{-3} \text{ mm}^2 \text{ s}^{-1}$. Reproduced with permission from [21].

**FIGURE 3.**

The Aslant tract within the frontal speech production network. Depicted here is the white matter tract reconstruction of Aslant tract within the frontal speech production network (SPN) in healthy controls using MNI brain template. White matter tracts traveling between pre-SMA and SMA to BA44 is shown in blue and to the ventral premotor cortex (BA6) is highlighted in green. Reproduced with permission from [46].

Table 1.

Primary progressive aphasia 2011 diagnostic consensus criteria algorithm

PPA clinical diagnostic criteria	
Inclusion criteria	
(1) Most prominent clinical feature is difficulty with language	
(2) Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease	
(3) These deficits are the principal cause of impaired daily living activities	
Exclusion criteria	
(1) Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders	
(2) Cognitive disturbance is better accounted for by a psychiatric diagnosis	
(3) Prominent initial episodic memory, visual memory, and visuosperceptual impairments	
(4) Prominent initial behavioural disturbance	
Clinical diagnosis	<p>Nonfluent/Agrammatic variant PPA</p> <p>Core features: (at least 1)</p> <p>(1) Agrammatism in language production</p> <p>(2) Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)</p> <p>Supporting features: (at least 2)</p> <p>(1) Impaired comprehension of syntactically complex sentences</p> <p>(2) Spared single-word comprehension</p> <p>(3) Spared object knowledge</p>
Imaging supported diagnosis (both present)	<p>(1) Clinical diagnosis of nfvPPA</p> <p>(2) Imaging: (at least 1)</p> <p>(a) Predominant left posterior frontoinsular atrophy on MRI</p> <p>(b) Predominant left posterior frontoinsular hypoperfusion or hypometabolism on SPECT or PET</p>
PPA with definite diagnosis	<p>Clinical diagnosis fulfilled</p> <p>AND</p> <p>(1) Histopathologic evidence of a specific neurodegenerative disorder (e.g. FTLD-tau, FTLD-TDP, AD, other)</p> <p>OR</p> <p>(2) Presence of a known pathogenic mutation</p>
Clinical diagnosis	<p>Semantic variant PPA</p> <p>Core features: (both)</p> <p>(1) Impaired confrontation naming</p> <p>(2) Impaired single-word comprehension</p> <p>Supporting features: (at least 3)</p> <p>(1) Impaired object knowledge, particularly for low frequency or low familiarity items</p> <p>(2) Surface dyslexia or dysgraphia</p> <p>(3) Spared repetition</p> <p>(4) Spared speech production (grammar and motor speech)</p>
Clinical diagnosis	<p>Logopenic variant PPA</p> <p>Core features: (both)</p> <p>(1) Impaired single-word retrieval in spontaneous speech and naming</p> <p>(2) Impaired repetition of sentences and phrases</p> <p>Supporting features: (at least 3)</p> <p>(1) Speech (phonologic) errors in spontaneous speech and naming</p> <p>(2) Spared single-word comprehension and object knowledge</p> <p>(3) Spared motor speech</p> <p>(4) Absence of frank agrammatism</p>
Imaging supported diagnosis (both present)	<p>(1) Clinical diagnosis of svPPA</p> <p>(2) Imaging: (at least 1)</p> <p>(a) Predominant anterior temporal lobe atrophy on MRI</p> <p>(b) Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET</p>
PPA with definite diagnosis	<p>Clinical diagnosis fulfilled</p> <p>AND</p> <p>(1) Histopathologic evidence of a specific neurodegenerative disorder (e.g. FTLD-tau, FTLD-TDP, AD, other)</p> <p>OR</p> <p>(2) Presence of a known pathogenic mutation</p>

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Adapted with permission from [8,9]. AD, Alzheimer's disease; FTD-tau, frontotemporal lobar degeneration-tau; FTLD-TDP, frontotemporal lobar degeneration-TAR DNA-binding protein; IvPPA, logopenic variant primary progressive aphasia; nfvPPA, nonfluent/agrammatic primary progressive aphasia; PPA, primary progressive aphasia; svPPA, semantic variant primary progressive aphasia.