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THE NON-FLUENT/AGRAMMATIC VARIANT OF PRIMARY PROGRESSIVE APHASIA

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Abstract

In an era of disease-modifying treatments, the non-fluent/agrammatic variant of primary progressive aphasia (naPPA) may help screen for a specific cause of neurodegenerative disease. However, there are controversies surrounding the identification of naPPA. This review describes the characteristic features associated with this discrete, young-onset neurodegenerative condition. Patients with naPPA have a distinct limitation in language emphasizing their poor grammatical comprehension and expression, as well as a disorder of speech sound production. Imaging studies associate an impairment of this uniquely human language capacity with disruption of a large-scale neural network centered in left inferior frontal and anterior-superior temporal regions. This corresponds to the pathologic burden of disease anatomically focused in left inferior frontal and anterior-superior temporal regions. A review of the histopathology underlying naPPA relates this condition to frontotemporal lobar degeneration spectrum pathology involving the microtubule-associated protein tau in a majority of cases. While much work remains to be done, these observations point to unique clinical-pathological correlations that can advance care for an important class of diseases while supplementing our knowledge of human cognitive neuroscience.

INTRODUCTION

The central feature of primary progressive aphasia (PPA) is declining language. Pick first described a woman with gradually worsening speech who eventually became mute in the context of a progressive social disorder characterized by disinhibited, socially inappropriate behavior¹. The first report of progressive difficulty limited to language was provided one year later². This case had declining speech fluency without difficulty in memory, social, or visuospatial domains. In the modern literature, Mesulam described five cases of declining speech fluency under the name of Slowly Progressive Aphasia³.

PPA, first defined by Mesulam⁴, refers to an *aphasic* disorder, that is, an impairment of language comprehension and expression without peripheral sensory and motor deficits that may mimic aphasia. Moreover, the language impairment must be insidiously *progressive* in nature. This is in order to rule out non-neurodegenerative etiologies such as stroke or head trauma. Finally, the language disorder must be the *primary* deficit that is present for about

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CONFLICT OF INTEREST STATEMENT

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two years. This eliminates other progressive neurodegenerative conditions associated with a variety of underlying pathologies, including: behavioral variant frontotemporal degeneration (bvFTD) characterized a social disorder; typical Alzheimer's disease (AD) associated with memory difficulty; posterior cortical atrophy that often has visuospatial deficits; corticobasal syndrome (CBS), progressive supranuclear palsy syndrome (PSPS), and parkinsonian syndromes like Lewy body disease that are associated with cognitive deficits and an extrapyramidal movement disorder; and amyotrophic lateral sclerosis (ALS) that can have cognitive difficulties associated with weakness.

PPA represents a spectrum of selective language disorders⁵. These are important to recognize because each syndrome potentially screens for a distinct underlying pathology. Following clinical screening, more definitive diagnosis may be supplemented by biofluid biomarkers⁶. In this review, we focus on one form of PPA known as the non-fluent/agrammatic variant (naPPA) or "progressive non-fluent aphasia." This variant of PPA has proven controversial because of difficulty defining the characteristic language deficits, heterogeneity in the anatomic distribution of disease, and the variety of underlying pathologies. This review is timely because of recently published clinical consensus criteria for naPPA⁷, important advances in understanding the spectrum of pathology contributing to PPA⁸, and the emergence of disease-modifying medication trials focused on tau. The typical clinical characteristics of naPPA, the anatomic distribution of disease defined by imaging studies, the genetic associations of this condition, and the common histopathologic underpinnings of naPPA are described below.

There are two other common variants of PPA. One is semantic variant PPA (svPPA) or "semantic dementia"⁹. This features a disorder of word and object meaning. The second is logopenic variant PPA (lvPPA) or "logopenic progressive aphasia"¹⁰. This is marked by impaired word-finding and repetition difficulty. Recently published clinical recommendations for identifying these common forms of PPA⁷ are summarized in Table 1.

Search Strategy and Selection Criteria

A search in pubmed and medline for English language publications for the years 1981-2012 using the key words "progressive non-fluent aphasia" and "primary progressive aphasia" was supplemented by reviews of relevant bibliographies to select papers representing a balanced view of perspectives on this condition. Because of the recent, narrowed definition of naPPA, some earlier work referring to "progressive non-fluent aphasia" should be interpreted cautiously.

CLINICAL CHARACTERISTICS OF NONFLUENT/AGRAMMATIC PRIMARY PROGRESSIVE APHASIA

Demographic Features of naPPA

We can estimate the frequency of naPPA by considering that the etiology is often in the spectrum of pathology related to frontotemporal lobar degeneration (FTLD). Estimates of the prevalence of FTLD are 2.7-15 per 100,000¹¹⁻¹³, while estimates of the incidence are 2.2-3.5 per 100,000^{14, 15}. In autopsy studies examining unselected clinical cases thought to be associated with FTLD spectrum pathology, up to 45% of FTLD cases have PPA, and a little less than half of these PPA patients have naPPA^{5, 16-23}. Based on an estimate that 20% of autopsied FTLD cases have naPPA, the prevalence naPPA due to FTLD pathology is 0.5-3.0 per 100,000 and incidence is 0.4-0.7 per 100,000. If up to 30% of naPPA cases are due to AD, then the approximate prevalence of naPPA due to any cause is 0.65-3.9 per 100,000 and incidence is 0.5-0.9 per 100,000.

naPPA is a young-onset condition with an average age of onset at about 60²⁴. The age of onset is quite broad, ranging from the 30's to the early 80's, and this differs from conditions like AD because of its poisson distribution around the average onset age rather than a skewed distribution that increases with age. Survival is about 7 years, although this too is quite variable^{17, 25-29}. There is no gender bias. There are no known environmental risk factors³⁰. We are highly dependent on language in day-to-day functioning, and a language disorder limits self-care activities and independence in daily living. There is a significant reduction in quality of life. Poor communicative efficacy in naPPA has profound consequences for psychological integrity and can be associated with depression³¹.

Speech and Language Deficits in naPPA

The clinical hallmark of naPPA is effortful, non-fluent speech^{32, 33}. This is best quantified by a semi-structured protocol that is long enough to reflect the variety of utterances that can occur in spontaneous speech, yet is standardized enough so that all participants have an opportunity to produce speech prompted by the same content. Our lab asks patients to review and then narrate a wordless children's picture story³⁴. Based on this technique, the rate of speech in naPPA averages 45 words per minute, less than one-third the speech rate of healthy adults³⁵. This is a robust marker of naPPA, and has been confirmed using a briefer speech sample³⁶. Speech does not emerge as a slow but steady flow. Instead, speech is interrupted by lengthy pauses within and between utterances. Even when controlling for pauses, naPPA patients produce fewer words per minute than controls³⁵. Another clinical characteristic of effortful, non-fluent speech is the distortion of prosody. Prosody is the pattern of pitch contours spanning words and sentences that helps provide emphasis, is critical for marking questions, and reflects the emotional content of speech. Prosody loses its normal contours in naPPA.

Several factors may contribute to effortful, non-fluent speech in naPPA³⁷. The most prominent factor is difficulty processing grammatical aspects of speech. A transcription of a speech sample from a naPPA patient is provided in Figure 1. A detailed analysis of a lengthy, semi-structured speech sample in naPPA reveals significant simplification of grammatical forms. There is also a significantly greater number of grammatical errors and omissions compared to controls and other PPA patients³⁵⁻³⁷. These characteristics result in a significantly abbreviated mean length of utterance. Verbs play a critical role in structuring a sentence, and naPPA patients use fewer verbs in their speech³⁵. They also have difficulty with verbs on other tasks that assess comprehension³⁸ and naming³⁹.

Another potential cause of slowed, effortful speech may be a motor speech disorder known as apraxia of speech (AoS). From this perspective, speech is slowed because the complex coordination of muscle groups underlying the motor speech apparatus has been compromised. There are at least two sources for the large number of speech sound errors in patients with naPPA: While some of these errors are due to a disturbance of the motor system responsible for coordinating and articulating speech sounds known as AoS, other speech sound errors are due to disturbance of the linguistic system of phonology that is responsible for the abstract representations of speech sounds and the rules governing their use in a speaker's language. Several reports describe an increased frequency of AoS in patients with naPPA⁴⁰⁻⁴². AoS is most prominent in conditions with co-occurring involuntary limb movements and poor limb motor control such as progressive supranuclear palsy syndrome (PSPS) and corticobasal syndrome (CBS), although AoS can occur without an accompanying extrapyramidal disorder, and AoS can occur as an isolated entity without other evidence of the language impairments found in naPPA^{43, 44}. An important problem has been difficulty quantifying AoS. Ash and her colleagues (2010) proposed one potential method for quantifying AoS. Specifically, they identified speech errors that are not part of the corpus of speech sounds in the speaker's native language. This is because "phonetic"

speech errors of this sort are more likely to emerge when an impaired motor coordination system produces sounds due to misplaced articulators. This contrasts with “phonologic” speech sound errors that violate the abstract rules for representing and ordering phonemes in the speaker’s native language. While this method rigorously characterizes the nature of the speech errors, this captures only some examples of AoS. With this caveat in mind, these investigators document many speech errors in naPPA, but phonetic errors consistent with AoS characterize only 21% of the speech sound errors of these patients⁴⁵.

One strategy to assess grammatical processing while minimizing confounds associated with a motor speech disorder involves assessment of grammatical comprehension³². naPPA patients thus have difficulty pointing to one of two pictures based on a sentence, where selecting the correct picture depends on appreciating the sentence’s grammatical structure⁴⁶. Another measure uses an anagram task to determine whether patients can order words printed on cards into a grammatically complex utterance describing a picture⁴⁷. Yet another task is entirely language-based and probes brief sentences varying in grammatical complexity with a simple question about “who did what to whom.” In the sentence “Boys that girls kick are unfriendly,” for example, naPPA patients often err when asked: “Who did the kicking?”⁴⁸. Grammatical difficulties such as this can be used to distinguish naPPA from healthy seniors and from other PPA variants^{48, 49}. Another mark of the “central” grammatical deficit in naPPA is the presence of parallel grammatical impairments in writing and reading³².

It is important to keep in mind that these measures of grammatical processing are performed “off-line” and may not fully reflect day-to-day natural language use. Thus, these tasks are under the control of an executive resource system that is making conscious, deliberative interpretations and decisions about sentence meaning, and as noted below, naPPA patients have limited executive resources and working memory that can confound interpretation of performance on these language tasks. A handful of studies have probed grammatical processing in an “on-line” manner that minimizes executive control during task performance. One study examined naPPA patients who were impaired in their comprehension of grammatically complex sentences using a traditional measure. The investigators reported that naPPA patients also have slowed processing of grammatically complex sentences in an on-line measure, suggesting that grammatically relevant information may degrade in working memory during the course of sentence processing⁵⁰. Another on-line study found that naPPA patients are selectively insensitive to grammatical violations in a sentence, although they are normal in their sensitivity to semantic violations⁵¹.

Several aspects of language are relatively preserved in naPPA. Oral production of over-learned sequences such as counting and repetition of phrases is more fluent than spontaneous speech. The ability to name orally and write a pictured object’s name to confrontation is performed relatively well, although there may be difficulty naming with verbs³⁹. There is relatively good comprehension of single words presented orally and in writing, although there may be difficulty with verb comprehension³⁸. Spelling is largely preserved and there is little difficulty reading written words aloud.

naPPA is a progressive disorder of language, but there have been few studies examining the longitudinal course of this condition. These patients appear to develop broad-based decline in their language functioning⁵², and a validated algorithm has been developed to quantify disease severity in naPPA⁵³. Two studies have documented progressive decline in grammatical comprehension in naPPA^{54, 55}, and their speech becomes progressively effortful and non-fluent to the point where speech consists of single words. While performance worsens in other domains of language such as naming, reading and spelling^{43, 56}, and while these patients deteriorate in their performance on measures of

working memory and executive control⁵⁶, effortful speech, grammatical deficits, and speech sound errors remain relatively more impaired throughout the course of the disease.

In sum, patients with naPPA appear to have profoundly slowed and effortful speech that is often related to an impairment of grammatical comprehension and production as well as poor motor speech control, but many other aspects of language do not appear to decline as much.

Other Cognitive Deficits in naPPA

Patients with naPPA may develop other neuropsychological deficits. For example, a limitation of executive resources often can be found. This includes difficulty with working memory, mental planning and dual-tasking⁵⁷. Thus, impairments can be seen on measures such as reverse digit span, where a sequence of digits is repeated in its reverse order. There is also difficulty on letter-guided naming fluency (e.g. providing as many words as possible beginning with a letter like “F”). Patients decline in their performance on these measures over time as well⁵⁶.

In contrast to performance on measures of executive functioning, patients with naPPA typically have relatively preserved episodic memory⁵⁷. Visuospatial functioning also is relatively preserved, although there are some exceptions such as naPPA presenting in the context of CBS⁵⁸. It is uncommon to observe a disorder of social functioning and personality early in the course of naPPA, although socially inappropriate behaviors seen in patients with behavioral variant FTD (bvFTD) can emerge over time, including apathy, disinhibition or repetitive behaviors with little empathy and poor self-insight^{59, 60}. The non-language spectrum of cognitive deficits in naPPA thus appears to involve limitations in working memory and executive control, but may implicate other cognitive and social domains particularly as the condition progresses.

Elementary Neurologic Deficits in naPPA

Many patients with naPPA have a normal elementary neurologic exam, but neurologic abnormalities can be seen in some patients. These may provide hints about the histopathologic basis for the patient’s disorder. Abnormalities on neurologic exam, when present, may involve an extrapyramidal disorder. This includes features of CBS such as unilateral rigidity, dystonia, myoclonus and limb apraxia^{58, 61}. There may also be a disorder of vertical gaze and axial rigidity associated with PSPS^{40, 62}. As noted above, some of these patients have prominent AoS.

naPPA also can be seen in the context of a pyramidal motor system disorder. This clinical picture suggests amyotrophic lateral sclerosis (ALS), with bulbar and limb weakness, muscle wasting, fasciculations, abnormal myotactic reflexes, and an extensor great toe⁶³⁻⁶⁵. Patients presenting with naPPA thus should be assessed neurologically since the presence of CBS or ALS may have a significant impact on prognosis.

THE NEUROANATOMIC BASIS FOR NONFLUENT/AGRAMMATIC PRIMARY PROGRESSIVE APHASIA

Structural and Functional Imaging Studies of naPPA

The term “primary” in “primary progressive aphasia” is intended to emphasize the absence of obvious structural abnormalities that can explain the impairment in these patients. This includes vascular disease, space-occupying lesions, infections, inflammatory conditions, head trauma, hydrocephalus, and other disorders.

Nevertheless, there is extensive imaging evidence suggesting focal CNS disease in naPPA. This clinical imaging marker of naPPA is centered in the left frontal lobe. Several imaging techniques have been used to help specify the anatomic distribution of disease associated with naPPA. Structural MRI studies of the brain emphasize gray matter atrophy in the inferior frontal region of the left hemisphere^{48, 66, 67} (Figure 2). This typically involves adjacent frontal operculum and anterior insula, and may extend more dorsally into left prefrontal regions and ventrally into superior portions of the left anterior temporal lobe⁵⁵. This may correspond to the anatomic distribution of atrophy in patients with known tau pathology, a frequent cause of naPPA, as discussed below⁶⁸. In patients with prominent AoS, imaging changes reported in premotor and supplementary motor areas somewhat more dorsally in the left hemisphere^{40, 45}. These structural findings are confirmed by functional imaging with single photon emission computed tomography, positron emission tomography (PET), and arterial spin labeling MRI. For example, PET glucose hypometabolism is seen in the left inferior frontal lobe, including the frontal operculum and the anterior insula⁶⁹.

Disease in naPPA also compromises white matter, as illustrated in Figure 2. This reflects histopathologic evidence for extensive white matter disease in these patients⁷⁰. Recent work using diffusion tensor imaging (DTI) demonstrates reduced fractional anisotropy (FA) that reflects changes in white matter integrity in projections related to the inferior frontal lobe^{71, 72}.

Imaging studies also can contribute to understanding the cause of naPPA. This is important because, as noted below, most naPPA patients have a tauopathy but up to 30% of patients with naPPA may have underlying AD pathology. Reduced parietal glucose metabolism thus is seen in PET scans of patients with pathologically-confirmed naPPA due to AD compared to naPPA patients with non-AD pathology⁷³. Likewise, MRI gray matter atrophy extending into the left inferior parietal region in naPPA is associated with biomarker and autopsy evidence for AD compared to naPPA patients with FTL spectrum pathology⁷⁴.

PET also can be used for radioligand imaging with Pittsburgh compound B (PiB). PiB can help determine the pathologic basis for naPPA more directly because PiB tags amyloid, a component of AD pathology that is not associated with FTL spectrum pathology. PiB studies of PPA thus may help distinguish between naPPA due to AD and non-AD pathology⁷⁵.

MR spectroscopy also can be informative by obtaining a chemical profile of the brain. In a study of naPPA occurring in the context of CBS⁷⁶, a reduction in the ratio of n-acetyl aspartate/creatine (NAA/Cr) relative to phosphocreatine was found in the left hemisphere. This is significant because NAA is thought to reflect neuronal integrity. Likewise, patients with a mutation of microtubule-associated protein - tau (MAPT) that codes for tau, a common pathology associated with naPPA, may have an abnormal reduction of NAA/Cr⁷⁷.

Structure-Function Relationships in naPPA

Additional work has begun to demonstrate how disease in the left inferior frontal and anterior-superior temporal regions as well as the associated white matter tracts interrupts a large-scale neural network contributing to the language disorder evident in this syndrome. This has been addressed with several approaches. The most straightforward method involves a regression analysis directly relating quantitative gray matter atrophy to a measure of language functioning. A cardinal characteristic of naPPA is reduced speech fluency, and quantification of this deficit in a semi-structured speech sample is related to atrophy in inferior frontal and anterior superior temporal regions of the left hemisphere^{35, 36, 78}. Reduced speech fluency in turn may be related to three factors, including grammatical difficulty, AoS, and executive dysfunction on measures like letter-guided naming fluency. In

one study, only difficulty associated with grammatical processing overlaps areas of cortical atrophy related to non-fluent speech, and this is evident in left inferior frontal and anterior superior temporal regions³⁷. Another study associates AoS with left inferior frontal atrophy⁴¹, although the operational definition of AoS included both phonetic errors consistent with AoS and phonologic errors resulting from an impairment of the linguistic system responsible for processing the abstract rules governing speech sounds.

Functional MRI also has been used to assess the role of left inferior frontal disease in naPPA. In one study, healthy controls, patients with naPPA, and patients with bvFTD silently read sentences featuring a complex grammatical structure and containing a prepositional phrase that stresses working memory⁷⁹. Controls activate both ventral portions of the left frontal lobe associated with grammatical processing and dorsal left frontal regions associated with working memory. By comparison, naPPA patients activate only dorsal portions of the left frontal lobe, but did not activate the ventral region associated with grammatical processing. Non-aphasic patients with bvFTD activate the ventral frontal region but not the dorsal area, in keeping with their prominent working memory deficit. Another fMRI study showed grammatically simple sentences and grammatically complex sentences to naPPA patients and healthy controls⁴⁶. Controls activate left inferior frontal regions during grammatically complex sentences more than simple sentences, while naPPA patients do not show a difference in left inferior frontal activation for these types of sentences. These findings emphasize the crucial contribution of left inferior frontal disease to the naPPA syndrome.

Recent DTI work such as that illustrated in Figure 2, when combined with areas of gray matter atrophy, emphasizes the breakdown of a large-scale neural network⁸⁰ that is responsible in part for the language deficits seen in naPPA. A ventral stream and a dorsal stream support connectivity within this peri-Sylvian language system. In Figure 2, interruption of the ventral stream may play a critical role in grammatical and lexical processing deficits related to major grammatical category found in naPPA. In Figure 2, ventral fiber tracts projecting posteriorly via the inferior frontal-occipital fasciculus that have reduced FA are green. Likewise, projections through the so-called dorsal stream appear to play an important role in the long-distance syntactic dependencies that contribute to the grammatical deficits of naPPA. Dorsal fiber tracts contributing to the arcuate fasciculus that have significantly reduced FA are red.

GENETIC ASSOCIATIONS OF NONFLUENT/AGRAMMATIC PRIMARY PROGRESSIVE APHASIA

A strongly positive family history approaches 30% in FTLN^{81, 82}. However, there is little evidence suggesting that the clinical syndrome of naPPA is inherited in an autosomal dominant manner. The gene first associated with FTLN – MAPT – is found on chromosome 17⁸³. Another common mutation associated with FTLN – progranulin (PGRN) – also is found on chromosome 17^{84, 85}. Recently, a common cause of familial FTLN and ALS was associated with a hexanucleotide repeat expansion in a non-coding region on chromosome 9 (C9ORF72)^{86, 87}. Each of these genetic mutations is associated with a specific histopathologic abnormality commonly associated with naPPA, as summarized in Table 2 and discussed in greater detail below. Other less common chromosomal mutations include VCP on chromosome 9⁸⁸, CHMP2B on chromosome 3⁸⁹, and a mutation of TARDBP on chromosome 1⁹⁰.

While FTLN is frequently inherited, well-documented families with naPPA appear to be rare. Hereditary dysphasic dementia (HDDD), for example, appears to be related to the FTLN spectrum of disease^{91, 92}. More recently, HDDD was associated with ubiquitin-positive, tau-negative pathology due to a PGRN mutation⁹³. Two families with naPPA have

been described, and this was associated with a PGRN mutation^{94, 95}. Other reports have described families with naPPA and a behavioral disorder due to a PGRN mutation^{96, 97}. While mutations of PGRN clearly can result in naPPA⁹⁸⁻¹⁰⁰, PGRN mutations do not appear to be predisposed to causing a naPPA phenotype. It is important to note in this context that clinical FTLT syndromes can be highly variable even in members of a family with the identical PGRN mutation^{100, 101}. Indeed, the presence of a PGRN mutation and a PPA phenotype do not appear to be highly correlated. One study, for example, reported that 60% of 25 patients with a PGRN mutation have reduced speech production for a variety of reasons, only half of these patients had speech difficulty at presentation, and only three of these patients appeared to have a naPPA phenotype at presentation without an accompanying social disorder⁹⁸. In another series, PPA appeared to be relatively uncommon at presentation, although a language disorder did eventually emerge in many individuals¹⁰².

Mutations of MAPT are associated with a tauopathy, and these also have been related at times to naPPA. For example, one sister of a positive sib-pair with a MAPT mutation had reduced speech fluency and was impaired on the Token test assessment of grammatical comprehension¹⁰³. The H1/H1 haplotype that is linked to the region on chromosome 17 coding for tau appears to be associated with PPA¹⁰⁴. While mutations of MAPT may be related to naPPA¹⁰⁵, a mutation of MAPT does not result in a disproportionately high frequency of naPPA. As with PGRN, the phenotype associated with a specific MAPT mutation within a family may be highly variable¹⁰⁶.

Recently, a hexanucleotide repeat expansion on chromosome 9 in a non-coding open reading frame location of unclear function (C9ORF72) was reported in families with FTD as well as ALS^{86, 87}. As in ALS-FTD, occasional patients with a C9ORF72 repeat expansion may have a naPPA phenotype^{107, 108}. Although other genetic mechanisms of disease remain to be elucidated, chromosomal mutations associated with an autosomal dominant disorder do not appear to be disproportionately associated with naPPA.

PATHOLOGY ASSOCIATED WITH NONFLUENT/AGRAMMATIC PRIMARY PROGRESSIVE APHASIA

Gross pathology in naPPA shows focal atrophy centered in the left inferior frontal and anterior-superior temporal region of the left hemisphere (Figure 3). This corresponds to the core area of disease seen in imaging studies during life. It has been proposed that the class of von Economo neurons found only in higher-order primates may be diseased in patients with FTLT¹⁰⁹. These neurons are found in inferior frontal regions that support uniquely human capacities like grammar, although this cannot account for the full spectrum of disease seen in naPPA.

Several different pathologies can result in naPPA. Microscopic examination of naPPA at autopsy often reveals frontotemporal lobar degeneration associated with a tauopathy (FTLT-tau). Some clinical-pathological series have associated naPPA only with tau-positive pathologies. In a comprehensive assessment of naPPA and AoS, cases with either naPPA or AoS clinical features have tau-positive forms of pathology⁴⁰. This included patients with progressive supranuclear palsy (PSP), although this was also seen in corticobasal degeneration (CBD) and dementia with Pick bodies (PiD). In another series, the clinical diagnosis of naPPA was associated only with PiD pathology¹¹⁰.

In other studies, the pathology associated with naPPA has been overwhelmingly associated with FTLT with transactive-response DNA-binding protein of ~43 kD (FTLT-TDP). For example, all but one of the naPPA patients in a large series had FTLT-TDP pathology¹¹¹. Four different forms of TDP-43 histopathology have been described^{112, 113}, and the variant

with frequent dystrophic neurites and neuronal cytoplasmic inclusions known as Type A was found to be particularly prominent in naPPA^{18, 114}.

In most series, however, the pathology underlying naPPA has been mixed, with a predominance of FTLD-tau pathology. Hodges noted mostly tau-immunoreactive pathology associated with naPPA²⁰. In follow-up studies, a variety of pathologies have been catalogued in their 23 naPPA patients, including FTLD-tau in 11 patients, AD in seven patients, dementia lacking distinctive histopathology in one patient, and “motor neuron disease inclusion dementia” (presumably FTLD-TDP) in four patients¹¹⁵⁻¹¹⁷. Among 10 cases with naPPA, another British series reported tau pathology in 7 cases, equally divided between PiD and CBD, and TDP-43 Type A pathology in 3 cases²³. Kertesz and his colleagues followed 20 naPPA patients longitudinally. In addition to 9 cases of tau-related pathology, they found AD pathology in 9 cases, and “motor neuron disease type inclusions” (presumably FTLD-TDP) in 2 patients¹⁷. Mesulam found mostly tau pathology associated with naPPA, but one of his 6 cases had FTLD-TDP pathology¹¹⁸. In another series of 9 naPPA cases followed longitudinally, FTLD-tau was found in 6 cases and AD pathology in 3 patients¹¹⁹. Among Knopman’s naPPA cases, most had tau-immunoreactive pathology but 2 had pathology consistent with FTLD-U and one of these cases had additional AD pathology²¹. Another series from the same institution found PiD, FTLD-U, PSP, and CBD pathologies in cases of naPPA¹²⁰. Two cases of dementia with Lewy bodies (DLB) have been associated with naPPA^{5, 17}. Two summaries of clinical-pathological series such as these have suggested that about 70% of naPPA patients have tau pathology, and many of the remainder have AD pathology^{5, 22}. While not definitive, the naPPA phenotype thus appears to be biased towards FTLD-tau pathology. In an era of disease-modifying treatments, naPPA thus may be a valuable screening tool for identifying patients likely to have FTLD-tau pathology who would then be eligible for additional biomarker studies defining the underlying cause of their disorder such as cerebrospinal fluid.

RESOLVING SOURCES OF CONFUSION IN NONFLUENT/AGRAMMATIC PRIMARY PROGRESSIVE APHASIA

Clinical identification

A major source of controversy has been clinical identification of patients with naPPA. The speech characteristic of naPPA involves grammatical processing difficulty, including simplified syntactic structures and grammatical errors. This is accompanied by difficulty understanding sentences that depend on grammatical relations. This may be accompanied by a specific pattern of errors in speech sound production that mark AoS. Effortful, non-fluent speech characteristic of naPPA is not the gradual diminution of speech initiation to the point of muteness that can be seen in bvFTD patients with apathy.

Likewise, effortful speech in naPPA is not a reduction of speech fluency due to lengthy, word-finding pauses that can be seen in lvPPA and even svPPA. Cases of lvPPA may be particularly difficult to distinguish from patients with naPPA because lvPPA also may manifest impaired sentence processing because of auditory-verbal short-term memory deficits. This can interfere with processing lengthy sentences and thus resemble the grammatical deficits found in naPPA. Written sentence materials can be used to help distinguish between the grammatical deficit of naPPA compared to the auditory-verbal limitations of lvPPA. Other features of lvPPA that can help distinguish this syndrome from naPPA include difficulty with multi-syllabic word and sentence repetition, and poor performance on neuropsychological measures like repeating sequences of digits^{10, 121}. While both lvPPA and naPPA may have gray matter atrophy in a left anterior peri-Sylvian distribution, cortical disease extends into the posterior peri-Sylvian region in lvPPA^{73, 74}.

Finally, since many patients with lvPPA can evolve to typical clinical Alzheimer's disease and often have underlying AD pathology^{5, 118, 122, 123}, cerebrospinal fluid tau:amyloid-beta ratio⁷⁴ and PiB PET imaging⁷⁵ studies can be helpful in identifying patients more likely to have lvPPA rather than naPPA.

Imaging abnormalities

There has been some controversy identifying clinical imaging markers of naPPA. The focus of disease detected by MRI and PET appears to be in the left inferior frontal lobe and adjacent frontal operculum and anterior insula. This frequently extends dorsally and anteriorly to involve additional frontal regions, and inferiorly to involve anterior-superior portions of the left temporal lobe. Recent diffusion-weighted imaging studies emphasize that there is extensive involvement of white matter that limits connectivity between these frontal regions and other language and cognitive areas in the cerebrum. Thus, an important consequence of this anatomic distribution of disease is the disruption of the large-scale peri-Sylvian neural network essential for sentence processing.

Pathologic basis for disease

The histopathologic abnormalities found in naPPA are not homogeneous. However, there appears to be a clear bias in a majority of clinical-pathological series toward finding a tauopathy in naPPA. The syndrome of naPPA thus may be a relatively inexpensive and non-invasive way to screen for underlying tau pathology. Follow-up studies with imaging and biofluid biomarkers thus may be used to rule out other pathologies and confirm the presence of tau-immunoreactive pathology. Imaging studies using agents such as Pittsburgh Compound B can help identify some patients who may have the histopathologic features of AD⁷⁵, and cerebrospinal fluid analyses can be used to rule out AD as well as patients who may have underlying TDP-43 pathology¹²⁴.

SUMMARY

naPPA is a progressive neurodegenerative condition that is important to recognize because it may help identify patients with underlying tau pathology. The sentinel clinical feature of naPPA is effortful, non-fluent speech. This can be quantified by reduced words per minute, and confirmed by grammatical simplifications and errors in grammatical comprehension and expression, and the presence of AoS. Limited executive resources also may be present, and other aspects of language and cognition may become compromised over time. There are many other characteristics of impaired language in naPPA that remain to be quantified, such as phonologic processing of speech sounds during reception, the role of executive resources in sentence processing, and the nature of disorders of prosody. Additional longitudinal work would be very valuable in optimizing our syndromic classification of the PPAs.

Many imaging modalities associate naPPA with disease centered in the inferior portions of the left frontal lobe. This is a useful clinical marker, but the language disorders characteristic of this syndrome appear to be compromised by disruption of a large-scale peri-Sylvian language network. A recent advance underlining this approach is the demonstration of significant white matter disease in diffusion-weighted imaging studies of naPPA. Future contributions can focus on defining the specific roles of disease in dorsal and ventral white matter tracts that are compromised in the large-scale neural networks of naPPA patients. The mechanism underlying these white matter imaging changes also remains to be elucidated, such as distinguishing between Wallerian degeneration associated with cortical disease compared to direct white matter pathology. This work will lead to important advances in the cognitive neuroscience of language.

Perhaps the most pressing clinical issue for the field is improving our ability to identify tauopathies. naPPA is most commonly associated with a form of FTLT-tau, and thus identifying the presence of this syndrome may be a useful clinical screen for tauopathy. With the emergence of disease-modifying substances, it becomes essential to recognize conditions like naPPA that are often caused by tauopathies because of the potential benefit that these patients may derive from these treatments. Additional biomarker work is needed to help identify a set of features that can identify a tauopathy with greater reliability.

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FIGURE 1. SEMISTRUCTURED SPEECH SAMPLE OF naPPA

1. Speech sample of a patient with naPPA narrating the children's wordless picture story *Frog, Where Are You?*⁸⁴. The narrative accompanying each of the three pictures is below the corresponding picture. While description of the content is accurate, the grammatical structure of the utterances is distorted and simplified, containing many errors. There are also speech sound errors. Pauses longer than 2 seconds are noted in parentheses in the transcript.

FIGURE 2. GRAY MATTER ATROPHY AND WHITE MATTER DISEASE IN naPPA

1. Patients (n=12) meeting published criteria for naPPA⁷ with CSF totaltau: amyloid-beta ratio <0.34 consistent with FTD spectrum pathology⁶. UPPER PANEL: Red areas show significant gray matter atrophy at $p < 0.0025$ (FDRcorrected) that is most evident in the left frontal lobe, including inferior, opercular, dorsolateral regions, extending into insula and anterior-superior temporal regions. There is also involvement of the right frontal lobe. LOWER PANEL: Solid areas show significantly reduced fractional anisotropy at $p < 0.01$ (FDRcorrected) that is more prominent on the left than the right. This includes left inferior frontal-occipital fasciculus as it courses through the external capsule (solid green), bilateral inferior frontal-occipital fasciculus, arcuate fasciculus and anterior thalamic radiations coursing through the anterior corona radiata and most anterior portion of the internal capsule bilaterally (solid red), and interhemispheric fibers of the corpus callosum (solid blue). blue=corpus callosum, red=internal capsule, green=external/extreme capsule, orange=fornix.

FIGURE 3. PATHOLOGY IN naPPA

1. Upper panel shows gross specimen of a patient with naPPA, illustrating significant inferior frontal and anterior-superior temporal atrophy. Lower panel left shows H & E preparation of histopathology demonstrating neuronal cytoplasmic inclusions consistent with Pick bodies; lower panel right shows tauimmunoreactive staining of neuronal inclusions.

TABLE 1

CLINICAL CHARACTERISTICS OF PRIMARY PROGRESSIVE APHASIA

Variant	Clinical Features ¹	Cortical Atrophy	Pathology ²	Alternative Nomenclature
naPPA	<ul style="list-style-type: none"> Grammatical simplification and errors in language production Effortful, halting speech with speech sound errors Two or more of the following: impaired syntactic comprehension; spared content word comprehension; spared object knowledge 	Left inferior frontal and insula	<ul style="list-style-type: none"> FTLD-tau (52%) AD (25%) FTLD-TDP (19%) Other (4%) 	<ul style="list-style-type: none"> Progressive nonfluent aphasia or PNFA Agrammatic PPA or PPA-G
svPPA	<ul style="list-style-type: none"> Poor confrontation naming Impaired single word comprehension Three or more of the following: poor object and/or person knowledge; surface dyslexia; spared repetition; spared motor speech 	Anterior and ventral temporal lobe	<ul style="list-style-type: none"> FTLD-TDP (69%) AD (25%) FTLD-tau (6%) 	<ul style="list-style-type: none"> Semantic dementia or SD Semantic PPA or PPA-S
lvPPA	<ul style="list-style-type: none"> Impaired single word retrieval Impaired repetition of phrases and sentences Three or more of the following: speech sound errors; spared motor speech; spared single word comprehension and object knowledge; absence of agrammatism 	Left posterior-superior temporal and inferior parietal	<ul style="list-style-type: none"> AD (50%) FTLD-TDP (38%) FTLD-tau (12%) 	<ul style="list-style-type: none"> Logopenic progressive aphasia or LPA Logopenic PPA or PPA-L Progressive mixed aphasia or PMA

Abbreviations: AD, Alzheimer's disease; FTLD-tau, frontotemporal lobar degeneration with tau-positive pathology; FTLD-TDP, frontotemporal lobar degeneration with ubiquitin- and TDP-43-positive pathology.

¹Based on expert consensus ⁷.

²From a literature survey of confirmed pathology in patients with PPA recruited without a priori bias ⁵.

TABLE 2

GENETIC-PATHOLOGICAL ASSOCIATIONS FOUND IN PATIENTS WITH NONFLUENT/
 AGRAMMATIC PRIMARY PROGRESSIVE APHASIA

Genetic Mutation	Pathology	
	FTLD-tau	FTLD-TDP
MAPT	X	
PGRN		X
C9ORF72		X
TARDBP		X