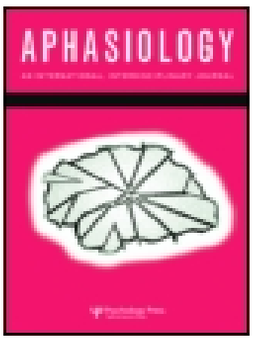

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Primary progressive apraxia of speech: from recognition to diagnosis and care

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ABSTRACT

Background: Apraxia of speech (AOS) can be caused by neurodegenerative disease and sometimes is its presenting sign (i.e., primary progressive apraxia of speech, PPAOS). During the last several decades, our understanding of PPAOS has evolved from clinical recognition to a fuller understanding of its core and associated clinical features, its distinction from but relationship with primary progressive aphasia, its temporal course and eventual progression to include other neurological deficits, and its neuroimaging correlates and underlying pathology.

Aims: This paper provides a comprehensive summary of the literature that has built the current knowledge base about PPAOS and progressive AOS as it co-occurs with progressive aphasia. It reviews the history of its emergence as a recognized syndrome; its relationship with the agrammatic/nonfluent variant of primary progressive aphasia; its salient perceptual features and subtypes; the acoustic and structural/physiological imaging measures that index its presence, severity, and distinction from aphasia; and principles and available data regarding its management and care.

Main Contribution: A broad summary of what is known about AOS as a manifestation of neurodegenerative disease.

Conclusions: Primary progressive apraxia of speech is a recognizable syndrome that can be distinguished from other neurodegenerative conditions that affect speech and language.

Abbreviations

AAC = augmentative and alternative communication; *AES* = Articulatory Error Score; *ALS* = amyotrophic lateral sclerosis; *AOS* = apraxia of speech; *AOS+PAA* = AOS plus the agrammatic/nonfluent variant of PPA; *ASRS* = Apraxia of Speech Rating Scale; *CBD* = corticobasal degeneration; *CBS* = corticobasal syndrome; *DAOS* = dominant AOS – aphasia present but AOS more severe; *MSD* = motor speech disorders; *nfPPA* = nonfluent variant of PPA, with or without AOS; *NVOA* = nonverbal oral apraxia; *PAOS* = progressive AOS, with or without aphasia; *PAA* = agrammatic variant of PPA, without AOS; *PPA* = primary progressive aphasia, with or without AOS; *PPAOS* = primary progressive AOS - no aphasia; *PSP* = progressive supranuclear palsy; *SMA* = supplementary motor area.

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Introduction

For more than a decade, any discussion about the causes of apraxia of speech (AOS) has recognized its association with neurodegenerative disease. This derives from an accumulation of supportive data ranging from case studies to prospective cohort studies.

In keeping with the focus of this special issue on AOS, this paper reviews the current state of understanding of neurodegenerative or progressive AOS (PAOS), with a primary focus on its relatively pure manifestation – PAOS in the absence of aphasia, now generally referred to as primary progressive AOS (PPAOS). However, such a review cannot ignore the disorder's close relative, primary progressive aphasia (PPA), because PPA and PAOS can be intertwined clinically, because the distinction between them has been a source of confusion and debate, and because the distinction has implications for clinical diagnosis, localization, prognosis, accompanying deficits, management, and underlying pathology.

In this paper, PPAOS will refer to a clinical syndrome dominated by AOS with no more than equivocal evidence of aphasia. AOS+PAA (progressive agrammatic/nonfluent aphasia) – the variant of PPA in which AOS most commonly occurs – will refer to a clinical syndrome in which both AOS and agrammatic aphasia are present, recognizing that many studies use the terms agrammatic and/or nonfluent PPA **(nfPPA)** to refer to patients who may or may not have both aphasia and AOS; the designation nfPPA will be used when this uncertainty is present. When referring to patients with nfPPA in which AOS is stated as not present, the designation PAA (progressive agrammatic aphasia) will be used. Because these distinctions are often indeterminate, unrecognized, or blurred in the literature and clinical practice, other labels will be used when there is uncertainty about whether the PPAOS, AOS+PAA, nfPPA, or PAA designations apply.

History

The presence of AOS as a component of neurodegenerative syndromes has been recognized since the early 1990 s and probably longer than that, although not necessarily by its current label. The dearth of cases reported early on likely partly reflect a failure to distinguish between AOS and aphasia and dysarthria. For example, in Mesulam's seminal paper on "slowly progressive aphasia" in 1982 (Mesulam, 1982), one case had, in addition to aphasia, "labored" and "dysarthric" speech as well as "buccofacial apraxia". Such features are as easily associated with AOS as with dysarthria, given what we now know about PPA and PAOS.

During the 1990 s and early 2000 s dozens of publications documented AOS as the only or most prominent component of a disorder that did not meet criteria for a more specifically defined disease (e.g., Alzheimer's disease, progressive supranuclear palsy). Among earlier noteworthy reports was that of Broussolle and colleagues who summarized eight cases with progressive "speech apraxia" as the initial sign of disease which the authors felt should be separated from PPA because of its distinctive features (Broussolle et al., 1996). Additional case reports similarly argued for recognizing the initial aphasia-free or AOS-predominant problem. Other papers noted that AOS was often present in nfPPA but not necessarily as the predominant problem. Vague descriptions of speech in other papers suggest that AOS was a prominent presence on the basis of conclusions that patients had, for example, "a disturbance in a motor speech output mechanism that

regulates the orderly production of phonemes" (Kartsounis et al., 1991, p. 126). Numerous papers used terms such as "aphemia", "progressive dysarthria", "slowly progressive anarthria", or "decline in articulate speech or loss of speech" to label speech abnormalities, at least some of which likely reflected AOS. During this period, which predated formalization of the consensus-based variants of PPA (M. L. Gorno-Tempini et al., 2011), AOS-like speech difficulties were among the features used to strengthen arguments that PPA, in general, was not always just an early manifestation of Alzheimer's disease (e.g., (Weintraub, 1990)). During this time, AOS also became associated with clinical conditions with underlying pathology of corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and Pick's disease.

In the early 2000 s, often without using the term AOS, the relationship between PAOS and PPA was more explicitly acknowledged. In probable reference to PAOS, Mesulam and colleagues advised that PPA be distinguished from "pure progressive dysarthria or phonological disintegration in which the formation rather than usage of words becomes disrupted" (Mesulam et al., 2003, p. S12), and considered the latter to be a "boundary sign" which tends to develop later in the disease course and is less prominent than aphasia. In contrast, an "aphemic variety" of PPA was recognized, with "predominantly phonological, articulatory errors and stuttering or verbal apraxia" (Kertesz et al., 2003, p. 175). Others began to question if the "nonfluency" of PPA had more to do with AOS than aphasia (e.g., (Clark et al., 2005)).

In spite of the fact that PAOS began to be viewed as distinguishable from PPA, there remained uncertainty about whether the distinction is necessary for purposes beyond that already achievable through broader diagnoses of PPA or frontotemporal dementia (FTD), in which nfPPA is one variant. Regarding PPAOS, the importance of distinguishing it from nfPPA has been questioned because many patients with PPAOS eventually develop aphasia, and because both disorders are often associated with the same underlying tau pathology (e.g., (Marshall et al., 2018; Rohrer, Paviour et al., 2010; Tee & Gorno-Tempini, 2019)). Although there is some merit to these arguments, because a disease may evolve over time to include new deficits does not seem to warrant initially calling it the condition for which it may eventually meet diagnostic criteria. For example, many patients with a diagnosis of PPA eventually develop nonlanguage cognitive deficits that reach threshold for a clinical diagnosis of probable Alzheimer's disease. This fact has not generally led to considering a diagnosis of PPA unimportant because it may eventually meet criteria for a broader diagnosis; admittedly, however, it was a point of debate a few decades ago when PPA was becoming a recognized diagnostic entity. This has not happened because it is recognized that aphasia can be the predominant clinical problem for a prolonged time, which can, at the least, substantially influence counseling and staging of specific management strategies. Until it is demonstrated that the distinction does not make a difference at several levels of inquiry and patient care, this reasoning should also apply to PPAOS (Josephs et al., 2013).

Evidence for AOS as a frequent presence in nfPPA has accumulated during the last 20 years. For example, Ogar et al. (2007) observed AOS in all of the 18 patients they studied. Similarly, Caso et al. (2014) noted that AOS was the most common feature in a study of 11 patients. Rohrer, Rossor et al. (2010) identified four subgroups of patients with nfPPA, one which included patients with AOS without aphasia, and another which

included patients with AOS plus agrammatism (i.e., AOS+PAA); the other two groups had no AOS. The two subgroups with AOS constituted the majority of patients. There was uncertainty about whether the AOS-only subgroup was simply a less severe form of nfPPA which would eventually develop aphasia, or if it represented a distinct group pathophysiologically. However, imaging evidence and recognition of a relationship between PPAOS and AOS+PAA with PSP and CBS support arguments for maintaining a distinction between AOS and PPA (e.g., (Josephs et al., 2013; Josephs, Duffy et al., 2006; Rohrer, Paviour et al., 2010)). It remains undetermined if distinguishing among PPAOS, AOS+PAA, and PAA predicts differences in underlying neuropathology or disease course (Vandenberghe, 2016).

In 2011, the widely influential diagnostic consensus criteria for PPA and its primary variants (Gorno-Tempini et al., 2011) identified "effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)" as one of two core features of the nfPPA variant, the second being agrammatic language production. Although language difficulty was considered essential to a root diagnosis of PPA (i.e., prior to identification of any PPA variant), the document states that "grammar, *motor speech*, sound errors, and word finding pauses" are speech features of the "main *language* domains" (p. 1008). This allows a diagnosis of nfPPA to be made without evidence of aphasia but with evidence of AOS (i.e., PPAOS), as long as single-word comprehension and object knowledge are spared. This possibility was tacitly recognized in the paper itself which stated that "apraxia of speech, is often the most common disturbance, and can be the initial sign …" (p. 1009), and that "effortful speech and production errors can be the first symptoms of this variant, even before clear apraxia of speech or agrammatic errors occur" (p. 1010). This has been supported by several research groups that have reported the presence versus absence of AOS in studies of the nfPPA variant (Josephs et al., 2010; Josephs, Duffy et al., 2006; Amici et al., 2006, 2007; Croot et al., 2012; Gorno-Tempini et al., 2004; Ogar et al., 2007; Rogalski et al., 2011; Rohrer, Paviour et al., 2010; Wilson et al., 2010). A review of motor speech disorders associated with PPA found a median AOS prevalence of 78% across studies and concluded that the frequency and/or severity of AOS sometimes exceeds that of aphasia in nfPPA (Duffy et al., 2014). Nonetheless, definitional issues related to nfPPA means that PPAOS sometimes/often remains hidden within a PPA diagnosis (Duffy & Josephs, 2012).

The term primary progressive apraxia of speech (PPAOS), as defined in the next section, emerged in the last 15 years (Duffy, 2006; Duffy & McNeil, 2008) and now has been studied under that label in numerous investigations. Recognition of PPAOS in the last decade as a disorder that is clinically distinct from PPA, CBS, and PSP is reflected in recent overview papers of PPA that have recognized "pure progressive AOS" or "speech apraxia-only" as the most important subvariant of nfPPA, one in which there is no agrammatism or other features of aphasia (Marshall et al., 2018; Vandenberghe, 2016), that "motor speech deficits are almost universally the most salient feature in nfvPPA", and that "the cardinal clinical feature in nfvPPA is a motor speech impairment consistent with apraxia of speech …" (Tee & Gorno-Tempini, 2019, pp. 257–258).

Basic definitions

Current definitions of AOS generally acknowledge that it represents an impaired capacity to plan or program movements that result in phonetically and prosodically normal speech

(Duffy, 2020). Understanding PAOS and PPAOS does not require modification of the basic definitions but does require recognition of their etiology, clinical milieu and course. Thus, PAOS can be defined broadly as *AOS due to a neurodegenerative condition that can occur in isolation or with various combinations and degrees of aphasia, nonaphasic cognitive impairments, and sensorimotor deficits that do or do not meet criteria for a more specific neurodegenerative condition (e.g., CBS, PSP)*. PPAOS can be more narrowly defined as *AOS of insidious onset and gradual progression, in the absence of more than equivocal evidence of aphasia, nonaphasic cognitive impairments or sensorimotor deficits that meet criteria for another specific neurodegenerative disease or other explanatory condition at the time of diagnosis*. Dysarthria can be present but cannot be more severe than the AOS at presentation. There is no clear consensus about diagnostic labeling when different degrees of both AOS and aphasia are present, or when a patient with PPAOS eventually evolves to meet criteria for another neurodegenerative disease. If aphasia emerges in someone with PPAOS, or both disorders are initially present but the AOS predominates, the designation Dominant AOS (DAOS) has been used (Josephs et al., 2013); this seems justified by neuroimaging in which DAOS appears more like that associated with PPAOS than nfPPA (Josephs et al., 2013).

Diagnosis of PPAOS is not always easy and can range from confident, probable, or possible to recognition of a not-otherwise-specifiable neurological communication disorder, to a misdiagnosis of PPA, dysarthria, or psychogenic disturbance. Misdiagnoses can occur across the severity spectrum but are more common when speech difficulty is mild. Evaluation over time may be necessary before a confident diagnosis can be made.

Epidemiology and demographics

There have been no formal epidemiologic studies but PAOS prevalence has been estimated at about 4.4 per 100,000 if patients with PPAOS and PAOS with mild aphasia are included (Whitwell et al., 2015); the prevalence of PPAOS alone is probably closer to 2 per 100,000 (Botha & Utianski, 2020). About two-thirds of affected individuals note onset after age 65 but onset ranges from the third to ninth decades. Men and women are affected about equally. In PPAOS, non-right handedness may be somewhat more common than expected (Botha, Duffy et al., 2018).

There have been no clearly identified socioeconomic, educational, or environmental risk factors (Botha & Josephs, 2019). Although about 25% of patients with PPAOS and PAOS report a family history of neurodegenerative disease, only 5% have a history of multiple affected first-degree relatives. PPAOS was not found to be associated with an increased risk of an underlying causal genetic mutation (Botha & Josephs, 2019; Flanagan et al., 2015).

Clinical features

Speech characteristics

A prospective (Josephs et al., 2012) and retrospective study (Duffy, 2006), with non-overlapping patients, have described specific speech features associated with PPAOS and PAOS. Those most frequently noted in both studies (Table 1) are quite similar and largely consistent with the core features typically associated with nondegenerative AOS

Table 1. Primary speech characteristics associated with primary progressive apraxia of speech (PPAOS) and progressive apraxia of speech (PAOS); listed in order from most to least prevalent among patients.

PPAOS	PAOS
(Josephs et al., 2012, N = 12)*	(Duffy, 2006, N = 80)**
Slow rate	Slow rate
Lengthened intersegment durations	Distorted substitutions
Increased distortions and distorted substitutions with increased length or complexity	Syllable segmentation/excess & equal stress
Syllable segmentation within words > 1 syllable	Poorly sequenced SMRs
Sound distortions	Increased errors with increased utterance length
Syllable segmentation across words in phrases	Sound sequencing errors
Audible or visible articulatory groping	Articulatory groping/false starts
Lengthened vowel &/or consonant segments	Distorted additions
Distorted substitutions	Reduced words per breath group in spite of adequate maximum vowel duration
Deliberate, slowly sequenced, segmented, &/or distorted SMRs in comparison to AMRs	Effortful orofacial movements during speech
Increased distortions or distorted substitutions with increased rate	Inaccurate speech AMRs
Distorted sound additions	Sound prolongations
Sound/syllable repetitions	
Sound prolongations (beyond lengthened segments)	
Inaccurate place or manner of speech AMRs	
Reduced words per breath group relative to maximum vowel prolongation	

*The first five features were present in all patients.
**The first six features were present in 50–85% of patients. Eleven percent of patients in this cohort probably had PPAOS.

(e.g., McNeil et al., 2009). They do not require further discussion. However, both studies noted a feature in a minority of patients (e.g., 26% of patients summarized by (Duffy, 2006)) that has not been associated with stroke-induced AOS, namely a reduced number of words per breath group during connected speech in spite of a noticeably better maximum vowel duration; dysarthria is an unlikely explanation because it is not always present with this feature. Because the depth of inspiration correlates with phrase length in normal speakers, this has been interpreted as possibly reflecting a reduced number of syllables that can be programmed at a time.

Impact on communication

Utianski et al. (accepted for publication) recently addressed the impact of PPAOS and AOS +PAA on communication participation using the Communicative Participation Item Bank (CPIB) (Baylor et al., 2013) and ASHA's Functional Communication Measures (FCMs) (Mullen, 2004). The CPIB and FCM Motor Speech and Expressive Language measures correlated with each other and a motor speech severity rating, but not with other impairment-related measures of AOS or language. This suggests that impairment-focused measures do not fully capture the impact of the disorders on day-to-day communication. They and other similar measures thus deserve attention for their sensitivity to these effects at baseline, longitudinally, and in response to management.

Subtypes

Variations in speech patterns among patients with PAOS are not entirely explained by severity or the influence of dysarthria or aphasia (Duffy & Josephs, 2012). This raises the possibility of PAOS subtypes, a notion that has long been entertained for AOS regardless

of etiology. Assuming that speech programming involves several processes occurring within a network that can accomplish its goals in more than one way, it is reasonable to hypothesize that PAOS might begin with degeneration in different brain areas or pathways that contribute to different stages or aspects of the programming process, leading to different patterns of speech abnormality (Josephs et al., 2013).

In fact, evidence suggests the presence of two distinguishable PAOS subtypes (Josephs et al., 2013; R. Utianski, Duffy et al., 2018; Whitwell, Duffy et al., 2017; Whitwell, Weigand et al., 2017). Historically, initial suspicions about these subtypes were driven by encounters with patients without apparent dysarthria who had slow, segmented speech but few perceptible articulatory distortions, distorted substitutions, or articulatory groping, a very different pattern than that usually associated with stroke-induced AOS for which the diagnosis typically hinges on recognizing articulation disruptions. This led to the eventual data-supported subtypes based on the degree to which phonetic versus prosodic abnormalities dominates the speech pattern.

Nearly all patients with PAOS have both phonetic and prosodic abnormalities, so subtype distinctions are based on their relative *predominance*, not their presence versus absence. The Phonetic subtype is characterised by a predominance of articulatory distortions, distorted sound substitutions or additions, and articulatory groping and attempts at self-correction of phonetic level errors. The Prosodic subtype is characterised by a predominance of slow rate and segmentation (lengthened intersegment durations) between words or between syllables within multisyllabic words. In a third subtype, called Mixed, neither phonetic nor prosodic abnormalities predominate. Interjudge reliability for the perceptual classification of these subtypes has been demonstrated (Josephs et al., 2013; Utianski, Duffy et al., 2018, 2018) and case studies have illustrated them (Duffy et al., 2015; Utianski, Duffy et al., 2018); supplementary material video samples of the subtypes are provided in Josephs et al. (2013), Utianski et al. (2018), and Utianski et al. (2018).

Going beyond the gestalt impressions usually used to determine subtypes, the Apraxia of Speech Rating Scale (ASRS) (Josephs, Duffy et al., 2006; Strand et al., 2014), currently a 13-item perceptual rating scale of phonetic, prosodic, and other features of AOS, can formalize and quantify contrasts between phonetic and prosodic abnormalities; each item is rated on a 0–4 scale (0 = feature not present; 4 = feature nearly always evident and/or marked in severity). A study of 21 patients with PPAOS, 10 with the Phonetic subtype, and 11 with the Prosodic subtype found that subscores for Phonetic and Prosodic items on the ASRS were consistent with gestalt clinical designations of AOS subtype (Utianski, Duffy et al., 2018). In addition, at least some patients with the Phonetic subtype have a relatively high percentage of articulatory errors relative to the degree of their slow rate as measured acoustically, whereas patients with the Prosodic subtype have a comparatively low percentage of articulatory errors relative to the degree of their slow rate (see (Duffy et al., 2015) for contrasting case studies that used these metrics). This possibility requires further study.

The distribution of the subtypes by age and among patients with PPAOS versus PAOS, data on clinical progression, and neuroimaging findings provide converging evidence that supports subtype validity. Regarding age, PPAOS patients with the Prosodic subtype, in general, are older at onset (median age = 73) than those with the Phonetic subtype (median age = 57), which raises the possibility that subgroup differences at least partly reflect an interaction between pathophysiology and age-related vulnerability in different components of the motor speech planning/programming network (Utianski, Duffy et al., 2018).

Table 2. Disease duration at the time of initial evaluation and distribution of PAOS subtypes in PPAOS and AOS+PAA.

	PPAOS	AOS+PAA		
	(n = 42)	AOS+PAA – Total (n = 56)	AOS > aphasia (n = 35)	Aphasia > AOS (n = 21)
Disease duration (years, median)	3	3	4	2.5
Subtype				
Phonetic	29%	55%	43%	76%
Prosodic	57%%	14%	23%	0%
Mixed	14%	30%	34%	24%
Dysarthria present	30%	27%	40%	5%

Table 2 summarizes the distribution of the subtypes within our current research cohort of 42 patients with PPAOS and 56 patients with AOS+PAA (previously unpublished). They show that in PPAOS the Prosodic subtype predominates, nearly **double** the prevalence of the Phonetic subtype. In contrast, in AOS+PAA the Phonetic subtype predominates, with about 4 times the prevalence of the Prosodic subtype and more Mixed than Prosodic cases. These differences are amplified for AOS+PAA patients whose aphasia predominates over AOS; a large majority is classified as Phonetic. Differences are attenuated when AOS predominates over aphasia, although the Phonetic subtype still predominates. It does not appear that severity can explain these differences because there are no differences in clinical judgements of AOS severity between the PPAOS and aphasia-dominant AOS+PAA groups.

Overall, these subtype distributions suggest that the phonetic features of PAOS are more tightly aligned with aphasia (the language network) than its prosodic features; this is compatible with challenges associated with distinguishing phonetic errors of AOS from phonologic errors associated with aphasia. The corollary of this is that the prosodic abnormalities associated with PAOS are more easily separated from aphasia and perhaps more tightly aligned with the motor speech network, which may facilitate distinctions between AOS and phonological errors, at least at a global diagnostic level.

The canonical features of the Phonetic and Prosodic subtypes may be most obvious at mild-moderate levels of severity, although when AOS is very mild distinctions may not become evident until severity increases. The distinctions do seem to blur as AOS becomes severe (Utianski, Duffy et al., 2018). Relatedly, the subtypes also seem to differ in pattern of disease evolution. A longitudinal study found that the Phonetic subtype was associated with faster rates of decline in motor speech and aphasia, whereas the Prosodic subtype had poorer scores on the Unified Parkinson's Disease Rating Scale (Goetz et al., 2008), suggesting that it is associated with the eventual emergence of some form of parkinsonism (Whitwell et al. (2017). The data suggest that the different subtypes are markers for the eventual emergence of different clinical problems with different underlying pathologic correlates. If confirmed, early recognition of AOS subtype may have implications for prognosis, counseling, speech therapy, underlying pathology, and disease-specific medical treatments when they become available.

Imaging data also support the validity of subtype distinctions. Utianski et al. (2018) found that both subtypes shared involvement of frontal lobe premotor regions, particularly the supplementary motor area (SMA). Some differences were apparent, however, generally in the direction of more widespread abnormalities in the Phonetic subgroup

which suggests the possibility of increased risk for the emergence of **behavioural**, language, and cognitive changes.

Accompanying speech-language features

Deficits that are mild and sometimes accompany PPAOS at initial evaluation or that emerge over time often are motoric in nature. Other possible accompanying features reflect disruptions in cognitive-language functions.

Dysarthria

Dysarthria frequently develops in PPAOS, although it nearly always remains less severe than the AOS. Overall, it was present at initial assessment in 30% of PPAOS cases in our current research cohort. Although it occurs nearly as frequently in those with AOS+PAA, it is less often present when aphasia predominates (only 5%). Although dysarthria type can be difficult to establish because of overlap features with AOS, the most commonly described types are spastic, hypokinetic, or mixed spastic-hypokinetic (Duffy et al., 2014). Dysarthria prevalence and type are similar in patients with nfPPA, many of whom have AOS+PAA; a review of several studies across several research groups found a median dysarthria prevalence of 36% (Duffy et al., 2014).

Nonverbal oral apraxia

As in stroke-induced AOS, in which AOS frequently but not invariably co-occurs with nonverbal oral apraxia (NVOA), NVOA occurs frequently in PPAOS and AOS+PAA (Botha et al., 2014). Table 3 summarizes findings regarding NVOA in neurodegenerative speech-language disorders. Taken together, the data suggest it occurs frequently but not invariably in PPAOS and AOS+PAA, although their co-occurrence increases with disease progression. They support a conclusion that NVOA and PPAOS/AOS+PAA are separable deficits.

Table 3. Summary of studies of neurodegenerative nonverbal oral apraxia (NVOA).

Reference(s)	Key findings re NVOA
Botha et al. (2014)	• Present in 59% of 30 patients with PPAOS or AOS > aphasia • Present in 78% of 9 patients with nfPPA (with no or less prominent AOS) • Associated with bilateral atrophy of SMA and prefrontal cortex anterior to premotor area
(Josephs, Duffy, Strand, Machulda, Senjem, Gunter et al., 2014; Josephs et al., 2013; Josephs et al., 2012; Josephs, Petersen et al., 2006; Utianski, Duffy et al., 2018).	• Prevalence range from 33% to 62% in other studies of PPAOS by Mayo Clinic research group; patient numbers ranging from 7 to 21 • Prevalence does not seem to differ between PPAOS subtypes
Ogar et al. (2007)	• Present in 61% of 18 patients with nfPPA (all with AOS)
(Gallassi et al., 2011; Laganaro et al., 2012; Ricci et al., 2008)	• Frequent co-occurrence of PPAOS and NVOA in case studies
Duffy, Peach, Strand (2007)	• Present in 71% of 7 patients with ALS and AOS+PAA on initial examination; present in all 7 patients on subsequent examination
(Josephs, Duffy, Strand, Machulda, Senjem, Gunter et al., 2014; Santos-Santos et al., 2016; Utianski, Duffy et al., 2018)	• Prevalence of NVOA increases over time in PPAOS

Yes/no reversals

It is not uncommon for patients with PPAOS to complain of saying or shaking their head yes when meaning no, or vice versa, and to exhibit that behaviour during examination in the absence of other evidence of aphasia (Josephs, Duffy, Strand, Machulda, Senjem, Gunter et al., 2014; Duffy et al., 2017; Utianski, Duffy et al., 2018); these reversals have also been noted in patients with PAOS (Code et al., 2009; Warren et al., 2016). They, and sometimes other high frequency "binary reversals" (e.g., up/down) (Warren et al., 2016), can be among the initial speech-related complaints associated with PPAOS and AOS +PAA. They are also noted in patients who meet criteria for CBS and PSP but who also have AOS and/or aphasia, with confirmatory autopsy data in some cases (Josephs et al., 2005; Josephs, Duffy et al., 2006; Frattali et al., 2003), consistent with the known association of PPAOS with CBD and PSP. The underlying explanation for this curious phenomenon is uncertain but appears related to impaired mental flexibility and inhibitory control, both suggestive of fronto-subcortical circuitry dysfunction (Frattali et al., 2003).

Reduced word fluency

Patients with PPAOS frequently perform poorly on letter fluency and action fluency tasks (timed rapid retrieval of words beginning with specified letters or verbs representing things people can do) which, in the absence of aphasia, may reflect problems with executive control associated with frontal lobe dysfunction (Shao et al., 2014) and/or motoric slowing of speech. As a group they receive below-average letter fluency scores and half to two-thirds of PPAOS patients in some studies have abnormal letter or action fluency scores (Whitwell, Weigand et al., 2017).

Phonological errors

Determining whether sound level errors are phonetic versus phonologic is a persisting challenge for clinicians and researchers. This difficulty may be greatest when attempting to classify an individual sound level error as apraxic versus phonologic, or if one feels obligated to classify all sound level errors in a given patient as either apraxic or phonologic. The latter effort seems to discount the probability that at least some patients with PAOS (e.g., those with AOS+PAA) make both types of errors. In fact, several studies have concluded that nfPPA can be associated with both apraxic and phonological errors, likely reflecting co-occurrence of AOS and aphasia (Ash et al., 2010; Dalton et al., 2018; Wilson et al., 2010).

In recent years, clearer specification of the articulatory and prosodic features uniquely tied to AOS, and their distinction from features that overlap with aphasia and aphasic phonological errors (e.g., (McNeil et al., 2017, 2009)), has probably improved differential diagnosis. Confirmatory clues to the distinction derive from a cluster analysis that suggested that anomia and errors on sentence repetition attributable to reduced verbal short-term memory are more likely associated with phonological than AOS errors (Leyton et al., 2014). However, the issue remains evident in some studies at the level of criteria for error type identification, or nosologically. Thus, for example, some studies label sound level errors associated with nfPPA as phonological in spite of acknowledging that substitution, addition and deletion errors may be more consistent with a motor programming deficit (Dalton et al., 2018). In our experience, at least some AOS-related sound level errors

are evident in most patients with nfPPA, recognizing that both apraxic and phonological errors can co-occur in any given patient. Most important relative to the focus of this paper, no study in recent years has concluded that all sound level errors in nfPPA are phonological.

Acoustic correlates

Acoustic measures can quantify diagnostically relevant features of stroke-induced AOS (Duffy, 2020; McNeil et al., 2017) and there is now converging evidence that they can also aid the description and differential diagnosis of PAOS (Ballard et al., 2014; Brodtmann et al., 2016; Cordella et al., 2019; Duffy et al., 2017, 2015; Laganaro et al., 2012; Utianski, Duffy et al., 2018; R. Utianski et al., Under Review; Wilson et al., 2010). Table 4 summarizes the key findings of studies that have used temporal acoustic measures to characterise PAOS and its distinction from PPA variants without AOS.

As a group, the findings demonstrate that several relatively simple measures can distinguish speakers with PPAOS (with or without dysarthria) from neurologically normal speakers and individuals with PPA who do not have AOS by quantifying the perceptual features of increased utterance duration, slow syllable production rate, and equalized stress which are among core features of PPAOS and PAOS. They can also index changes in severity. Their validity is supported by their correlation with clinical judgements of AOS presence and severity, and with atrophy in brain areas important to motor speech planning/programming and production. It is reasonable to infer that they have potential as indices of stability or improvement in response to speech therapy or medical treatments, and possibly as predictors of an emerging need for augmentative or alternative communication (Ballard et al., 2014; Cordella et al., 2019; Poole et al., 2017; Utianski, Duffy et al., 2018).

Neuroimaging correlates

Imaging correlates of PPAOS have been examined through a number of modalities and techniques that can detect abnormalities indicative of degeneration. Table 5 summarizes relevant neuroimaging studies, with references. The key findings are as follows:

- Studies consistently point to grey and white matter involvement in cortical and subcortical regions that are linked to speech planning/programming, production, and monitoring. The brunt of cortical abnormalities are usually in the superior lateral premotor area and SMA of the left or left greater than right hemisphere, with white matter loss extending to the inferior premotor cortex and body of the corpus callosum. Longitudinal imaging demonstrates increased atrophy and hypometabolism in the same regions, with spread into the left inferior frontal lobe, basal ganglia, and thalamus in those who develop aphasia over time.
- A single functional imaging study of patients with PPAOS revealed reduced connectivity between the right SMA and the rest of the speech-language network, and abnormalities in the speech-language, face sensorimotor, and left working memory and salience networks. The suggestion of SMA disconnection from other speech-language regions supports the importance of the SMA in the pathophysiology of PPAOS.

Table 4. Summary of acoustic indices of PAOS.

Reference	Acoustic measure	Key findings
Description and differential diagnosis		
Ackermann et al. (1997)	• Long versus short vowel duration	• Impaired durational contrast in one patient with AOS+PAA, relative to controls and patients with spastic dysarthria
Wilson et al. (2010)	• Maximum speech rate (i.e., rate of three most rapid sequences of 10 or more words)	• Speech rate reduced in nfPPA • Speech rate associated with left inferior frontal gyrus, ventral precentral gyrus, and SMA atrophy
Ballard et al. (2014)	• Periods of silence during reading • Pairwise variability index (PVI; i.e., comparison of the duration of the unstressed and stressed vowels in the first two syllables of "catastrophe")	• Median silence duration elevated in nfPPA relative to logopenic PPA and control speakers • PVI differentiated nfPPA from control and logopenic PPA speakers • PVI associated with imaging findings in precentral gyrus, SMA, and inferior frontal gyrus bilaterally in nfPPA. • Acoustic measures correlated with judgements of AOS presence and severity
Duffy et al. (2017)	• Word duration and syllable rate during imitative speech (words and sentences) • PVI	• Reduced articulation rate in PPAOS compared to PPA and control speakers • PVI demonstrated equalization of stressed and unstressed syllables in PPAOS relative to controls and patients with PPA without AOS • Acoustic measures correlated with judgements of AOS presence and severity
Cordella et al. (2019)	• Articulation rate during spontaneous speech	• Reduced articulation rate in nfPPA, relative to PPA and control speakers • Articulation rate correlated with atrophy in left-hemisphere premotor and supplementary motor regions
Disease progression		
Laganaro et al. (2012)	• Articulation rate during spontaneous speech, imitative speech (words and sentences), and reading	• At baseline, slower than expected articulation rate in PPAOS • Progressive decline in articulation rate.
Duffy et al. (2015)	• Word duration and syllable rate during imitative speech and speech-like tasks • PVI	• At baseline, slower than expected articulation rate in PPAOS • Progressive increase in syllable duration and associated decline in overall syllable rate; corresponded to increased AOS severity • PVI showed equalization of stressed and unstressed syllables, attributable to increased stress on unstressed syllables
Utianski et al. (2018)	• Word duration and syllable rate during imitative speech (words)	• At baseline, slower than normal articulation rate in PPAOS • Progressive increase in syllable duration and associated decline in overall syllable rate; patients eventually unable to complete task
Cordella et al. (2019)	• Articulation rate during spontaneous speech	• Progressive decline in articulation rate in nfPPA • Greater rate of decline in nfPPA compared to patients with PPA

(*Continued*)

Table 4. (Continued).

Reference	Acoustic measure	Key findings
Utianski et al. (Under Review)	• Word duration and syllable rate during imitative speech (words)	• Cross-sectionally, patients with prosodic-predominant PPAOS produced words more slowly than those with phonetic-predominant PPAOS. • Patients with either aphasia or dysarthria produced words more slowly than those without. • Speech rate of patients with phonetic-predominant PPAOS reduced by 0.5 syllables/second per year. • Patients with prosodic-predominant AOS changed less quickly than patients with phonetic-predominant AOS.

- The Phonetic and Prosodic subtypes of PPAOS are both associated with premotor abnormalities, particularly in the SMA. Bilateral involvement of the SMA, precentral gyrus, and cerebellar crus, and hypometabolism in the insula is evident in the Phonetic subtype. The Prosodic subtype has more focal SMA and right superior cerebellar peduncle involvement.
- Volume loss and hypometabolism in PPAOS are more focal than in AOS+PAA in which abnormalities include the SMA, posterior inferior, middle and superior frontal gyri, precentral cortex, and parietal lobes. Midbrain atrophy is not evident in PAA but is present in PPAOS and AOS+PAA, particularly in those who develop parkinsonism.
- In vivo studies of the distribution of tau using [^{18} F]flortaucipir PET scanning demonstrate abnormalities in anatomically relevant areas in PPAOS and AOS+PAA. Longitudinal changes in tau uptake are detectable in PPAOS in a pattern similar to that seen in PSP.

Clinical course

PPAOS

Although PPAOS can remain the only or predominant deficit for a long time (i.e., 5 years or longer), it inevitably worsens and other neurologic problems emerge. However, AOS usually remains the most severe clinical deficit (Josephs et al., 2013; Duffy et al., 2015; Utianski et al., 2020). The rate of AOS progression and the time to emergence of additional deficits vary considerably among individuals.

The time frame for the clinical course may best be appreciated in the context of group-level survival data. Whitwell et al. (in press) recently summarized findings for 109 patients with PPAOS, AOS+PAA, or PAA at initial assessment, among whom 57 have died (42 with PPAOS, with 20 deaths; 56 with AOS+PAA, with 33 deaths; 11 with PAA, with 4 deaths). Median time post symptom onset to initial assessment was two to 3 years; initial AOS severity for the PPAOS and AOS+PAA groups was similar and rated as mild or moderate. Median survival time from the first visit was 5.9 years for PPAOS, 4.3 years for AOS+PAA, and 5.3 years for PAA, which translates to about 9 year survival for PPAOS, and 7–8 year survival for AOS+PAA and PAA. Among those with PPAOS, increasing AOS severity was

Table 5. Summary of neuroimaging correlates of progressive AOS. Note: The referenced techniques include: magnetic resonance imaging (MRI, to identify atrophy); diffusion tensor imaging (DTI, to estimate MRI-imaged white matter connectivity patterns); functional magnetic resonance imaging (fMRI, to measure brain activity through changes in blood flow); [^{18} F]fluorodeoxyglucose positron emission tomography (FDG-PET, an index of metabolic brain activity); molecular PET imaging using ligands such as C11-Pittsburgh Compound B (PiB) to detect abnormal accumulations of beta-amyloid (Aβ, related to Alzheimer's disease) or flortaucipir ([^{18} F]AV-1451; related to tau pathology); electroencephalography (EEG; related to overall brain health); and dopamine transporter scans (DaT; related to parkinsonism).

Reference	Imaging modality	Key findings
Description and differential diagnosis		
(Botha et al., 2015; Botha, Utianski et al., 2018; Josephs et al., 2010; Josephs et al., 2013; Josephs et al., 2012; Josephs, Petersen et al., 2006; Laganaro et al., 2012)	• MRI • DTI • PiB-PET • FDG-PET	• In PPAOS, grey and white matter involvement in cortical and subcortical regions linked to speech planning/programming, production, and monitoring • Structural and metabolic measures suggest superior lateral premotor area and left SMA are primary areas of involvement • White matter loss in inferior premotor cortex and body of corpus callosum • Basal ganglia sometimes affected
Botha, Utianski, et al. (2018)	• Task-free MRI	• In PPAOS, reduced connectivity between right SMA and rest of speech-language network; correlated with AOS articulatory severity • Abnormalities in speech-language, face sensorimotor, and left working memory and salience networks
Utianski et al. (2018)	• MRI • FDG-PET • DTI	• Both Prosodic and Phonetic PPAOS subtypes had abnormalities in premotor regions, particularly in SMA • Phonetic subtype showed bilateral involvement of SMA, precentral gyrus, and cerebellar crus, and hypometabolism in insula • Prosodic subtype had more focal involvement of SMA and right superior cerebellar peduncle
(Josephs et al., 2010; Josephs et al., 2013; Josephs, Petersen et al., 2006; Ogar et al., 2007; Santos-Santos et al., 2016; Tetzloff, Duffy, Clark et al., 2018)	• MRI • DTI • FDG-PET	• Areas of involvement in PPAOS typically more focal than in AOS+PAA • In AOS+PAA, abnormalities involve SMA, posterior inferior, middle and superior frontal gyrus, temporal precentral cortex sand parietal lobes • In PAA, abnormalities observed in prefrontal and anterior temporal lobes, particularly on left
(Josephs et al., 2013; Josephs et al., 2012; Tetzloff, Duffy, Clark et al., 2018; Whitwell et al., 2013)	• MRI	• Midbrain atrophy can be evident in PPAOS and AOS+PAA, in contrast to PAA
(Botha & Josephs, 2019; Josephs et al., 2010; Josephs, Duffy, Strand, Machulda, Senjem, Gunter et al., 2014; Josephs et al., 2012)	• MRI • FDG-PET	• Structural imaging evidence revealing localization pattern of PPAOS and AOS+PAA derives from group analyses that are not necessarily readily apparent at individual level • FDG-PET may be more sensitive to localization and disease progression on individual patient basis than MRI, but can still be quite heterogeneous across individual patients
(Josephs et al., 2010; Josephs, Duffy, Strand, Machulda, Senjem, Lowe et al., 2014; Leyton et al., 2014; Whitwell et al., 2016)	• PiB-PET	• PiB-PET abnormal in 12–20% of PPAOS and AOS+PAA patients

(*Continued*)

Table 5. (Continued).

Reference	Imaging modality	Key findings
Josephs et al. (2016)	• *In vivo* tau (flortaucipir-PET) • *Ex vivo* tau at autopsy	• Abnormal tau uptake correlated with quantitatively measured 4 R-tau at autopsy in one patient presenting with PPAOS
Utianski et al. (2018)	• *In vivo* tau (flortaucipir-PET)	• Abnormal tau uptake noted in precentral gyrus, pallidum, and mid and superior frontal gyri in patients with PPAOS
Utianski et al. (2018)	• *In vivo* tau (flortaucipir-PET)	• Patients with AOS+PAA had abnormal tau uptake in anatomically relevant areas (SMA bilaterally, frontal lobes, precuneus, and precentral gyrus) • Patients with PAA had abnormal tau uptake in left frontal and temporal lobes and relatively less abnormal uptake in left precentral gyrus
Utianski et al. (2019)	• EEG	• Patients with PPAOS had normal EEGs • Theta slowing evident in most patients with AOS+PAA
Seckin et al. (2020)	• DaT	• Abnormal DaTscan observed early in disease course in about 30% of patients with AOS +PAA; abnormalities observed in the putamen
Disease progression		
Josephs et al. (2014)	• MRI • FDG-PET • DTI	• Increased rates of brain atrophy and hypometabolism in PPAOS compared to age-matched controls over average of 2.4 years • Areas of change include prefrontal, premotor, and motor cortex, and basal ganglia and midbrain, with spread into white matter tracts in splenium of corpus callosum and motor cortex
Santos-Santos et al. (2016)	• MRI	• Significant longitudinal progression of atrophy in patients with AOS+PAA
Whitwell et al. (2019)	• MRI	• Rates of midbrain atrophy greater in patients who develop parkinsonism and PSP features compared to those who do not
Whitwell et al. (2017)	• MRI	• Deterioration in Broca area, thalamus, and basal ganglia (putamen) associated with development of agrammatic aphasia over a two-year period in patients initially presenting with PPAOS
Utianski et al. (2020)	• *In vivo* tau (flortaucipir-PET)	• Longitudinal changes in tau uptake in PPAOS after average of one year • Patterns of change similar to those seen in PSP

associated with a greater risk of death, with a hazard ratio of 1.35 (a 35% increase in death risk) for a 1-point increase in severity on a 0–4 AOS severity scale. PPAOS survival and risk for death were, statistically, significantly better than for AOS+PAA; PAA survival did not differ statistically from PPAOS or AOS+PAA, perhaps due to small sample size.

The progression of PPAOS, independent of emergence of additional deficits, has been documented in several ways. The most commonly used measures for which longitudinal data are available for more than a single case include a simple rating of AOS severity on a 0–4 scale (0 = normal; 4 = severe); a 10-point Motor Speech Disorders rating (MSD rating;

see (Duffy, 2020), as modified from (Hillel et al., 1989)) which primarily judges intelligibility (1 = nonvocal; 10 = normal speech); the ASRS which quantifies the presence, frequency, and prominence of specific AOS features; an Articulatory Error Score (AES) based on the percentage of words in which articulatory errors occur on a word and sentence repetition task (see (Duffy et al., 2015) for stimuli and scoring criteria); several simple temporal acoustic measures (already discussed). Group and case level data convey the collective theme and range of changes that occur on these measures. Because a limited number of patients have been followed during their full disease course, the data should be interpreted cautiously. Table 6 summarizes clinical changes in AOS reported in longitudinal studies of PAOS. Table 7 summarizes information about additional deficits that often emerge over time.

(Insert Tables 6 and 7 about here)

It is clear that a number of the measures can document the progression of PPAOS. Each has advantages and disadvantages and, in general, they may be most useful when two or more of them are combined. They differ to varying degrees in what they index, their sensitivity to change, their challenges to establishing reliability, and time demands for scoring. The 0–4 AOS severity rating, while useful as an impressionistic index of global severity, likely does not capture subtle changes that may occur over a 1-year period. The 0–10 MSD scale is probably more sensitive to change and it more explicitly describes intelligibility and overall speech disability. The ASRS, which requires more challenging, fine-grained perceptual ratings, documents changes in specific features of AOS and, given its broad range of possible scores, may capture changes that occur over relatively short intervals during the disease course. The AES appears sensitive to changes in articulatory accuracy. Several easily measured, relatively objective acoustic measures quantify the equalization of syllable durations and the slowing of speech rate that seems to universally occur in the disorder. While the 0–4 AOS severity rating and the 1–10 MSD scale can be used throughout the disease course, the ASRS, AES, and acoustic measures may cease to be valid or cannot be administered or scored in later stages as speech becomes limited. As a group, at least at yearly or somewhat longer intervals these measures are sensitive to the obvious clinical progression that occurs. It remains to be seen if one or more of them will prove useful in documenting improvement or slowing of progression in response to therapeutic interventions.

Regarding the evolution of PPAOS subtypes, patients with the Phonetic or Prosodic subtype tend to evolve to a Mixed subtype as severity increases, dysarthria emerges, speech becomes limited, and distinctions between phonetic versus prosodic characteristics become blurred. Thus, for example, among the four cases detailed by Utianski et al. (2018), two were initially classified as Phonetic, one as Prosodic, and one as Mixed, but all were classified as Mixed by the time of their fourth or later visit. As already noted, those with the Phonetic subtype tend to have faster rates of decline than those characterised as Prosodic (Whitwell, Weigand et al., 2017).

While imperfect, these data can be very useful during the early-mid stage of PPAOS when counseling patients and their significant others about the degree to which the disorder can be expected to change over time.

Table 6. Summary of clinical changes in longitudinal studies of patients presenting with PPAOS.

Reference	Sample size and clinical measures	Key findings
Group-level changes		
Josephs et al. (2014)	• 13 patients with PPAOS • Median of 4.5 years post symptom onset at visit 1 • 2–3 year follow-up • ASRS	• ASRS = 16 at baseline (scores above about 8–9 considered consistent with AOS) and 26.5 at follow-up • Annualized change: 2.5 points (practical meaning difficult to interpret)
Whitwell, Weigand et al. (2017)	• 20 patients with PPAOS • Median of 3.5 years post symptom onset at visit 1 • 2-year follow-up • AOS severity rating and MSD rating	• 8 patients developed aphasia at follow-up; 60% of patients still without aphasia at about 5 to 6 years post symptom onset • Median AOS severity rating = 1 (mild) to 1.5 (mild-moderate) at initial visit, regardless of aphasia; annualized rate of change = 0.5 points for entire group • Median MSD rating at initial assessment = 7; annualized rate of change = 0.7 points and 0.8 points, regardless of aphasia
Utianski et al. (2020)	• 13 patients with PPAOS • Median of 4 years post symptom onset at visit 1 • 1-year follow-up • ASRS and AOS severity rating	• 8/13 patients (62%) declined on both measures
Individual-level changes		
Duffy et al. (2015)	• 2 patients with PPAOS Case 1: seen at 5 and 7.5 years post-onset • Case 2: seen at 2 and 4 years post onset • AOS severity rating, MSD severity rating, ASRS, AES, and temporal acoustics	• Case 1: AOS severity changed from moderate (2) to severe (4); MSD severity from 6 to 3; ASRS from 21 to 35, and AES from 52% to 63% • Case 2: AOS severity changed from mild (1) to moderate (2), MSD severity from 7 to 6; ASRS from 18 to 21; AES from 7% to 13% • Syllables per second for three multisyllabic words, a sentence, and speech AMRs and SMRs was abnormal at first testing for both cases and further reduced at second visit for both patients
Utianski et al. (2018)	• 4 patients with PPAOS • 1.5, 2, 4, and 10 years post symptom onset at visit 1 • Followed yearly for 5–6 years • AOS severity rating, MSD severity rating, ASRS, AES, and temporal acoustics	• AOS severity worsened from mild to marked or severe in all patients • MSD severity dropped from 6, 7, or 8 to 1 or 2 over time • ASRS scores increased from 33 to 48, 15 to 30, 11 to 34, and 1 to 29 between first and last measurable assessment • AES changed from 68% to 86%, 13% to 41%, 5% to 47%, and 11% to 78% between first and last measurable assessment • Acoustically measured syllable per second rate for the word "catastrophe" abnormally slow for all patients at initial assessment and became slower over time until they were no longer able to produce four syllable word • All patients using AAC (writing tablet, iPad with speaking app) by 7 to 10 years post symptom onset
Tetzloff, Duffy et al. (2018)	• 1 patient with PPAOS • Followed 5, 8, 9, and 10 years post symptom onset • MSD severity rating, ASRS	• MSD rating scale scores of 6, 3, 3, and 1 across visits • ASRS scores of 20, 38, 39, and untestable at last visit • Dysarthria, aphasia, and parkinsonism emerged by 8 years post onset • Diagnostic criteria for CBS met by 9 years • CBD pathology at autopsy

Table 7. Problems that may emerge during disease course of patients initially presenting with PPAOS, with survival estimates.

Dysarthria
• Evident in minority (<30%) of patients at 2–4 years post symptom onset
• May not be evident in majority of patients until 5–6 years post symptom onset
• Dysarthria type most often spastic, hypokinetic, or mixed spastic-hypokinetic
Aphasia
• Emerges in 40–50% of patients by about 5 years post symptom onset
• Prevalence increases after 5 years but onset can be delayed until 10+ years
• Onset may be later in disease course in those with Prosodic subtype of AOS
Dysphagia
• Typically does not develop until after dysarthria has emerged
Emerging broader neurodegenerative syndrome
• Commonly evolves to PSP and/or CBS after 5+ years disease duration but may meet criteria before 5 years in substantial minority
• Uncommonly evolves to ALS
Survival
• Estimated survival ~9 years post-symptom onset for PPAOS
• Estimated survival ~7–8 years post-symptom onset for AOS+PAA and PAA

Emergence of dysarthria

As noted, dysarthria is evident in less than 30% of patients early in the course of PPAOS and AOS+PAA, but its prevalence increases over time; dysphagia may become evident after dysarthria emerges. To illustrate, in a longitudinal study of 13 patients with PPAOS, dysarthria was evident in 15% of the patients at initial evaluation conducted at a median of 4 years post onset, but it was evident or equivocally evident in 62% at follow-up 1.5 to 3 years later (Josephs, Duffy, Strand, Machulda, Senjem, Gunter et al., 2014). In four patients with PPAOS who were followed for 5–6 years, beginning at 1.5 to 10 years post onset, none had dysarthria initially but all developed it by 2–4 years later; AOS was more severe than dysarthria in each case (Utianski, Duffy et al., 2018). Dysarthria can confound or complicate judgements or interpretation of several measures discussed above for documenting the severity and course of the AOS but such measures would remain valid for documenting the collective severity and course of the motor speech disorder. When intelligibility becomes severely compromised the distinguishing features of AOS may be difficult to discern.

Emergence of aphasia

By definition, aphasia is not present in people with PPAOS at the time of initial diagnosis. It may not emerge for several years, may remain mild once it does, and with progression, the AOS usually remains predominant. To illustrate, in their study of 13 patients with PPAOS, seen initially at a median of 4 years post onset, and then again 1.5 to 3 years later, Josephs, Duffy et al. (2014) found unequivocal evidence of agrammatic aphasia at follow-up in 5 patients (38%); AOS remained the dominant communication deficit. Whitwell, Duffy et al. (2017), in their study of 20 patients with PPAOS, initially seen at a median of 3–4 years post onset, found that half had developed aphasia at follow-up two years later. Patients with the Phonetic subtype developed more severe aphasia at faster rates than those with the Prosodic subtype; in general, patients with the Prosodic subtype seem less likely to develop aphasia (Josephs, Duffy, Strand, Machulda, Senjem, Gunter et al., 2014).

At the individual case level within our research cohort, we have seen patients in whom aphasia did not become evident until 9 or 12 years post symptom onset (Utianski et al. (2018)). Once aphasia emerges, it seems appropriate to convert the diagnosis to AOS +PAA, assuming the aphasia is consistent with the agrammatic designation (if not, the appropriate diagnosis would be AOS+aphasia) and that criteria for a more specific neurologic diagnosis are not met at the time (e.g., PSP, CBS).

Emergence of broader neurodegenerative syndromes

There is now considerable evidence that PPAOS or AOS+PAA may be markers for the eventual emergence of clinical manifestations of PSP and CBS (Josephs et al., 2005; Burrell et al., 2018; Josephs & Duffy, 2008; Roh et al., 2010; Rohrer, Rossor et al., 2010; Santos-Santos et al., 2016; Whitwell et al., 2013, 2019). About 40% of patients with PPAOS will develop some signs of one or both of those syndromes by about 5 years after symptom onset (Botha & Josephs, 2019), with 100% developing features among eight PPAOS patients followed beyond 9 years from onset (Seckin et al., Under Review). Common manifestations of typical PSP include vertical gaze paralysis, early falls due to postural instability, and parkinsonism. Common manifestations of typical CBS include asymmetric limb rigidity and apraxia, and parkinsonism.

That PPAOS can be the first sign of PSP was once surprising because AOS (and aphasia) were considered very unusual at any time in "typical" PSP (Duffy et al., 2014; Litvan et al., 1996). The most recent diagnostic criteria for PSP, however, now include a "Speech and Language" variant to acknowledge this relationship (Hoglinger et al., 2017). Pre-dating that, a study that examined PPAOS progression in 13 patients showed that all eventually developed extrapyramidal (parkinsonian) signs, with five of them evolving to a PSP-like syndrome within about 5 years (Josephs, Duffy, Strand, Machulda, Senjem, Gunter et al., 2014). Studies of patients with AOS+PAA have documented similar and sometimes early emergence of features associated with PSP or extrapyramidal motor signs (e.g., Caso et al., 2014; Rohrer, Paviour et al., 2010; Santos-Santos et al., 2016), and DAT scan imaging (which measures presynaptic dopamine transporter function) found striatal abnormalities similar to those associated with PSP and CBS in 29% of 17 patients with PAOS (Seckin et al., 2020). In addition, although there are neuroimaging differences in the relative distribution of cortical versus midbrain involvement between PPAOS/AOS+PAA and PSP, they share involvement of brain areas to a degree that suggests a common underlying pathophysiology (Josephs et al., 2005; Josephs, Duffy, Strand, Machulda, Senjem, Gunter et al., 2014; Rohrer, Paviour et al., 2010; Whitwell et al., 2013). Patients with PPAOS who do develop PSP have smaller midbrain volume compared to those who do not (Whitwell et al., 2019).

Unlike in PSP, AOS and aphasia are common and sometimes among early signs of "typical" CBS (Blake et al., 2003; Gorno-Tempini et al., 2004). Similar to PSP, PPAOS can progress to a syndrome that meets criteria for a CBS diagnosis, and pathology consistent with CBD (Josephs, Petersen et al., 2006; Amici et al., 2006; Blake et al., 2003; Josephs & Duffy, 2008; Kertesz et al., 2000; Gorno-Tempini et al., 2006; Tetzloff, Duffy, Strand et al., 2018).

Finally, although probably very uncommon, AOS can occur in amyotrophic lateral sclerosis (ALS), sometimes as the predominant motor speech disorder (Duffy et al.

(2007)). It is uncertain if PPAOS can be the first sign of ALS or if AOS can occur prior to dysarthria in ALS.

Pathology

Most published autopsied cases with an initial PPAOS diagnosis have had a 4-repeat (4R) tauopathy (a subcategory of proteinopathies), with CBD and PSP being the most common PPAOS-associated disease subtypes (e.g., Josephs et al., 2005, 2016; Boeve et al., 2003; Josephs & Duffy, 2008; Gorno-Tempini et al., 2011; Tetzloff, Duffy, Strand et al., 2018).[1] A few cases have had Pick disease pathology (a 3R tauopathy), or even non-tau pathology, but it is uncertain if the AOS was the only speech, language, or nonaphasic-cognitive disorder at onset in those cases (Botha & Josephs, 2019).

Pathology in nfPPA (with or without AOS) is less predictable than for PPAOS, although when AOS is present it also is most likely a 4R tauopathy, perhaps especially when AOS predominates over any aphasia (Josephs et al., 2005; Josephs, Petersen et al., 2006; Deramecourt et al., 2010; Gorno-Tempini et al., 2006; Santos-Santos et al., 2016; Vandenberghe, 2016). However, nfPPA can also be associated with Pick disease, transactive response DNA-binding protein 43 (TDP-43), or Alzheimer disease (AD) (Botha & Josephs, 2019; Caso et al., 2014; Deramecourt et al., 2010; Mesulam et al., 2014). When associated with AD pathology, the aphasia seems to predominate over any AOS that may be present (Rogalski et al., 2016). Taken together, findings suggest that the presence of AOS is the most reliable clinical predictor of 4R tau in the so-called agrammatic/nonfluent variant of PPA.

PPAOS and stroke-induced AOS

Because stroke is the most common cause of acquired AOS in most clinical settings and most studies of the disorder (Ballard et al., 2015; J. Duffy, 2020), it has had a substantial influence on the characterization and understanding of the disorder and its treatment. From a "root etiology" perspective, stroke-induced AOS and PPAOS differ in several ways. In stroke, onset is sudden; the damaged brain area is in a vascular distribution; impairment is worst at onset; some recovery usually occurs and any remaining impairment tends to be relatively stable; and there is evidence that impairment-focused speech therapy can be effective. In PPAOS, onset is gradual; impairment is mildest at onset; affected brain areas may lie within a functional network that is not tied to a vascular territory; severity increases over time with frequent emergence of deficits not present at onset; and the effect of impairment-focused speech therapy is largely unknown. Even when localization is similar, some evidence suggests that stroke may lead to different connectivity disturbances than neurodegenerative disease (García-Cordero et al., 2015). In addition, the influence of neural plasticity is likely considerably different for the two etiologies, as are biopsychosocial influences on associated disability and handicap.

These differences suggest that careful study of PPAOS can contribute to the understanding of AOS through the identification of commonalities and differences in clinical features and neurologic underpinnings between the two etiologies. Results could modify clinical diagnostic criteria for AOS; contribute to determining if there are AOS subtypes tied to, or independent of, etiology; contribute to the understanding of the anatomy of the speech programming network and the levels of breakdown in planning

or programming that may occur; and refine therapy approaches (Duffy et al., 2015; McNeil et al., 2017). PPAOS also can increase substantially the number of cases with relatively isolated AOS that can be studied, adding power to the generalizability of findings.

Unfortunately, only one study has compared PPAOS to stroke-induced AOS without aphasia. Takakura et al. (2019) compared three patients with PPAOS to eight patients with stroke-induced "pure" AOS. The groups shared features but three attributes noted in the PPAOS patients were not present in those with stroke: prominent lengthened syllables; reduced ability to produce multisyllabic words in a single breath, and abnormalities in the SMA bilaterally. The results were interpreted as support for the validity of PAOS subtypes for both stroke-induced and degenerative AOS. This clearly warrants further study with a larger cohort of patients.

McNeil et al. (2017) emphasized similarities across etiologies, noting that PPAOS "not only provides converging evidence for the kernel signs composing the perceptually identifiable AOS cluster but also suggests that AOS may manifest with the same set of behaviours regardless of underlying etiology" (p. 8). Utianski et al. (2018) suggested that stroke-induced AOS might most often have a relatively equal mix of phonetic and prosodic abnormalities, or be predominated by phonetic features. Formal comparison along these lines seems warranted.

Until the similarities and differences between PAOS and stroke-induced AOS are more completely understood, it has been recommended that they be explicitly separated in both group and case series studies that include both etiologies, and that results be compared as a function of etiology (Duffy & Josephs, 2012).

Management

Data regarding care for people with PPAOS are very limited but the larger evidence base for stroke-induced AOS, PPA, and other degenerative motor speech disorders provide useful guidelines. In the discussion that follows we will also address aspects of management that we consider important based on clinical experience.

In general, appropriate care begins with diagnosis and then includes the not-necessarily-sequential staging of counseling and support; the possibility of impairment-focused speech therapy; development of compensatory (including augmentative and alternative) strategies to maximize communication; and anticipating and addressing the emergence of additional problems that can affect communication.

See Botha and Utianski (2020) and Duffy et al. (2014) for overviews of principles, strategies, and resources specific to treatment and management of PPAOS and the other neurological deficits that tend to emerge during its course.

Diagnosis as management

Many patients and their families have been on a long diagnostic journey before the diagnosis of PPAOS is made, at least partly because of inexperience with it in the health-care community. Unlike in stroke and other conditions in which the cause is already known, it is the diagnosis of PPAOS that, by definition, carries information about cause and prognosis (i.e., a neurodegenerative condition, likely a tauopathy). Optimally,

diagnosis reflects a collaborative effort, with the clinical syndrome identified or confirmed by a speech-language pathologist, and other possible causal explanations ruled out by a neurologist through a thorough history, clinical examination, and appropriate laboratory tests and neuroimaging.

Initial patient responses to the diagnosis may include but not be limited to surprise, devastation, disagreement, limited initial understanding, relief that the problem is not imminently life threatening, or stoic acceptance with or without a desire to "fight" the condition or adapt to it. Because more than a few patients have received a prior diagnosis of PPA, explaining the difference between the two disorders may be important for both their social and working lives. Many are relieved when told that the condition very unlikely reflects Alzheimer's disease. Many want information about the short- and long-term prognosis, if and when they might "lose" their speech, and whether, when and what other problems may emerge and how they might be managed. There is considerable variability among patients' desire for immediate versus more gradual acquisition of this information and counseling. There can be little doubt that the manner and time devoted to addressing these issues early on are a crucial aspect of care, one which establishes an alliance for ongoing management efforts. The importance of staged counseling and support also cannot be overemphasized and are felt to be invaluable (Rabinovici & Miller, 2010). For some patients and their families, this diagnostic and supportive care may be the most crucial care ingredient, including throughout the disease course.

Medical and adjunctive treatments

There are currently no disease-modifying pharmacologic agents for PPAOS (or PPA), but clinical trials targeting the presumed underlying proteinopathy are underway (Botha & Josephs, 2019; Botha & Utianski, 2020). When they become available they will quite possibly be used in conjunction with speech therapy, as has been suggested for PPA (Marshall et al., 2018). Even if pharmacologic treatments are not combined with speech therapy, the continued development of reliable and sensitive measures of AOS severity will be important as outcome measures in any treatment study regardless of treatment modality.

Repetitive transmagnetic stimulation and transcranial direct current stimulation have been applied in a number of studies of PPA (including nfPPA, sometimes with AOS), and a single study of PPAOS (Shpiner et al., 2019), but current evidence is insufficient to support meaningful treatment effects for PAOS beyond those achieved by behavioural treatment alone (Rising & Beeson, 2020). Both interventions will likely continue to receive attention as possible adjunctive treatments for PPAOS and PPA with or without AOS.

Speech therapy (impairment based and compensatory)

Although it is generally felt that speech therapy, if undertaken, should focus on maximizing communication rather than restoration of function, at this time whether or not impairment-directed speech therapy for PAOS can slow progression or improve speech in the short term should be considered an open question (Duffy, 2020). Articulatory-

kinematic and rate/rhythm approaches for which there is evidence of strong treatment effects for nondegenerative causes (Ballard et al., 2015) deserve attention in this regard. They may be most appropriate for highly motivated individuals with relatively mild PPAOS that does not appear to be progressing rapidly, and who accept the probable necessity for ongoing practice to maintain improvement or stability, and the near certainty of eventual progression. A few studies seem to justify such attention; these and other observations and resources to aid care are summarized in Table 8.

Beyond efforts to maintain or improve speech, staging of management to develop effective speaker and listener compensatory strategies, with early and ongoing involvement of partners, preferably in advance of reduced intelligibility, are essential and achievable in many cases. Techniques frequently used to maintain or improve articulation, rate, and prosody in people with motor speech disorders, in general, may be

Table 8. Summary of treatment studies and related information resources.

Treatment studies		
Reference	Approach	Key Findings
Henry et al. (2018)	Repeated rehearsal of scripts with clinician plus intensive home practice with audiovisual model (script training, guided by Youmans et al. (2011))	• Improved production of scripted words for trained topics and improved intelligibility for trained and untrained topics in 10 individuals with mild-moderate nfPPA, all who had AOS • Gains for trained scripts maintained for up to 1 year • Untrained scripts and standardized test scores remained relatively stable during follow-up period
Henry et al. (2013)	Oral reading	• Decreased speech errors in untrained text and improved self-correction of errors in single participant with mild AOS+PAA • Connected speech remained stable up to 1 year post-treatment
Authors' clinical practice (anecdotal)	Oral reading	• Anecdotal patient reports of benefit or maintenance of speech when adhering to home program of oral reading (e.g., 3–5 minutes at a time, several times daily), following short period of practice with clinician to set targets
Beber et al. (2018)	Rate and rhythm strategies	• Qualitatively increased production of single words and short sentences, in uncontrolled study of one patient with AOS +PPA who had difficulty initiating speech primarily because of blocks and sound repetitions
Ballard et al. (2015); Duffy (2020) (overviews)	• Articulatory-kinematic and rate/rhythm approaches • Multiple compensatory strategies	• Various levels of evidence of effectiveness for patients with nondegenerative AOS and other neurodegenerative motor speech disorders • May be applicable to PAOS, particularly compensatory strategies
Related resources (not specific to PPAOS)		
Topic	Association	Website
AOS in general	American Speech-Language Hearing Association	https://www.asha.org/practice-portal/
PPA	National Aphasia Association	https://aphasia.org
Atypical Alzheimer's disease	Alzheimer's Association	https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/frontotemporal-dementia
Frontotemporal dementia	Association for Frontotemporal dementia	https://www.theaftd.org/what-is-ftd/primary-progressive-aphasia/
Rare dementias	Rare Dementia Support	https://www.raredementiasupport.org/primary-progressive-aphasia/ppa-early-stages/
Tauopathies	National Organization for Rare Disorders	https://rarediseases.org/

helpful, such as "clear speech" strategies, intelligibility drills, and rate reduction strategies (e.g., hand-finger tapping, rhythmic cueing, alphabet supplementation) (Duffy, 2020). Early introduction and ongoing modification of augmentative and alternative means of communication (AAC) and environmental modifications are eventually necessary in most cases; people with PPAOS without significant upper extremity or visual problems generally are better candidates for AAC than are those with AOS+PAA. The degree to which any of these techniques and strategies can be implemented successfully depends on patient investment and can be complicated by the emergence of aphasia and other cognitive and motor deficits that emerge over time (Duffy et al., 2014; Utianski, Duffy et al., 2018).

Other symptom management

Because many patients with PAOS develop parkinsonian, PSP and CBS features, it may become important for them to have physical and occupational therapy targeting specific signs and symptoms, once such features develop. It remains unclear whether beginning these therapies prior to the emergence of Parkinsonian features would have any influence on the onset, severity, or rate of progression of such features.

Summary

This review has documented substantial progress in our understanding of PPAOS and PAOS. PPAOS is now recognized as a clinical syndrome that, while related to the nonfluent variant of primary progressive aphasia, is distinct from it in its clinical and neuroimaging profiles, and predictive of a clinical evolution toward broader clinical diagnoses such as progressive supranuclear palsy and corticobasal syndromes that are associated with underlying tau pathology. Its clinical features are detectible perceptually but they also have acoustic correlates that are sensitive to its presence, evolution, distinction from PPA, and, potentially, effects of behavioural and medical interventions. There are perceptually distinct subtypes (Phonetic and Prosodic) that have somewhat different patterns of localization, associated deficits, and evolution and that invite comparison to stroke-induced AOS in ways that may help refine our understanding of AOS in general. Treatment studies, limited but encouraging, are very likely to increase in the near future. They likely will share management principles and ingredients with other neurogenic motor speech disorders and PPA, but impairment and compensation-focused therapies will also need to consider the unique features of PPAOS and the associated problems that may emerge during its course.

Note

1. Tau, a protein found in neurons and glial cells in the central nervous system, normally stabilizes microtubules which are found in cytoplasm and are important for a number of cellular processes. Primary tauopathies are a major class of Frontotemporal Lobar Degeneration (FTLD) disorders that involve the pathological aggregation of the microtubule protein tau in the brain. Tauopathies are classified as 4R, 3R, or 3R:4R tau (Irwin, 2016).

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