The non-fluent/agrammatic variant of primary progressive aphasia

Murray Grossman

The non-fluent/agrammatic variant of primary progressive aphasia (naPPA) is a young-onset neurodegenerative disorder characterised by poor grammatical comprehension and expression and a disorder of speech sound production. In an era of disease-modifying treatments, the identification of naPPA might be an important step in establishing a specific cause of neurodegenerative disease. However, difficulties in defining the characteristic language deficits and heterogeneity in the anatomical distribution of disease in naPPA have led to controversy. Findings from imaging studies have linked an impairment of this uniquely human language capacity with disruption of large-scale neural networks centred in left inferior frontal and anterior superior temporal regions. Accordingly, the pathological burden of disease in naPPA is anatomically focused in these regions. Most cases of naPPA are associated with the spectrum of pathological changes found in frontotemporal lobar degeneration involving the microtubule-associated protein tau. Knowledge of these unique clinical-pathological associations should advance care for patients with this important class of neurodegenerative diseases while supplementing our knowledge of human cognitive neuroscience.

Introduction

The central feature of primary progressive aphasia (PPA) is declining language ability. In 1892, Pick1 described a woman with gradually worsening speech who eventually became mute in the context of a progressive social disorder characterised by disinhibited, socially inappropriate behaviour. The first report of progressive difficulty limited to language was provided 1 year later by Siretoux,2 who described a patient with declining speech fluency but without difficulty in memory, social, or visuospatial domains. More recently, Mesulam3 described five cases of declining speech fluency under the term slowly progressive aphasia.

PPA, first defined by Mesulam,4 refers to an aphasic disorder—that is, an impairment of language comprehension and expression without peripheral sensory and motor deficits that might mimic aphasia. The language impairment must be insidiously progressive in nature to rule out non-neurodegenerative causes such as stroke or head trauma. Finally, the language disorder must be the primary deficit for about 2 years or more. This criterion eliminates other progressive neurodegenerative disorders associated with various underlying pathologies, including the following: behavioural variant frontotemporal degeneration (bvFTD), which is characterised by a social disorder; typical Alzheimer’s disease (AD), which is associated with memory deficits; posterior cortical atrophy, which often includes visuospatial deficits; corticobasal syndrome (CBS), progressive supranuclear palsy syndrome (PSPS), and parkinsonian syndromes such as Lewy body disease, which are associated with cognitive deficits and an extrapyramidal movement disorder; and amyotrophic lateral sclerosis (ALS), which can cause cognitive difficulties associated with weakness.

PPA represents a spectrum of selective language disorders,5 and the variant of PPA might provide clues to the underlying pathology. After clinical screening, a more definitive diagnosis can be obtained with biofluid biomarkers.6 In this Review, I focus on one form of PPA known as non-fluent/agrammatic PPA (naPPA) or progressive non-fluent aphasia. This variant of PPA has proven controversial because of difficulty in defining the characteristic language deficits, heterogeneity in the anatomical distribution of disease, and the variety of underlying pathologies. An overview of the disorder is timely because of recently published clinical consensus criteria for naPPA,7 advances in our understanding of the spectrum of pathological changes that contribute to PPA,8 and the emergence of trials of disease-modifying drugs that target tau pathology, which is associated with naPPA. The typical clinical characteristics, anatomical distribution of disease defined by imaging studies, genetic associations, and common histopathological underpinnings of naPPA are described.

There are two other common variants of PPA. One is semantic variant PPA (svPPA) or semantic dementia,9 which is a disorder of word and object meaning. The other is logopenic variant PPA (lvPPA) or logopenic progressive aphasia,9 which is marked by impaired word finding and repetition difficulty. Table 1 summarises clinical recommendations for the identification of these common forms of PPA.7

Clinical characteristics

Demographic features

The frequency of naPPA can be estimated by considering that the cause is often in the spectrum of pathology related to frontotemporal lobar degeneration (FTLD). Estimates of the prevalence of FTLD are 2.7–15.0 per 100 000 people10–13 and estimates of the incidence are 2.2–3.5 per 100 000 people per year.14,15 In autopsy studies of unselected clinical cases thought to be associated with FTLD spectrum pathology, up to 45% of FTLD cases had PPA and almost half of those patients with PPA had naPPA.16–21 If 20% of autopsied FTLD cases had naPPA, the prevalence of naPPA due to FTLD pathology would be 0.5–3.0 per 100 000 people and incidence 0.4–0.7 per 100 000 people per year. If up to 30% of naPPA cases
were due to AD, then the rough prevalence of naPPA due to any cause would be 0·7–3·9 per 100000 people and incidence 0·5–0·9 per 100000 people per year.

naPPA is a young-onset neurodegenerative disorder with an average age of onset of about 60 years.34 However, the age of onset is broad, ranging from the 30s to the early 80s, and differs from that of disorders such as AD because of its Poisson distribution around the mean age of onset rather than a skewed distribution that increases with age. Survival is about 7 years from the onset of symptoms, although this too is variable and ranges from 2 years in cases associated with ALS to about 12 years in cases without any motor disorder.17,25–29 There is no gender bias. There are no known environmental risk factors.35 We are highly dependent on language in day-to-day functioning, and a language disorder limits self-care activities and independence in daily living. Patients with naPPA have a significant reduction in quality of life. Poor communicative ability in naPPA has profound consequences for psychological integrity and can be associated with depression.36

Speech and language deficits

The clinical hallmark of naPPA is effortful, non-fluent speech,32,33 which is best quantified by a semi-structured speech sample.34 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, patients with naPPA produce fewer words per minute than control individuals.35

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 to provide emphasis, is crucial for marking questions, and reveals the emotional content of speech. Prosody loses its normal contours in naPPA.

Several factors can contribute to effortful, non-fluent speech in naPPA.37 The most prominent factor is difficulty processing grammatical aspects of speech. Figure 1 shows a transcript of a speech sample from a patient with naPPA. A detailed analysis of a lengthy, semi-structured speech sample in naPPA reveals significant simplification of grammatical forms. There are also significantly more grammatical errors and omissions compared with control individuals and patients with other PPA variants.35–37 These characteristics result in a significantly abbreviated mean length of utterance. Verbs play a crucial part in structuring a sentence, and patients with naPPA use fewer verbs in their speech than control individuals.38 They also have difficulty with verbs on tasks that assess comprehension38 and naming.39

Another potential cause of slowed, effortful speech is 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 causes of the large number of speech sound errors in patients with naPPA: although some of these errors are due to a disturbance of the motor system

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**Table 1: Clinical characteristics of primary progressive aphasia**

<table>
<thead>
<tr>
<th>Clinical features*</th>
<th>Cortical atrophy</th>
<th>Pathological changes†</th>
<th>Alternative nomenclature</th>
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<tbody>
<tr>
<td>Non-fluent/agrammatic PPA</td>
<td>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, or spared object knowledge</td>
<td>Left inferior frontal and insula</td>
<td>FTLD-tau (52%), AD (25%), FTLD-TDP (19%), and other (4%)</td>
</tr>
<tr>
<td>Semantic variant PPA</td>
<td>Poor confrontation naming Impaired single-word comprehension Three or more of the following: poor object or person knowledge or both; surface dyslexia; spared repetition; or spared motor speech</td>
<td>Anterior and ventral temporal lobe</td>
<td>FTLD-TDP (69%), AD (25%), and FTLD-tau (6%)</td>
</tr>
<tr>
<td>Logopenic variant PPA</td>
<td>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, or absence of agrammatism</td>
<td>Left posterior superior temporal and inferior parietal</td>
<td>AD (50%), FTLD-TDP (38%), and FTLD-tau (12%)</td>
</tr>
</tbody>
</table>

AD=Alzheimer’s disease. FTLD-tau=frontotemporal lobar degeneration with tau-positive pathology. FTLD-TDP=frontotemporal lobar degeneration with ubiquitin-positive and TDP-43-positive pathology. PPA=primary progressive aphasia. *Based on expert consensus. †From a literature review of confirmed pathological changes in patients with PPA recruited without a-priori bias.

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responsible for coordinating and articulating speech sounds (AoS), other speech sound errors are caused by 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 have described an increased frequency of AoS in patients with naPPA. AoS is most prominent in disorders with co-occurring involuntary limb movements and poor limb motor control, such as PSPS and CBS, although AoS can occur without an accompanying extrapyramidal disorder and as an isolated entity without other evidence of the language impairments found in naPPA. An important problem has been the quantification of AoS. Ash and colleagues proposed one potential method. Specifically, they identified speech errors that are not part of the corpus of speech sounds in the speaker’s native language. Phonetic speech errors of this sort are more likely to emerge when an impaired motor coordination system produces sounds due to misplaced articulators. These errors contrast with phonological speech sound errors that do not follow the abstract rules for representation and ordering of phonemes in the speaker’s native language. Although this method rigorously characterises the nature of the speech errors, it captures only some examples of AoS. With this caveat in mind, Ash and colleagues documented many speech errors in naPPA, but phonetic errors consistent with AoS characterised only 21% of the speech sound errors of these patients.

One strategy to assess grammatical processing while minimising confounds associated with a motor speech disorder involves the assessment of grammatical comprehension. Patients with naPPA have difficulty pointing to one of two pictures on the basis of a sentence, where selection of the correct picture requires appreciation of the grammatical structure of the sentence. Another measure uses an anagram task to determine whether patients can order words printed on cards into a grammatically complex question that describes a picture. Another task is entirely language based and probes brief sentences varying in grammatical complexity by a simple question about who did what to whom. In the sentence “Boys that girls kick are unfriendly”, for example, patients with naPPA often make a mistake when asked: “Who did the kicking?”

Grammatical difficulties such as these can be used to distinguish patients with naPPA from healthy seniors and from people with other PPA variants. Another mark of the central grammatical deficit in naPPA is the presence of parallel grammatical impairments in writing and reading. A handful of studies have probed grammatical processing in an online manner that minimises executive control during task performance. One study examined patients with naPPA who were...
impaired in their comprehension of grammatically complex sentences according to a traditional measure.56 The investigators reported that patients with naPPA also had slowed processing of grammatically complex sentences in an online measure, suggesting that grammatically relevant information might degrade in working memory during the course of sentence processing. Another online study found that patients with naPPA are selectively insensitive to grammatical violations of word use in a sentence, although they have normal sensitivity to semantic violations.51

Several aspects of language are 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 upon request is done well, although the patient might have difficulty naming with verbs.59 Patients with naPPA have good comprehension of single words presented orally and in writing, although they might have difficulty with verb comprehension.18 Spelling is largely preserved and patients have 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 disorder. These patients seem to develop a broad-based decline in their language functioning,53 and a validated algorithm has been developed to quantify disease severity in PPA.54 Two studies have documented a progressive decline in grammatical comprehension in patients with naPPA,54,55 where speech becomes progressively effortful and non-fluent to the point at which it consists of single words. Although performance worsens in other domains of language such as naming, reading, and spelling,54,56 and although these patients deteriorate in their performance on measures of working memory and executive control,56 effortful speech, grammatical deficits, and speech sound errors remain more impaired throughout the course of the disease.

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

Other cognitive deficits
Patients with naPPA can develop other neuropsychological deficits. For example, a limitation of executive resources often occurs, including difficulty with working memory, mental planning, and dual tasking.57 Thus, impairments can occur on measures such as reverse digit span, where a sequence of digits is repeated in reverse order. There is also difficulty on letter-guided naming fluency (eg, providing as many words as possible beginning with a particular letter). Patients also decline in their performance on these measures over time.56

By contrast with performance on measures of executive functioning, patients with naPPA typically have relatively preserved episodic memory.57 Visuospatial functioning is also relatively preserved, although there are some exceptions, such as naPPA presenting in the context of CBS.58 A disorder of social functioning and personality early in the course of naPPA is uncommon, although socially inappropriate behaviours noted in patients with bvFTD can emerge over time, including apathy, disinhibition, or repetitive behaviours with little empathy and poor self-insight.59,60 The non-language spectrum of cognitive deficits in naPPA thus seems to involve limitations in working memory and executive control, but might include other cognitive and social domains, particularly as the disorder progresses.

Elementary neurological deficits
Many patients with naPPA have a normal elementary neurological examination, but neurological abnormalities can be identified in some patients. These can provide hints about the histopathological basis of the disorder. Abnormalities on neurological examination, when present, might involve an extrapyramidal disorder, including features of CBS such as unilateral rigidity, dystonia, myoclonus, and limb apraxia.54,55 There might also be a disorder of vertical gaze and axial rigidity associated with PSPS.61,62 As noted above, some of these patients have prominent AoS.

naPPA can also occur in the context of a pyramidal motor system disorder. This clinical picture suggests ALS, with bulbar and limb weakness, muscle wasting, fasciculations, abnormal myotactic reflexes, and an extensor great toe (positive Babinski response).63–65 Thus, patients presenting with naPPA should be assessed neurologically because the presence of CBS or ALS has important implications for prognosis and management. Prognosis and the rate of clinical decline will be affected depending on the presence and nature of these features.

Neuroanatomical basis
Structural and functional imaging studies
The term “primary” in “primary progressive aphasia” is intended to emphasise the absence of obvious structural abnormalities that might explain the impairment in these patients, including vascular disease, space-occupying lesions, infections, inflammatory conditions, head trauma, hydrocephalus, and other disorders.

Nevertheless, there is extensive imaging evidence to suggest that focal CNS disease occurs in naPPA. This clinical imaging marker of naPPA is centred in the left frontal lobe. Several imaging techniques have been used to determine the anatomical distribution of disease associated with naPPA. Findings from structural MRI studies of the brain show grey matter atrophy in the inferior frontal region of the left hemisphere (figure 2).54,56,60 This atrophy typically involves adjacent frontal operculum and anterior insula, and can extend more dorsally into left prefrontal regions and ventrally into superior portions of the left anterior temporal lobe.51
This pattern might correspond to the anatomical distribution of atrophy in patients with known tau pathology, a frequent cause of naPPA, as discussed below. In patients with prominent AoS, imaging changes have been reported in premotor and supplementary motor areas somewhat more dorsally in the left hemisphere. These structural findings have been confirmed by functional imaging with SPECT, PET, and arterial spin labelling MRI. For example, PET glucose hypometabolism is seen in the left inferior frontal lobe, including the frontal operculum and the anterior insula.

As shown in figure 2, disease in naPPA also compromises white matter, and there is histopathological evidence for extensive white matter disease in these patients. Reduced fractional anisotropy seen on diffusion tensor imaging shows changes in white matter integrity in projections related to the inferior frontal lobe.

Imaging studies can also contribute to our understanding of the cause of naPPA. As I discuss later, most patients with naPPA have a tauopathy, but up to 30% of patients with this variant of PPA might have underlying AD pathological abnormalities. Thus, reduced parietal glucose metabolism is seen in PET scans of patients with pathologically confirmed naPPA due to AD compared with patients with naPPA without AD pathology. Likewise, MRI grey matter atrophy extending into the left inferior parietal region in naPPA is associated with biomarker and autopsy evidence of AD rather than FTLD spectrum pathology.

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

Magnetic resonance spectroscopy can also be informative by providing a chemical profile of the brain. In a study of naPPA occurring in the context of CBS, a reduction in the ratio of n-acetyl aspartate/creatine (NAA/Cr) relative to phosphocreatine was noted in the left hemisphere. This finding is important because NAA is thought to be a marker of neuronal integrity. Likewise, patients with a mutation of MAPT, which codes for microtubule-associated protein tau, a common pathology associated with naPPA, might have an abnormal reduction of NAA/Cr.

**Structure-function relations**

Additional work has begun to show how disease in the left inferior frontal and anterior superior temporal regions and the associated white matter tracts interrupts large-scale neural networks that contribute to the language disorder evident in naPPA. Several methods have been used, the most straightforward involving a regression analysis that directly relates quantitative grey matter atrophy to a measure of language functioning. A cardinal characteristic of naPPA is reduced speech fluency, and the magnitude of this deficit, as quantified in a semi-structured speech sample, is related to atrophy in inferior frontal and anterior superior temporal regions of the left hemisphere. Reduced speech fluency in turn can be related to three factors: grammatical difficulty, AoS, and executive dysfunction on measures such as letter-guided naming fluency. In one study, only areas of cortical atrophy associated with grammatical processing difficulty overlapped, and this was evident in left inferior frontal and anterior superior temporal regions. Another study associated AoS with left inferior frontal atrophy, although the operational definition of AoS included both phonetic errors consistent with AoS and phonological errors resulting from an impairment of the linguistic system responsible for processing the abstract rules governing speech sounds.

Functional MRI has also been used to assess the role of left inferior frontal disease in naPPA. In one study, healthy control individuals, patients with naPPA, and patients with bvFTD silently read sentences featuring a complex grammatical structure and containing a prepositional phrase that relies on working memory. In control individuals, both ventral portions of the left frontal lobe associated with grammatical processing and dorsal left frontal regions associated with working

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**Figure 2:** Grey matter atrophy and white matter disease in non-fluent/agrammatic primary progressive aphasia

Structural MRI from patients (n=12) meeting published criteria for non-fluent/agrammatic primary progressive aphasia with CSF total-tau:amyloid-β ratio less than 0·34 consistent with frontotemporal degeneration spectrum pathological changes. (A) Red areas show significant grey matter atrophy at p<0·0025 (false-discovery-rate corrected), which is most evident in the left frontal lobe, including inferior, opercular, and dorsolateral regions, extending into the insula and anterior superior temporal regions. There is also involvement of the right frontal lobe. (B) Solid areas show significantly reduced fractional anisotropy at p<0·01 (false-discovery-rate corrected), which is more prominent on the left than the right. Affected areas include the left inferior frontal-occipital fasciculus as it courses through the external capsule (solid red), 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 fibres of the corpus callosum (solid blue). Blue=corpus callosum. Red=internal capsule. Green=external capsule. Orange=fornix.
memory were activated. By comparison, in patients with naPPA only dorsal portions of the left frontal lobe were activated, and not the ventral region associated with grammatical processing. In non-fl aphasic patients with bvFTD, the ventral frontal region but not the dorsal area was activated, in keeping with the prominent working memory deficit in these patients. In another functional MRI study, grammatically simple sentences and grammatically complex sentences were shown to patients with naPPA and healthy participants. In control participants, left inferior frontal regions were activated more during grammatically complex sentences than during simple sentences, whereas in patients with naPPA there was no a difference in left inferior frontal activation for these types of sentences. These findings show the crucial contribution of left inferior frontal disease to naPPA.

Recent diffusion tensor imaging work, such as that shown in figure 2, when combined with areas of grey matter atrophy, shows the breakdown of large-scale neural networks that are responsible in part for the language deficits seen in naPPA. A ventral stream and a dorsal stream support connectivity within this perisylvian language system. As shown in figure 2, interruption of the ventral stream might play a crucial part in grammatical and lexical processing deficits related to major grammatical category found in naPPA. Ventral fibre tracts projecting posteriorly via the inferior frontal-occipital fasciculus that have reduced fractional anisotropy are shown in green in figure 2. Likewise, projections through the so-called dorsal stream seem to play an important part in the long-distance syntactic dependencies that contribute to the grammatical deficits of naPPA. In figure 2, dorsal fibre tracts with significantly reduced fractional anisotropy that contribute to the arcuate fasciculus are shown in red.

**Genetic associations**

About 30% of patients with FTLD have a strong family history of the disorder. However, there is little evidence to suggest that the clinical syndrome of naPPA is inherited in an autosomal dominant manner. The gene first associated with FTLD, MAPT, is located on chromosome 17. Other common mutations associated with FTLD are found in progranulin (PGRN), which is also found on chromosome 17. Recently, a hexanucleotide repeat expansion in a non-coding region on chromosome 9 (C9ORF72) was identified as a common cause of familial FTLD and ALS. Each of these genetic mutations is associated with a specific histopathological abnormality commonly associated with naPPA, as summarised in table 2 and discussed in greater detail below. Other less common chromosomal mutations include VCP on chromosome 9, CHMP2B on chromosome 3, and a mutation of TARDBP on chromosome 1.

Although FTLD is frequently inherited, well-documented families with naPPA seem to be rare. Hereditary dysphasic dementia (HDDD), for example, seems to be related to the FTLD spectrum of disease. More recently, HDDD-2 was associated with ubiquitin-positive, tau-negative pathology due to a PGRN mutation. Two families with naPPA associated with a PGRN mutation have been described. Other reports have described families with naPPA and a behavioural disorder due to a PGRN mutation. Although PGRN mutations can result in naPPA, the presence of a PGRN mutation does not seem to be highly correlated with a PPA phenotype. One study, for example, reported that 60% of 25 patients with a PGRN mutation had reduced speech fluency and was impaired on the token test assessment of grammatical comprehension. The H1/H1 haplotype that is linked to the region on chromosome 17 that codes for tau seems to be associated with PPA. Although mutations of MAPT might be related to naPPA, they do not result in a disproportionately high frequency of naPPA. As with PGRN, the phenotype associated with a specific MAPT mutation within a family can be highly variable.

As in ALS-FTD, some patients with a C9ORF72 repeat expansion can have a naPPA phenotype. Although other genetic mechanisms of disease remain to be elucidated, chromosomal mutations associated with an autosomal dominant disorder do not seem to be disproportionately associated with naPPA.

**Pathology**

Pathological assessment in naPPA shows focal atrophy centred in the left inferior frontal and anterior superior...
temporal region of the left hemisphere (figure 3), which corresponds to the core area of disease seen in imaging studies during life. The class of von Economo neurons, found only in high-order primates, might be diseased in patients with FTLD. These neurons are found in inferior frontal regions that support uniquely human capacities such as grammar; however, this finding cannot account for the full spectrum of disease seen in naPPA.

Several different pathologies can result in naPPA. Microscopic assessment of naPPA at autopsy often reveals FTLD associated with a tauopathy (FTLD-tau). Some clinical-pathological series have associated naPPA only with tau-positive pathologies. In a comprehensive assessment of naPPA and AoS, cases with clinical features of either naPPA or AoS had tau-positive forms of pathology. Patients with these changes included those with PSP as well as patients with corticobasal degeneration (CBD) and dementia with Pick bodies (PiD). In another series, the clinical diagnosis of naPPA was associated only with PiD pathology.

In other studies, the pathology associated with naPPA has been almost exclusively associated with FTLD with transactive-response DNA-binding protein of about 43 kDa (FTLD-TDP). For example, all but one of the patients with naPPA in one large series had FTLD-TDP pathology. Four different forms of TDP-43 histopathology have been described, and the variant with frequent dystrophic neurites and neuronal cytoplasmic inclusions, known as type A, was particularly prominent in naPPA.

However, in most series, the pathology underlying naPPA was mixed, with a predominance of FTLD-tau pathology. Hodges and colleagues noted mostly tau-immunoreactive pathology associated with naPPA in 23 patients. In follow-up studies, various pathological abnormalities were catalogued in these patients, including FTLD-tau in 11 patients, AD in seven patients, dementia without distinctive histopathology in one patient, and motor neuron disease inclusion dementia (presumably FTLD-TDP) in four patients. Among ten cases with naPPA, a UK series reported tau pathology in seven cases, equally divided between PiD and CBD, and TDP-43 type A pathology in three cases. Kertesz and colleagues assessed 20 patients with naPPA longitudinally. In addition to nine cases with tau-related pathology, they noted AD pathology in nine cases, and motor neuron disease-type inclusions (presumably FTLD-TDP) in two patients. Mesulam and colleagues reported mostly tau pathology associated with naPPA in nine cases, but one of his six cases had FTLD-TDP pathology. In another series of nine patients with naPPA who were assessed longitudinally, FTLD-tau was found in six patients and AD pathology in three patients. Among naPPA cases assessed by Knopman and colleagues, most patients had tau-immunoreactive pathology but two had abnormalities consistent with FTLD with ubiquitin-positive inclusions (FTLD-U), one of whom had additional AD pathology. Another series from the same institution found PiD, FTLD-U, PSP, and CBD pathologies in cases of naPPA. Two cases of dementia with Lewy bodies have been associated with naPPA. Findings from two summaries of clinical-pathological series such as these have suggested that about 70% of patients with naPPA have tau pathology and many of the remainder have AD pathology. Although not definitive, the naPPA phenotype thus seems to be biased towards FTLD-tau pathology.

Figure 3: Pathology in non-fluent/agrammatic primary progressive aphasia
(A) Gross specimen from a patient with non-fluent/agrammatic primary progressive aphasia, showing substantial inferior frontal and anterior superior temporal atrophy. (B) Haematoxylin and eosin preparation of histopathological samples showing neuronal cytoplasmic inclusions consistent with Pick bodies; the right-hand panel shows tau-immunoreactive staining of neuronal inclusions. Magnification 40×.

Resolving sources of confusion
Clinical identification
A major source of controversy has been the clinical identification of patients with naPPA. The speech characteristic of naPPA involves grammatical processing difficulty, including simplified syntactic structures and grammatical errors, which is accompanied by difficulty understanding sentences that depend on grammatical relations. These features might be accompanied by a specific pattern of errors in speech sound production (AoS). The effortful, non-fluent speech characteristic of naPPA is not the gradual diminution of speech initiation to the point of muteness that can occur in patients with bvFTD and apathy.
Likewise, effortful speech in naPPA is not a reduction of speech fluency due to lengthy, word-finding pauses that can occur in lvPPA and even svPPA. Patients with lvPPA can be particularly difficult to distinguish from those with naPPA because lvPPA can also manifest impaired sentence processing because of auditory-verbal short-term memory deficits. This impairment can interfere with the processing of lengthy sentences and can thus resemble the grammatical deficits noted in naPPA. Written sentence materials can help to distinguish between the grammatical deficit of naPPA and the auditory-verbal limitations of lvPPA. Other features of lvPPA that can help to distinguish this syndrome from naPPA include difficulty with multi-syllabic word and sentence repetition and poor performance on neuropsychological measures such as repeating sequences of digits.10,11 Although both lvPPA and naPPA can be accompanied by grey matter atrophy in a left anterior perisylvian distribution, cortical disease extends into the posterior perisylvian region in lvPPA.74,75 Finally, because many patients with lvPPA can evolve to typical clinical AD and often have underlying AD pathology,1,13,14,15 CSF tau:amyloid-β ratio16 and PiB PET imaging17 studies can be helpful in the identification of patients who are more likely to have lvPPA than naPPA.

Imaging abnormalities

There has been some controversy regarding the identification of clinical imaging markers of naPPA. The focus of disease detected by MRI and PET seems to be in the inferior portions of the left frontal lobe. This focus of atrophy is a useful clinical marker, but the language disorders characteristic of this syndrome seem to be caused by disruption of large-scale perisylvian language networks. A recent advance that supports this hypothesis is the finding of substantial white matter pathology. This work will lead to important advances in the cognitive neuroscience of language.

Pathological basis of disease

The histopathological abnormalities found in naPPA are not homogeneous. However, there seems to be a clear bias in most clinical-pathological series towards a finding of taupathy in naPPA. Thus, screening for the syndrome of naPPA might be an inexpensive and non-invasive way to begin to identify patients with underlying tau pathology. Follow-up studies with imaging and biofluid biomarkers could be used to rule out other pathologies and to confirm the presence of tau-immunoreactive pathology. Imaging studies with agents such as PiB can help to identify patients who might have the histopathological features of AD,17 and CSF analyses can be used to rule out AD as well as the possibility of underlying TDP-43 pathology.124

Conclusion

naPPA is a progressive neurodegenerative disorder, the recognition of which could help to identify patients with underlying tau pathology. The sentinel clinical feature of naPPA is effortful, non-fluent speech, which can be quantified by reduced words per minute and confirmed by grammatical simplifications, errors in grammatical comprehension and expression, and the presence of AoS. Limited executive resources might also be present, and other aspects of language and cognition can become compromised over time. There are many other characteristics of impaired language in naPPA that remain to be quantified, such as phonological 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 valuable for optimisation of the syndromic classification of PPAs.

Many imaging modalities associate naPPA with disease centred in the inferior portions of the left frontal lobe. This focus of atrophy is a useful clinical marker, but the language disorders characteristic of this syndrome seem to be caused by disruption of large-scale perisylvian language networks. A recent advance that supports this hypothesis is the finding of substantial white matter disease in diffusion-weighted imaging studies of naPPA. Future studies could focus on defining the specific roles of disease in dorsal and ventral white matter tracts that are compromised in patients with naPPA. The mechanism underlying these white matter changes in imaging studies also remains to be elucidated, such as distinguishing between Wallerian degeneration associated with cortical disease compared with direct white matter pathology. This work will lead to important advances in the cognitive neuroscience of language.
with these disorders might derive from such treatments. Additional biomarker work is needed to identify tauopathies with greater reliability.

Conflicts of interest
MG participates in clinical trials sponsored by Allon Pharmaceuticals, Forest Laboratories, and Bristol-Myers Squibb; is a consultant for Allon and Bristol-Myers Squibb for treatment trials unrelated to naPPA; and receives travel funds directly from academic institutions to support speaking at Grand Rounds periodically.

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