# Quantitative assessment of motor speech impairment in primary progressive aphasia

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**Abstract**

Primary progressive aphasia is a neurodegenerative aphasic syndrome that can be classified into three main variants: agrammatic/non-fluent (nfvPPA), logopenic (lvPPA), and semantic (svPPA). Motor speech impairment is a key diagnostic marker used to aid classification of the clinical variants of PPA. Identification of motor speech symptoms is useful not only for differential diagnosis of PPA subtypes but may also inform hypotheses related to anatomic localization of disease and underlying pathophysiologic mechanisms. However, the diagnosis and characterization of motor speech impairment poses unique challenges when applied to the PPA population. First, motor speech impairment must be differentiated from comorbid language impairment and second—upon identification of a motor speech impairment—a disorder of motor planning (i.e., apraxia of speech) must be differentiated from one of motor execution (i.e., dysarthria).

The proposed series of acoustic, kinematic, and imaging-based analyses were designed to assess the diagnostic efficacy and biological validity of quantitative speech measures for identifying motor speech impairment in PPA, and to determine if motor speech impairments in PPA are consistent with apraxia of speech and/or dysarthria. In Study 1, we investigate the diagnostic accuracy of quantitative measures of speech rate as compared to clinician-rated measures to identify nfvPPA (cf. lvPPA, svPPA). Study 1 results provide evidence that an articulation rate (AR) measure may be a useful quantitative proxy of motor speech impairment. Study 2 extends this finding and evaluates whether the AR measure sensitively detects very mild motor speech impairment in PPA, and whether the AR measure is responsive to longitudinal changes in motor speech function. We also investigate the neuroanatomical basis of motor speech impairment in PPA by relating the AR measure to cortical thickness in motor speech regions of interest. Lastly, in Study 3, we go beyond mere identification of motor speech

impairment and seek to characterize individual profiles of motor speech impairment—with specific reference to apraxic and dysarthric features—using acoustic and kinematic measures of motor speech function. Results of the study series are interpreted in light of potential contributions to (1) diagnostic subtyping, (2) clinical monitoring, and (3) development of speech motor outcome measures.

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# **Chapter 1.** Introduction

Primary progressive aphasia (PPA) is a neurodegenerative aphasic syndrome characterized by a slowly progressive decline in language function in the relative absence, at least in initial stages of disease, of other non-language (e.g., episodic memory, visuospatial) impairments (Gorno-Tempini et al., 2011; Mesulam, 2001). There are three main PPA variants differentiated primarily on the basis of salient speech and language characteristics. These variants include (a) the non-fluent variant (nfvPPA), with primary deficits in motor speech function and agrammatism, (b) the logopenic variant (lvPPA), with primary deficits in spontaneous word retrieval, repetition, and auditory comprehension, and (c) the semantic variant (svPPA), with primary deficits in confrontation naming and single-word comprehension (Gorno-Tempini et al., 2011).

The heterogeneity of speech and language features in the PPA population often presents clinical challenges to differential diagnosis of subtypes. Accurate subtyping is especially important in PPA because probabilistic associations have been identified linking clinical subtype and underlying pathology: nfvPPA is most often associated with tau-positive pathology, lvPPA is typically associated with Alzheimer's disease pathology, and svPPA has been linked to ubiquitin-positive or TDP-43-positive pathology. Importantly, pathological diagnoses can be confirmed only at autopsy, thus making reliable pre-mortem diagnosis essential, especially as targeted, protein-specific clinical trials emerge. Apart from in-vivo biomarker approaches (e.g., CSF, PiB)—many of which demonstrate good accuracy for AD pathology, but relatively less success in identifying tauopathies (Murray et al., 2014; Rabinovici & Jagust, 2009; Rabinovici et al., 2008)—speech/language phenotyping is the primary pre-mortem method for diagnosing clinical variants of PPA. This diagnostic challenge makes research into reliable, potentially diagnostic speech/language features critical in this population.

Motor speech impairment (MSI) is one of several domains important for the differential diagnosis of PPA subtypes because MSI is associated uniquely with nfvPPA. However, prior literature has shown reliable identification of MSI to be challenging, particularly the differentiation of MSI from higher-level language deficits (Graff-Radford et al., 2014; Leyton, Ballard, Piguet, & Hodges, 2014). Another long-standing clinical challenge in PPA has been the determination of MSI type: whether the impairment is

best-described as a deficit of speech motor planning/programming (i.e., apraxia of speech) v. a deficit of motor execution (i.e., dysarthria), as well the extent of comorbidity and individual heterogeneity of MSI in PPA.

*Differentiating language from motor speech impairment*

Motor speech impairment is a key diagnostic marker used to aid classification of the clinical subtypes of PPA, with apraxia of speech (AOS) as a core diagnostic inclusion criterion for nfvPPA (Gorno-Tempini et al., 2011). Motor speech symptoms may also be the sole or dominant presenting symptom of a neurodegenerative process, as is in primary progressive apraxia of speech (PPAOS; Josephs et al., 2012). Apraxia of speech is a disorder of speech motor planning and/or programming that is distinguishable from aphasia and dysarthria. It most commonly results from vascular insults but can occur in degenerative diseases where it has typically been subsumed under aphasia, or it occurs in the context of more widespread neurodegeneration. The aim of this study was to determine whether apraxia of speech can present as an isolated sign of neurodegenerative disease. In recent years, there has been a considerable amount of research effort in PPA dedicated to the identification and quantification of surface speech features that may indicate motor speech impairment. The vast majority of work in this body of literature has focused on motor speech features associated with AOS, including segmental distortions (Ash et al., 2009; Grossman, 2012; Josephs et al., 2013; Ogar, Dronkers, Brambati, Miller, & Gorno-Tempini, 2007), reduced speech rate (Catani et al., 2013; Gunawardena et al., 2010; Wilson et al., 2010), and dysprosodic stress patterns (Ballard et al., 2014; Duffy et al., 2017), among other features.

However, many of these same surface speech deficits can also result from higher-level linguistic impairment (e.g., phonological impairment) and not motor speech impairment *per se*. This confound is particularly problematic in PPA because most variants have a prominent aphasic component, making it difficult to distinguish linguistic deficit from motor speech impairment where present. A subset of more recent studies in PPA make an explicit attempt to differentiate between higher-level language impairment and more downstream motor speech impairment (Ballard et al., 2014; Cordella, Dickerson, Quimby, Yunusova, & Green, 2017; Croot, Ballard, Leyton, & Hodges, 2012; Duffy et al., 2017; Wilson et al.,

2010). Results from these studies have shown that speech measures that theoretically differentiate levels of impairment are better able to differentiate between clinical subtypes (e.g., nfvPPA v. lvPPA), suggesting a diagnostic utility for quantitative measures that are specific for motor speech impairment.

*Differentiating between types of motor speech impairment*

A secondary limitation of current investigations of motor speech in PPA is the consistent neglect of the full range of motor speech disorders, which include not only apraxia of speech (AOS) but also dysarthria. In comparison to AOS, dysarthria is less well documented in the PPA literature and its incidence is often unreported, even in studies looking specifically at motor speech impaired PPA subgroups (e.g., nfvPPA, PPAOS). To our knowledge, no study has yet been published that seeks to explicitly quantify dysarthric features in a PPA population, despite reports of dysarthria incidence as high as 60% in the nfvPPA population (Poole, Brodtmann, Darby, & Vogel, 2017). Further complicating matters, many features reported as diagnostic features of apraxia of speech (e.g., slowed rate, segmental distortions) are also consistent with characterizations of dysarthria (Josephs et al., 2012; Strand, Duffy, Clark, & Josephs, 2014). This overlap of surface features confounds diagnosis of motor speech impairment in PPA in that it fails to differentiate between a motor planning/programming disorder (i.e., apraxia of speech) and motor execution disorder (e.g., dysarthria).

There is emerging evidence that dysarthric features may be particularly useful for early diagnosis of motor-prominent phenotypes, thereby demonstrating the necessity of more specific characterization of motor speech impairment as it occurs in PPA. For instance, longitudinal studies of PPAOS have revealed later-emerging dysarthric features in a majority of study participants and the eventual emergence of limb motor parkinsonian features in nearly all participants, some of whom were ultimately diagnosed with progressive supranuclear palsy (PSP-S; Duffy et al., 2015; Josephs et al., 2014). This recasting of the diagnostic formulation illustrates a common theme in PPA, in which patients tend to progress from a broad ‘first phenotype’ diagnosis (e.g., nfvPPA) to a more specific ‘second phenotype’ diagnosis (e.g., PSP-S) as more identifiable symptoms emerge late in the course of the disease (Dickerson, 2016).

The apparent progression in a subset of PPA patients from apraxia of speech to concomitant dysarthria to non-speech parkinsonism suggests the potential prognostic value of motor speech measures for earlier identification of the 'second phenotype.' Recent work looking at patients with a syndromic nfvPPA classification and post-mortem pathological diagnosis of PSP or corticobasal degeneration (CBD) reported a significantly higher incidence of dysarthric symptoms in the nfvPPA-PSP group as compared to the nfvPPA-CBD group (Santos-Santos et al., 2016). This finding extends prior work that had associated motor speech impairment with tauopathies more generally (Deramecourt et al., 2010; Duffy, Strand, & Josephs, 2014; Josephs et al., 2006), and suggests that specific motor speech disorders may be associated with different underlying pathologies within the family of tauopathies. More specifically, it suggests dysarthric speech features as an early-emerging symptom associated with PSP, thus providing an opportunity for earlier diagnosis of a more specific 'second phenotype' (i.e., PSP-S). If early-emerging symptoms could be reliably associated with these more specific phenotypes, there is the potential that a more accurate subtype diagnosis could be made in mild stages of disease.

*Need for improved assessment of motor speech impairment*

Taken together, motor speech impairment has been associated with both syndromic presentations (nfvPPA, PPAOS, PSP-S) and importantly, with different types of underlying tau pathology (Josephs et al., 2006; Santos-Santos et al., 2016). This association underscores the importance of early and accurate characterization of motor speech impairment, in which motor speech dysfunction is not only identified but subcategorized in terms of apraxic versus dysarthric features. There is, therefore, a pressing need for objective measures of motor speech function that have the potential to (1) uniquely identify motor speech impairment (cf. phonological deficit) in PPA in the early stages of disease and (2) differentiate a motor planning disorder (i.e., apraxia) from a motor execution disorder (i.e., dysarthria).

*The current dissertation*

The dissertation is comprised of three studies that, together, aim to answer the question of whether quantitative speech measures can improve the identification, monitoring, and characterization of motor speech impairment in PPA. The purpose of each study is detailed below (Table 1.1) in terms of its primary research question, specific sub-aims and hypotheses.

*Table 1.1. Research questions, aims and hypotheses for each study comprising the dissertation*

| | |
|---|---|
| **Chapter 2** | *Slowed articulation rate is a sensitive diagnostic marker for identifying non-fluent variant primary progressive aphasia*<br><br>*Research Question*: Can quantitative measures of speech fluency—specifically subcomponent measures of speech rate—differentiate PPA subtypes?<br><br>*Study Aims*: (1a) Compare diagnostic accuracy of quantitative v. clinician-rated measures of speech fluency; (1b) Identify quantitative measures of speech rate that best differentiate PPA subtypes, especially the non-fluent group (nfvPPA) from the more fluent groups (lvPPA, svPPA).<br><br>*Study Hypotheses*: Quantitative rate measures will have higher diagnostic accuracy for identifying nfvPPA as compared to clinician-rated measures (Hyp. 1a). Diagnostic accuracy will be greatest for the articulation rate (AR) measure, because this measure is sensitive to the motor speech impairment (MSI) in the nfvPPA population (Hyp. 1b). |
| **Chapter 3** | *Quantification of motor speech impairment and its anatomic basis in primary progressive aphasia*<br><br>*Research Question*: Does the AR measure have potential for early identification and monitoring of motor speech impairment in PPA, and is it a biologically valid measure?<br><br>*Study Aims*: Assess in a PPA population whether the AR measure (2a) sensitively detects MSI in very mild stages of disease, (2b) captures changes in MSI over time, and (2c) correlates with cortical thickness in motor speech ROIs.<br><br>*Study Hypotheses*: Diagnostic accuracy of AR for MSI will be high even in very mild stages of disease (Hyp. 2a). Longitudinal rate of decline in AR will be greater for the motor speech impaired PPA group as compared to non-motor speech impaired PPA groups (Hyp. 2b). Reduced AR will correlate with cortical thinning in motor speech ROIs (Hyp. 2c). |
| **Chapter 4** | *Acoustic and kinematic assessment of motor speech impairment in patients with suspected 4-Repeat (4R) tauopathies: A pilot study*<br><br>*Research Question*: Can a broader range of quantitative speech measures be combined to differentiate subtypes of MSI (AOS, dysarthria)?<br><br>*Study Aims*: (3a) Identify acoustic and kinematic markers (beyond articulation rate) of MSI in individuals with 4R tauopathy-associated syndromes (nfvPPA, CBS, PSP); (3b) characterize type of motor speech impairment (AOS, dysarthria) using acoustic/ kinematic measures to derive quantitative motor speech impairment profiles.<br><br>*Study Hypotheses*: Quantitative measures to identify MSI in 4RT syndromes include shared, AOS-, and dysarthria- specific measures (Hyp. 3a). There exist heterogenous profiles of MSI within the 4RT group, wherein both apraxic and dysarthric features are present and characterizable using acoustic and kinematic measures (Hyp. 3b). |

*Significance and contribution of the dissertation*

The findings of this proposed research are expected to advance the understanding of motor speech impairment in PPA in several clinically important ways related to (1) diagnostic subtyping, (2) clinical monitoring, and (3) development of speech motor outcome measures. The identification of reliable, objective measures of motor speech impairment in PPA has important implications for subtype diagnosis in PPA, as quantification of motor speech impairment stands to lessen the current reliance on clinician judgement as the diagnostic gold standard for motor speech impairment. Furthermore, quantitative speech measures that reflect dysarthric, in addition to apraxic, deficits are particularly promising for their ability to identify motor-prominent phenotypes prior to the onset of limb motor symptoms.

Beyond diagnostic subtyping, quantitative measures of motor speech impairment are useful for clinical monitoring of disease progression in motor speech impaired subgroups. These measures are a first step in collecting more standardized, population-level information about clinical milestones to motor speech decline, from initial symptoms to mutism. Such information provides clinicians as well as patients and families with critical clues to inform decision-making, for instance with regard to the timing of augmentative and alternative communication (AAC) intervention planning. In the same way that quantitative measures of motor speech impairment could be used to track population-level trajectories of decline, they may also be useful as outcome measures for improved speech function following a therapeutic drug intervention or targeted speech therapy program (Dickerson, 2011).

**Chapter 2.** Slowed articulation rate is a sensitive diagnostic marker for identifying non-fluent primary progressive aphasia[1]

[1] A version on this chapter has been previously published: Cordella, C., Dickerson, B. C., Quimby, M., Yunusova, Y., & Green, J. R. (2017). Slowed articulation rate is a sensitive diagnostic marker for identifying non-fluent primary progressive aphasia. *Aphasiology*, *31*(2), 241–260. doi: 10.1080/02687038.2016.1191054

Contributions of respective authors are as follows: Design and conceptualization of study (CC, JG); acquisition of data (CC, MQ); analysis and interpretation of data (CC), drafting of manuscript for intellectual content (CC, BCD, JG), editing of manuscript for intellectual content (BCD, JG, YY).

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## Abstract

***Background***: Primary progressive aphasia (PPA) is a neurodegenerative aphasic syndrome with three distinct clinical variants: non-fluent (nfvPPA), logopenic (lvPPA), and semantic (svPPA). Speech (non-) fluency is a key diagnostic marker used to aid identification of the clinical variants, and researchers have been actively developing diagnostic tools to assess speech fluency. Current approaches reveal coarse differences in fluency between subgroups, but often fail to clearly differentiate nfvPPA from the variably fluent lvPPA. More robust subtype differentiation may be possible with finer-grained measures of fluency.

***Aims***: We sought to identify the quantitative measures of speech rate-including articulation rate and pausing measures-that best differentiated PPA subtypes, specifically the non-fluent group (nfvPPA) from the more fluent groups (lvPPA, svPPA). The diagnostic accuracy of the quantitative speech rate variables was compared to that of a speech fluency impairment rating made by clinicians.

***Methods and Procedures***: Automatic estimates of pause and speech segment durations and rate measures were derived from connected speech samples of participants with PPA (N=38; 11 nfvPPA, 14 lvPPA, 13 svPPA) and healthy age-matched controls (N=8). Clinician ratings of fluency impairment were made using a previously validated clinician rating scale developed specifically for use in PPA. Receiver operating characteristic (ROC) analyses enabled a quantification of diagnostic accuracy.

***Outcomes and Results***: Among the quantitative measures, articulation rate was the most effective for differentiating between nfvPPA and the more fluent lvPPA and svPPA groups. The diagnostic accuracy of both speech and articulation rate measures was markedly better than that of the clinician rating scale, and articulation rate was the best classifier overall. Area under the curve (AUC) values for articulation rate were good to excellent for identifying nfvPPA from both svPPA (AUC=.96) and lvPPA (AUC=.86). Cross-validation of accuracy results for articulation rate showed good generalizability outside the training dataset.

***Conclusions***: Results provide empirical support for (1) the efficacy of quantitative assessments of speech fluency and (2) a distinct non-fluent PPA subtype characterized, at least in part, by an underlying disturbance in speech motor control. The trend toward improved classifier performance for quantitative rate measures demonstrates the potential for a more accurate and reliable approach to subtyping in the fluency domain, and suggests that articulation rate may be a useful input variable as part of a multi-dimensional clinical subtyping approach.

## Introduction

Primary progressive aphasia (PPA) is a neurodegenerative aphasic syndrome characterized by a primary language impairment, and relative preservation of non-linguistic cognitive function. PPA can be further classified into three main variants: agrammatic/non-fluent (nfvPPA), logopenic (lvPPA), and semantic (svPPA). The distribution of neuropathology, and consequently the type of language impairment (e.g., agrammatism, word-finding difficulties, naming impairments) vary according to subtype (Mesulam, 2007; Rogalski et al., 2011). Performance measures across multiple speech and language domains are central components to the differential diagnosis of PPA subtypes, making language phenotype a primary determiner of subtype assignment (Gorno-Tempini et al., 2011). Recent research has also demonstrated an association between clinical subtype—as determined by language phenotype—and underlying biological pathology (Grossman, 2010; Mesulam et al., 2014). This makes language-based subtyping especially important for advancing ongoing efforts to identify the neural basis of PPA.

The language-based classification criteria for PPA subtypes assess performance in several speech and language domains, of which speech fluency is a primary one (Ballard et al., 2014; Fraser et al., 2014; Wilson et al., 2010). Speech fluency and non-fluency are variably defined in the broader aphasia literature, with definitions based on a wide range of speech characteristics, including speech rate, articulatory accuracy, articulatory effort, phrase length, pausing, and prosody (Ash et al., 2010; Kerschensteiner, Poeck, & Brunner, 1972). In the PPA literature, definitions of non-fluency center primarily on slowed rate of speech and increased numbers of speech sound errors (Gorno-Tempini et al., 2011; Wilson et al., 2010). The identification of non-fluent speech is crucial to subtype assignment in PPA because non-fluent or apraxic speech—typified by slow, halting speech and/or speech sound errors—is a core feature of nfvPPA, in addition to agrammatism (Gorno-Tempini et al., 2011). In contrast, lvPPA and svPPA are typically characterized as more fluent subtypes (Catani et al., 2013; Mesulam, 2007), though lvPPA patients are often described as having variable or intermediate fluency depending on the lexical constraints of the exchange (Gorno-Tempini et al., 2008; Rohrer, Rossor, &

Warren, 2012; Teichmann et al., 2013; Thompson et al., 2012). Spared motor speech is considered a characteristic of both lvPPA and svPPA (Gorno-Tempini et al., 2011).

Because speech (non-)fluency is a key diagnostic marker used to aid identification of clinical subtypes, researchers have been actively developing diagnostic tools to assess speech fluency, using both clinical rating scales and quantitative analyses. Sapolsky and colleagues (2010) proposed a clinician rating scale that included a fluency domain, and established the validity of the scale using correlative analyses relating clinician judgment to relevant standardized test scores (e.g., WAB Fluency in the fluency domain). Several quantitative metrics of speech fluency have also been proposed, which include the rate of speech (Ash et al., 2010; Fraser et al., 2014; Wilson et al., 2010) and/or the type and number of sound distortions (Ash et al., 2010; Croot et al., 2012; Sajjadi, Patterson, Tomek, & Nestor, 2012; Wilson et al., 2010). Although these measures reveal coarse differences in fluency between subgroups, they are less effective for differentiating nfvPPA from the variably fluent lvPPA (Sajjadi et al., 2012). More robust subtype classification may be possible with finer- grained measures of speech rate (Ballard et al., 2014; Wilson et al., 2010) that distinguish between the amount of pausing versus the rate of articulator movement, both of which can affect overall speech rate. As an example, a global measure of speech rate was not as effective in differentiating nfvPPA from both svPPA and lvPPA as was a measure of maximum speech rate, which approximates an articulation rate measure by calculating rate (words/minute) over a speech period with minimal pausing (Wilson et al., 2010).

Prior research suggests the potential for a speech rate measure to be a reliable indicator of non-fluent speech in the PPA population, which could provide an effective basis for differentiation of nfvPPA from both lvPPA and svPPA. The use of speech rate as a metric for speech non-fluency has several advantages: it is objective, automatable and most importantly, conveys information about both the motor speech system as well as higher-level cognitive and linguistic processing. In terms of the motor speech system, speakers can alter their rate of speech by changing the speed of movement or displacement of the articulators (Campbell & Dollaghan, 1995; Nip & Green, 2013). Speakers can also alter speech rate by changing the amount of time spent pausing, where pausing reflects higher-level cognitive/linguistic

functioning (e.g., due to word finding, sentence planning difficulties). This decomposition of speech rate yields the subcomponent measures of articulation rate and pause amount, which represent motor and cognitive/linguistic contributions to speech, respectively.

To our knowledge, no research has looked specifically at the subcomponent measures of speech rate—including (1) articulation rate and (2) pausing measures—across all three main PPA variants. Separating out articulation rate from pausing will provide theoretically relevant information about the sources of non-fluency across groups, specifically whether these are primarily motor or cognitive/linguistic in nature. This may prove an especially useful approach for distinguishing between lvPPA individuals—for whom overall speech rate may be slowed due to increased pausing associated with word-finding problems, and nfvPPA individuals—for whom overall speech rate may be slowed due to reduced speed of articulator movement secondary to a motor speech impairment. Over and above this theoretical utility, the use of quantitative subcomponent measures of speech rate for clinical applications is particularly appealing because they can be automatically and reliably extracted from continuous speech samples (Green, Beukelman, & Ball, 2004).

The main goal of the current study is to compare the diagnostic efficacy of quantitative measures to clinician ratings of fluency for identifying nfvPPA. Our hypothesis is that these subcomponent measures of speech better differentiate PPA subtypes (especially nfvPPA from the non-motor speech impaired lvPPA and svPPA groups) than do clinical rating scales or extant measures used to quantify speech fluency. For this analysis, we identified the quantitative measures of speech rate that best differentiated PPA subtypes, specifically the non-fluent group (nfvPPA) from the more fluent groups (lvPPA, svPPA). Second, we determined if the diagnostic accuracy of these select quantitative speaking rate variables was greater than that of ratings of speech fluency impairment made by clinicians (Sapolsky et al., 2010). We hypothesized that quantitative rate measures will identify nfvPPA with greater accuracy than will the subjective clinician ratings, and that both types of measures will perform significantly better than chance identification. We predict diagnostic accuracy to be greatest for the articulation rate measure,

because this measure is sensitive to the motor speech deficits that characterize many patients in the nfvPPA population.

## Methods

***Participants***. Participants included individuals with a diagnosis of PPA (N= 38; 11 nfvPPA, 14 lvPPA, 13 svPPA) recruited through the Massachusetts General Hospital (MGH) Frontotemporal Disorders Unit PPA Program and healthy age-matched controls (N =8) enrolled as part of a larger study in the Speech and Feeding Disorders Lab at the MGH Institute of Health Professions. A diagnosis of PPA, and subsequent subtype classification, was made by consensus after extensive clinical assessments by an experienced neurologist and speech language pathologist (SLP) as described elsewhere (Sapolsky et al., 2010) based on published consensus criteria (Gorno-Tempini et al., 2011). These evaluations included behavioral observations of a patients' spontaneous speech and language and a structured interview with the patient and an informant (both neurologist and SLP), a neurological exam and cognitive assessment (neurologist), and a formal speech-language evaluation (SLP), which consisted of a battery of tests evaluating expressive and receptive language abilities (e.g., syntax, lexical retrieval, confrontation naming, repetition). For the nfvPPA group, participants met one of two core inclusion criteria: (1) agrammatism and/or (2) apraxia of speech. All 11 nfvPPA participants were judged clinically by the speech-language pathologist (MQ) to have at least mild features of agrammatism. This judgment was based on qualitative assessment of agrammatic features (e.g., incorrect word order, omission of functor words or grammatical markers) in spontaneous speech and during a picture description task, as well as scores from the Northwestern Anagram Test (NAT; Thompson, Weintraub, & Mesulam, 2012).
If multiple longitudinal samples for a single patient were available, only the first sample was selected for analysis. Exclusionary criteria for participants included prior history of stroke and other non- degenerative pathologies. Severity of disease progression was measured for participants with PPA using the sum of boxes score on the Progressive Aphasia Severity Scale (PASS; Sapolsky et al., 2010). A one-way ANOVA indicated that PPA subtype groups were not significantly different in terms of overall disease severity (Table 2.1). Measures of reliability and validity of PASS ratings across several domains have

been previously reported (Sapolsky et al., 2010). In the current study, PASS ratings in the Fluency domain were reliability checked for a subset of patient population (18/38 participants). There were a total of three unique rater pairs: neurologist (BCD) / speech language pathologist (DS), speech language pathologist (DS) / speech language pathologist (MQ), speech language pathologist (MQ) / speech-language pathology graduate student (CC). Weighted Cohen's kappa (κw) per rater pair were 1.0 (BCD/DS), .78 (DS/MQ), and .83 (MQ/CC). The overall index of inter-rater agreement was .87, calculated as the arithmetic mean of κw across the three rater pairs, following Light (1971).

Age-matched healthy controls were also included for analysis. These participants were screened for exclusionary medical history as well as basic speech, language, hearing, and cognitive functioning, and were determined to be unimpaired in all domains. The experimental and control groups were matched for age and education. One-way ANOVAs showed no significant difference between any groups in age or education level. Table 2.1 summarizes all participant demographic information.

*Table 2.1. Participant demographic information*

| | **PPA** | | | **Normal controls (NC)** | **Omnibus significance** |
|---|---|---|---|---|---|
| | ***nfvPPA*** | ***lvPPA*** | ***svPPA*** | | |
| Age (yrs) | 66.4 ±11.40 | 71.8 ±7.75 | 66.0 ±9.03 | 61.7 ±8.44 | ns |
| Sex (M/F) | 6/5 | 9/5 | 4/9 | 4/4 | ns |
| Education (yrs) | 16.6 ±3.29 | 16.9 ±2.45 | 17.2 ±2.38 | 15.8 ±0.71 | ns |
| Severity (PASS SoB) | 6.05 ±4.44 | 6.43 ±3.89 | 5.73 ±2.64 | -- | ns |

**PASS SoB** = Progressive Aphasia Severity Scale sum of boxes score

***Materials and collection***. Participants were shown the black and white picnic scene picture of the Western Aphasia Battery (Kertesz, 2007) and asked to use sentences to describe the picture. No further prompting was given by the clinician except in cases where the participant's initial response was less than 30 seconds; in this case, the clinician prompted the participant by asking, "Can you tell me anything else about the picture?" The clinician did not provide explicit feedback on participant response during or after administration. Participants were given no maximum time limit for this task. Participants' descriptions were audio recorded using an Olympus VN-702PC digital recorder placed on a table approximately one foot in front of the participant (PPA participants) or a Countryman B3P4FF05B B3 head-mounted omnidirectional microphone positioned approximately 5 cm from the mouth (control participants).

***Preprocessing of speech recordings***. Audio samples were parsed in Adobe Audition 2.0 using an initial cut point immediately prior to the first content word and a final cut point immediately following the last content word. All instances of clinician cross-talk were deleted from the file. Parsed samples were noise-reduced (also in Audition 2.0) and any filled pause (e.g., um, uh) or non-speech vocalization (e.g., laughter, audible breathing) were manually zeroed in the waveform.

***Extraction of quantitative fluency measures***. The preprocessed audio were then analyzed using a MATLAB-based program, Speech Pause Analysis (SPA), which algorithmically estimated speech and pause segments in continuous speech (Green et al., 2004). The speech and pause thresholds were set at 25ms and 100ms, respectively. Thus any speech segment greater than 25 ms was counted as a speech event and any silent duration greater than 100 ms was counted as a pause event (Fletcher, 2010). Manual transcriptions of each participant's audio samples were done using English orthography, and syllables were counted per transcription using an online syllable-counting tool (http://www.online-utility.org/text/analyzer.jsp). True words, phonemic paraphasias, and phonetically distorted words were all counted toward the overall syllable count. Unintelligible sequences—as judged by the transcriber—were not counted toward the syllable count. For repeated syllables, words and short phrases (≤ 3 words), only the first occurrence was counted. In a case where a phonemic paraphasia preceded a real word self-correction, it was considered a repetition, and only the first occurrence was counted.

Syllable counts and automatic SPA output regarding the frequency and duration of pause and speech events were combined to derive the following quantitative measures of speech fluency: speech rate, articulation rate, proportion speech/pause, mean pause duration, and pause event frequency. Table 2.2 lists all the quantitative fluency measures and their mathematical derivation.

*Table 2.2. Quantitative fluency measures*

| Variable Name | Derivation |
|---|---|
| Speech rate | = # total syllables / total response duration (s) |
| Articulation rate | = # total syllables / total speech duration (s) |
| Mean pause duration | = total pause duration (s) / # pause events |
| Proportion pause | = total pause duration (s) / total response duration (s) |
| Pause event frequency | = # pause events / total response duration (s) |

***Progressive Aphasia Severity Scale***. The current study compared the quantitative fluency measures in Table 2.2 to a set of subjective clinician rating scales, known as the Progressive Aphasia Severity Scale (PASS; Sapolsky et al., 2010). The PASS is an instrument currently in use by some clinicians to rate severity of impairment across ten primary speech and language domains—articulation, fluency, syntax, word retrieval & expression, repetition, auditory comprehension, single word comprehension, reading, writing and functional communication. Impairment in each domain is rated from normal/no impairment to severe on a 0-3 interval scale (Table 2.3). Severity ratings across all PASS domains can be summed to yield a sum of boxes score representing overall severity. A fluency domain subscore was also obtained from the PASS, which reflected a clinician's estimation of speech fluency in terms of perceived rate of speech, phrase length, and number/frequency of hesitations and fillers.

*Table 2.3. PASS rating scale*

| PASS Rating | Description of Impairment |
|---|---|
| 0 | Normal/no impairment |
| .5 | Questionable/very mild |
| 1 | Mild |
| 2 | Moderate |
| 3 | Severe |

***Statistical analyses***. Statistical analyses were conducted to (1) identify which variables differentiated PPA subgroups, (2) determine the sensitivity and specificity of differentiating variables and (3) evaluate diagnostic accuracy of differentiating variables using estimates of the area under the curve (AUC), cross-validated AUC (cvAUC), and partial area under the curve (pAUC). Both full-set and cross-validated AUC values are reported to maximize the comparability of current results with previously reported statistics. A series of one-factor ANOVAs were run using the R statistical software (R Core Development Team, 2015) to detect significant group differences in each of the experimental variables, with post-hoc tests (Tukey HSD) conducted as appropriate. Receiver operating characteristic (ROC) analyses were also conducted to generate AUC values as approximate measures of the diagnostic accuracy (DeLong, DeLong, & Clarke-Pearson, 1988). Because ROC analysis assumes a binary classification, a series of pairwise subgroup comparisons (i.e., nfvPPA~lvPPA, nfvPPA~svPPA, nfvPPA~NC) was conducted. Significance testing of AUC values was done using the pROC package (Robin et al., 2011) in R.

Sensitivity, specificity, accuracy, cvAUC and pAUC were also calculated as part of ROC analyses (López-Ratón, Rodríguez-Álvarez, Cadarso-Suárez, & Gude-Sampedro, 2014). Cross- validated AUC was computed using a *k*-fold cross-validation technique as part of the DAAG package (Maindonald, 2012). pAUC was calculated for a restricted low-FPR range [(0,0.2)] and is reported as both an uncorrected raw value and a corrected value. This corrected value is standardized such that 1 is the maximum AUC and .5 represents the non-discriminant AUC in the designated region (Robin et al., 2011).

## Results

Table 2.4 gives summary statistics for each of the quantitative fluency measures, as well as the PASS Fluency clinician rating scale.

*Table 2.4. Mean, standard deviation and significance for quantitative fluency measures*

| | p-value | nfvPPA (n=11) | lvPPA (n=14) | svPPA (n=13) | NC (n=8) |
|---|---|---|---|---|---|
| Speech rate (syll/s) | <.001 | .93±.46[c,d] | 1.51 ±.55[c,d] | 2.16 ±.81[a,b] | 2.88 ±.5[a,b] |
| Articulation rate (syll/s) | <.001 | 2.35 ±.75[b,c,d] | 3.53 ±.64[a,d] | 4.13 ±.69[a] | 4.78±.32[a,b] |
| Mean pause duration (s) | .001 | 1.25 ±.55[c,d] | .91 ±.34 | .77 ±.33[a] | .50 ±.19[a] |
| Proportion pause | .002 | .61 ±.13[d] | .58 ±.12[d] | .49 ±.14 | .40 ±.09[a,b] |
| Pause event frequency | .014 | .56 ±.19[d] | .67 ±.13 | .70 ±.21 | .85 ±.20[a] |
| PASS Fluency rating | <.001 | 1.0 ±.67[c] | .57 ±.33[c] | .15 ±.24[a,b] | -- |

**NC** = Normal controls. p-value refers to overall between-groups significance per variable. Superscript letters denote post-hoc significance relative to the [a]nfvPPA [b]lvPPA [c]svPPA and [d]NC at p<0.05

***Speech measures***. Speech measures included speech rate and articulation rate. Speech rate was a significant groups differentiator, $F(3,42)=18.22$, $p<.001$, as was articulation rate, $F(3,42)=25.71$, $p<.001$. All PPA subgroups had a lower overall speech rate when compared to normal controls (Figure 2.1), though this difference was significant only for nfvPPA ($p<.001$) and lvPPA ($p<.001$) groups. Within the PPA groups, svPPA individuals had significantly higher speech rates as compared to either lvPPA ($p=.04$) or nfvPPA ($p<.001$) individuals. Although speech rates were lowest for nfvPPA individuals, they were not statistically differentiable from lvPPA. Articulation rate showed a step-wise trend similar to speech rate, with the rate for nfvPPA significantly decreased relative to lvPPA ($p<.001$), svPPA ($p<.001$) and normal controls ($p<.001$; Figure 2.2). Articulation rate was also significantly decreased for lvPPA individuals compared to normal controls ($p<.001$). There was no significant difference in articulation rate between lvPPA and svPPA, or between svPPA and normal controls.

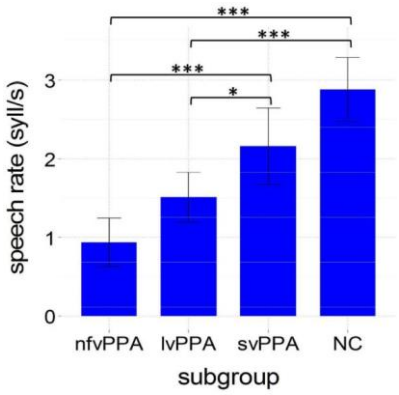


*Figure 2.1. Speech rate by subgroup*

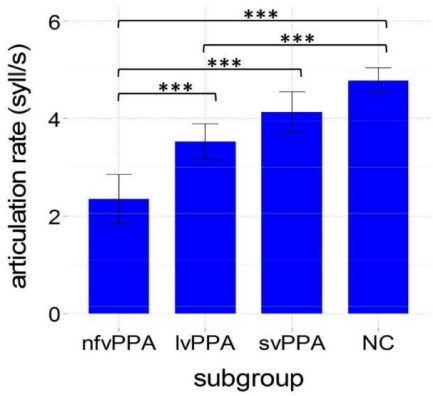


*Figure 2.2. Articulation rate by subgroup*

NC = normal controls; Error bars = 95% CI; ***p<.001, **p<.01,*p<.05.

Pause measures included proportion pause and component submeasures of mean pause duration and pause event frequency. Proportion pause was a significant between-groups differentiator, $F(3,42)=5.47$, $p=.002$, along with both mean pause duration, $F(3,42)=6.50$, $p=.001$, and pause event frequency, $F(3,42)=3.97$, $p=.014$. Importantly, mean pause duration was the only pause measure to significantly differentiate among any of the PPA subgroups.

Overall, nfvPPA and lvPPA groups paused for a greater proportion of total response times (i.e., pause + speech time) compared to normal controls. Proportion pause time did not differentiate among PPA subgroups, although svPPA individuals paused for the smallest proportion of time compared to lvPPA and nfvPPA (Figure 2.3).

Mean pause duration was a significant group differentiator overall (Figure 2.4), showing a step-wise trend in the opposite direction as speech and articulation rate. Average pause times were longer for nfvPPA relative lvPPA, svPPA and normal controls; however, only the nfvPPA and svPPA groups were statistically differentiable ($p=.02$)

The nfvPPA group paused less frequently than lvPPA, svPPA and normal controls, although between-groups differences for the pause event frequency measure were significant only for the nfvPPA groups relative to the normal controls (Figure 2.5). Taken together, pause measure results show that the

nfvPPA group is pausing less frequently, but for a longer (per pause) duration, compared to other groups. The opposite directional trends of component pause measures accounts for the non-significant finding with regards to the gross proportion pause measure.

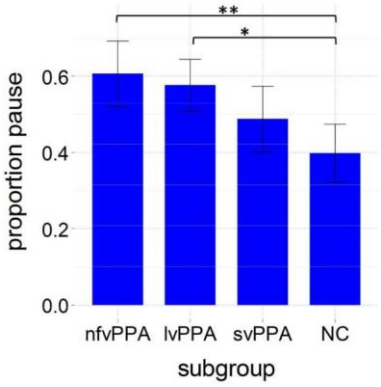


*Figure 2.3. Proportion pause time by subgroup*

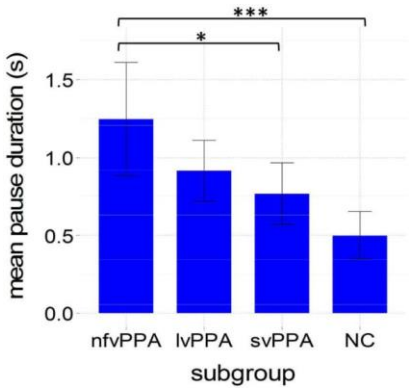


*Figure 2.4. Mean pause duration by subgroup*

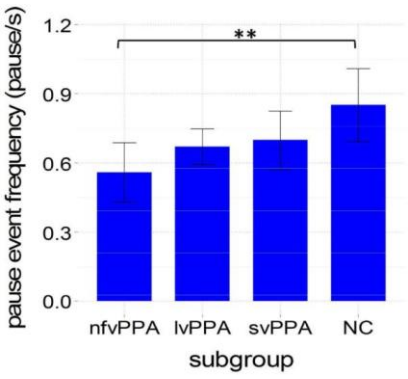


*Figure 2.5. Pause event frequency by subgroup*

NC = normal controls; Error bars = 95% CI; ***p<.001, **p<.01,*p<.05.

***PASS Fluency subscale rating***. The PASS Fluency subscale rating significantly differentiated PPA subgroups overall, $F(2,35)=11.3$, $p<.001$. Mean PASS Fluency ratings were marginally higher (indicating greater impairment) for nfvPPA compared to both lvPPA ($p=.05$) and substantially higher for nfvPPA compared to svPPA ($p<.001$). Mean PASS Fluency ratings were also higher for lvPPA compared to svPPA ($p=.045$; Figure 2.6).

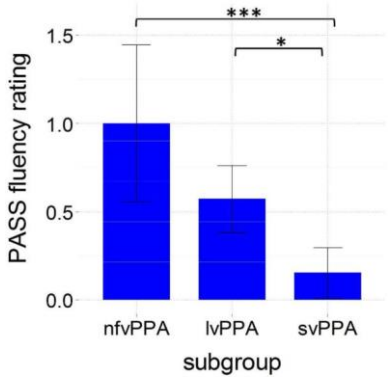


*Figure 2.6. PASS fluency ratings by subgroup*

NC = normal controls; Error bars = 95% CI; ***p<.001, **p<.01,*p<.05.

***Classifier performance***. Sensitivity, specificity and ROC analyses were conducted for the speech rate and articulation rate measures because these variables were the best between-groups differentiators ($p$<.001). For comparison, the same set of analyses was conducted for the PASS Fluency subdomain measure, which was also a good between-groups differentiator ($p$<.001). Each measure was treated as an independent classifier, and analyses focused exclusively on groups comparisons relative to nfvPPA (i.e., nfvPPA~lvPPA, nfvPPA~svPPA, nfvPPA~NC).

Sensitivity, specificity and accuracy values are reported in Table 2.5. The overall accuracy in identifying nfvPPA versus lvPPA was greatest for the articulation rate measure (92%). Values for both sensitivity (82%) and specificity (100%) suggested good to excellent discriminant accuracy. Sensitivity and specificity values for differentiating nfvPPA from svPPA were likewise high for the articulation rate measure (82%, 100%, respectively) and speech rate measure (91%, 85 %, respectively). Sensitivity and specificity values for differentiating nfvPPA from normal controls were 100% for both the articulation and speech rate measures.

*Table 2.5. Classifier performance of select fluency measures*

| | Groups Comparison | | Sensitivity (%) | Specificity (%) | Accuracy (%) | AUC | cvAUC | pAUC uncorrected/ corrected |
|---|---|---|---|---|---|---|---|---|
| AR | nfvPPA | lvPPA | 81.8 | 100.0 | 92.0 | 0.86 | .84 | .16/.90 |
| | | svPPA | 81.8 | 100.0 | 91.7 | 0.96 | .83 | .17/.91 |
| | | NC | 100.0 | 100.0 | 100.0 | 1.00 | .95 | .20/1.00 |
| SR | nfvPPA | lvPPA | 90.9 | 78.6 | 84.0 | 0.83 | .76 | .09/.68 |
| | | svPPA | 90.9 | 84.6 | 87.5 | 0.94 | .79 | .15/.87 |
| | | NC | 100.0 | 100.0 | 100.0 | 1.00 | .90 | .20/1.00 |
| PASS | nfvPPA | lvPPA | 27.3 | 100.0 | 68.0 | 0.66 | .56 | .07/.63 |
| | | svPPA | 100.0 | 61.5 | 79.2 | 0.90 | .67 | .12/.78 |
| | | NC | -- | -- | -- | -- | -- | -- |

**AR**=Articulation rate, **SR**=Speech rate, **PASS**=PASS Fluency subscore. **Sensitivity** = True Positive (TP)/(TP +False Negative (FN)), **Specificity** = True Negative (TN)/(TN + False Positive (FP)), **Accuracy** = (TN + TP)/(TN+TP+FN+FP). **AUC**= Area under the curve, **cvAUC**= Cross-validated AUC. **$pAUC_{uncorrected}$** =absolute AUC for FPR [0, 0.2]. **$pAUC_{corrected}$** = scaled AUC for FPR [0.0.2] using McClish correction (Maindonald & Braun, 2012).

ROC curves for each pairwise group comparison are shown in Figures 2.7-2.9. Table 2.5 gives corresponding AUC values per classifier for each of the group comparisons. In differentiating nfvPPA

from lvPPA, articulation rate was the best-performing classifier (AUC=.86), followed closely by the speech rate classifier (AUC=.83), and finally the PASS Fluency classifier (AUC=.66). In differentiating nfvPPA from svPPA, articulation rate was again the best-performing classifier (AUC=.96), followed closely by both the speech rate (AUC=.94) and PASS Fluency classifiers (AUC=.90). Speech and articulation rate perfectly differentiated (AUC=1.00) nfvPPA from normal controls.

Although articulation rate and speech rate classifiers outperformed the PASS Fluency classifier in differentiating nfvPPA from both of the more fluent subtypes, no differences in AUC values were significant, possibly owing to the small sample size.

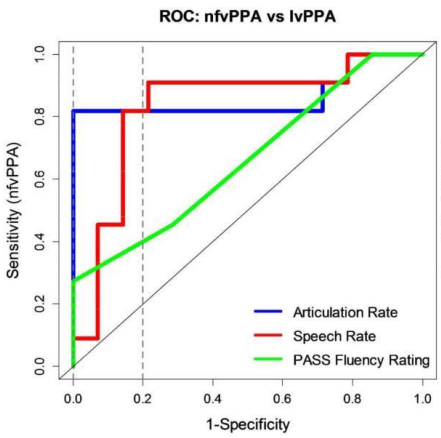


*Figure 2.7. ROC curve for nfvPPA v. lvPPA*

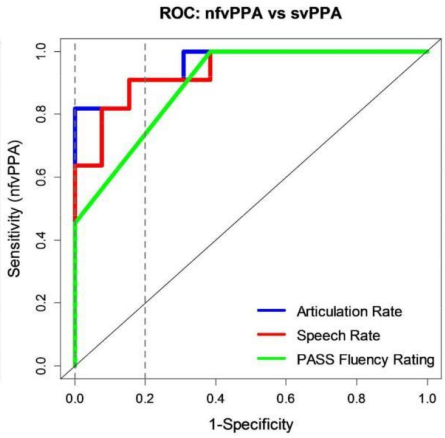


*Figure 2.8. ROC curve for nfvPPA v. svPPA*

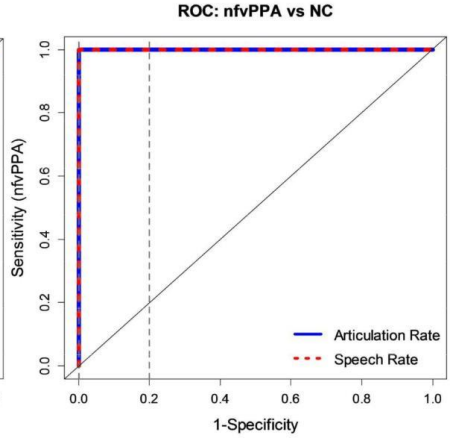


*Figure 2.9. ROC curve for nfvPPA v. NC*

Dashed vertical lines correspond to restricted false positive range (FPR; 0,0.2)

To evaluate generalizability of classifier performance, all ROC analyses were cross-validated using a *k*-fold (*k*=5) cross-validation technique. This approach yielded adjusted AUC estimates for each of the classifiers (Table 2.5). These estimates, though marginally lower than full-set AUCs, suggest good predictive performance for the articulation rate classifier (AUC=.84), fair performance for the speech rate classifier (AUC=.76) and relatively poorer performance for the PASS Fluency clinician rating scale classifier (AUC=.56) in identifying nfvPPA from lvPPA.

Partial AUC (pAUC) was estimated for a clinically relevant False Positive Rate (FPR; = (1-Specificity)) range (Dodd & Pepe, 2003).[2] Table 2.5 gives pAUC values calculated for each of the three classifiers using a restricted FPR range (FPR [0-.2]). Figures 2.7-2.9 show the restricted FPR range graphically. In this focused analysis, articulation rate was again the best performing classifier and differentiated nfvPPA from lvPPA, svPPA and normal controls with excellent diagnostic accuracy ($AUC_{corrected}$=.90, .91, 1.00, respectively). Both articulation rate and speech rate out-performed the PASS Fluency measure in identifying nfvPPA. The pAUC for the articulation rate classifier (nfvPPA~lvPPA) was significantly greater than the PASS Fluency pAUC ($p<.001$); no statistically significant differences in pAUC were found between articulation rate and speech rate classifiers or speech rate and PASS Fluency classifiers for either of the clinical groups comparisons.

## Discussion

This investigation examined the diagnostic efficacy of speech rate, and its subcomponent measures of articulation rate and pausing, for differentiating between non-fluent and fluent subtypes of PPA. Among the quantitative measures, articulation rate was the most effective for differentiating between nfvPPA and the more fluent lvPPA or svPPA groups. The diagnostic accuracy of these quantitative measures was markedly better than that of the clinician rating scale. These findings provided additional empirical support for (1) the efficacy of quantitative assessments of speech fluency and (2) a distinct non-fluent PPA subtype characterized, at least in part, by an underlying disturbance in speech motor control.

### *Speech rate differences driven by articulation rate*

Consistent with previous research (Ballard et al., 2014; Fraser et al., 2014; Wilson et al., 2010), our results revealed a predictable slowing in speech rate from the most fluent svPPA to the variably fluent lvPPA to the least fluent nfvPPA. The findings from this study revealed that this difference is primarily

[2] Summary AUC estimates quantify classifier performance across the entire FPR/(1-Specificity) range, the upper limit of which is operationally undesirable for a clinically useful test. Partial AUC analyses allow for the estimation of AUC across a restricted, clinically relevant FPR range (i.e., low FPR).

driven by group differences in articulation rate rather than in pausing. More specifically, of the subcomponent measures of speech rate, only articulation rate differentiated between non-fluent nfvPPA and the more fluent lvPPA and svPPA groups.

The failure of the overall pausing measure to differentiate nfvPPA from lvPPA and svPPA is surprising given the association between agrammatic output and increased pausing in other agrammatic Aphasias (Beeke, Wilkinson, & Maxim, 2009; Lesser & Milroy, 2014). Results showed that although individuals with nfvPPA tended to pause longer per pause compared to the lvPPA and svPPA groups, these individuals also paused less frequently. These opposite trends in pausing behavior could account for the non-significance between clinical subgroups of the overall proportion pause measure. The decreased frequency in pausing in the nfvPPA group is an unexpected finding and could be the result of a failure to pause at appropriate grammatical junctions, possibly related to the impaired sentence planning that is characteristic of the nfvPPA population (Gorno-Tempini et al., 2011; Grossman, 2012; Levelt, Roelofs, & Meyer, 1999).

All pause measures did significantly differentiate nfvPPA from normal controls, suggesting some degree of abnormal pausing behavior in the former group. However, several pause measures also differentiated the lvPPA group from normal controls. This finding suggests a more complicated picture of pausing behavior in PPA, in which both nfvPPA and lvPPA individuals are pausing more than normal controls but likely for different reasons. In the nfvPPA group, increased pausing is most likely a function of agrammatism, whereas in lvPPA, increased pausing likely results from impaired lexical retrieval (Gorno-Tempini et al., 2004; Henry & Gorno-Tempini, 2010). It is possible that more fine-grained pausing measures (e.g., durational distribution of individual pauses, occurrence of pauses relative to syntactic boundaries) may differentiate between PPA subtypes.

*Decreased articulation rate reflects motor impairment in nfvPPA*

The decreased rate of articulation for non-fluent individuals relative to more fluent individuals is consistent with previous research done by Wilson and colleagues (Wilson et al., 2010), who showed a significantly reduced maximum speech rate for nfvPPA relative to both lvPPA and svPPA. By definition,

articulation rate is determined by parameters of articulatory performance such as articulator displacement and articulator speed (Nip & Green, 2013). Reduced articulation rate in nfvPPA, therefore, reflects motor impairment as a primary source of nonfluency in this population. This result is also consistent with clinical descriptions that establish apraxia of speech—and less frequently, dysarthria—as co-morbid conditions associated with nfvPPA (Duffy et al., 2014). In the current sample, 10 out of 11 participants diagnosed with nfvPPA had apraxic speech characteristics as judged by a speech language pathologist, thus providing additional correlative support for slowed articulation rate as a reflection of a speech motor impairment in this group. Both apraxia of speech and dysarthria disrupt speech motor output, and a supporting body of research has established a connection between motor speech impairment and reduced articulation rate in other speech-disordered populations, including ALS (Yunusova et al., 2010) and multiple sclerosis (Rodgers, Tjaden, Feenaughty, Weinstock-Guttman, & Benedict, 2013).

Results of the current study showed no significant difference in articulation rate between lvPPA, svPPA, and normal controls. This result is consistent with the absence of a primary motor deficit among the more fluent subtypes, although a marginally significant difference in articulation rate between lvPPA and svPPA subgroups is also consistent with reports of secondary motor speech involvement in a minority of lvPPA individuals (Duffy et al., 2014).

*High diagnostic accuracy of quantitative speech measures improves subtype classification*

Results from the current investigation demonstrated higher diagnostic accuracy for speech and articulation rate measures compared to an existing clinician rating scale. This was especially true within a restricted, clinically relevant false positive range. Numeric cutoffs on rate measures enabled the highly sensitive and specific identification of nfvPPA relative to the more fluent subtypes and normal controls. Articulation rate, in particular, showed good overall accuracy in identifying nfvPPA, and good generalizability of accuracy results outside the training dataset. The trend toward improved classifier performance for quantitative rate measures (i.e., speech rate, articulation rate) suggests the potential for more accurate and reliable single-dimension (i.e., articulation rate) mapping of PPA subtypes, especially nfvPPA versus lvPPA, svPPA.

The importance of clinical subtyping within PPA has been well-established in previous research. One goal of this line of research is to test hypotheses about (1) the extent to which fluency characteristics among the three PPA variants can be attributed to one or multiple domains of spoken language production (i.e., motoric, syntactic, semantic) as well as (2) the clinicoanatomic validity of three PPA variants. More robust subtyping is particularly critical given the different probabilistic associations of the variants with Alzheimer's disease (AD) versus frontotemporal lobar degeneration (FTLD) pathology (e.g., Grossman, 2010). The use of language-based measures to reliably group PPA patients in accordance with probable underlying pathology is a clinically useful goal that links behavioral phenotypes with associated genotypes.

Successful subtyping algorithms have typically used two- or three-dimensional mapping approaches that consider multiple orthogonal language domains (Hu et al., 2010; Mesulam et al., 2009; Savage et al., 2013; Wilson et al., 2009), or a combination of linguistic and imaging features (Wilson et al., 2009). In theory, these multi-variable approaches are optimized when input variables are themselves optimal subtype differentiators. The improved diagnostic accuracy of quantitative rate measures (cf. clinician rating scales) in this study offers a more optimal approach to subtyping in the fluency domain, and suggests that fluency may be a useful input domain as part of a multi-dimensional subtyping approach. Besides improved diagnostic accuracy, quantitative rate measures can be automatically and reliably extracted from continuous speech samples (Green et al., 2004). In the clinical setting, an accurate and automatable fluency classifier system has the potential to be a valuable diagnostic tool.

**Chapter 3**. Quantification of motor speech impairment and its anatomic basis in primary progressive aphasia[3]

[3] A version on this chapter is currently under review: Cordella, C., Quimby, M., Touroutoglou, A., Brickhouse, M., Dickerson, B. C., & Green, J. R. (2018). Quantification of motor speech impairment and its anatomic basis in primary progressive aphasia.

Contributions of respective authors are as follows: Design and conceptualization of study (CC, BCD, JG); acquisition of data (CC, MQ); analysis and interpretation of data (CC, MB), drafting of manuscript for intellectual content (CC, AT, BCD, JG), editing of manuscript for intellectual content (BCD, JG).

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## Abstract

***Objective*:** To evaluate whether a quantitative speech measure is effective in identifying and monitoring motor speech impairment (MSI) in patients with primary progressive aphasia (PPA), and to investigate the neuroanatomical basis of MSI in PPA.

***Methods*:** Sixty-four patients with PPA were evaluated at baseline, with a subset (N=39) evaluated longitudinally. Articulation rate (AR), a quantitative measure derived from spontaneous speech, was measured at each timepoint. MRI was collected at baseline. Differences in baseline AR were assessed across PPA subtypes, separated by severity level. Linear mixed-effects models were conducted to assess groups differences across PPA subtypes in rate of decline in AR over a one-year period. Cortical thickness measured from baseline MRIs was used to test hypotheses about the relationship between cortical atrophy and MSI.

***Results*:** Baseline AR was reduced for patients with non-fluent variant PPA (nfvPPA), as compared to other PPA subtypes and controls, even in mild stages of disease. Longitudinal results showed a greater rate of decline in AR for the nfvPPA group over one year, as compared to logopenic and semantic variant subgroups. Reduced baseline AR was associated with cortical atrophy in left-hemisphere premotor and supplementary motor cortices.

***Conclusions*:** The AR measure is an effective quantitative index of MSI that detects MSI in mild disease stages and tracks decline in MSI longitudinally. The AR measure additionally demonstrates anatomic localization to motor-speech specific cortical regions. Our findings suggest that this quantitative measure of MSI might have utility in diagnostic evaluation and monitoring of motor speech impairments in PPA.

## Introduction

Motor speech impairment (MSI) is a key feature used to classify clinical variants of primary progressive aphasia (PPA), with apraxia of speech (AOS) as a diagnostic feature of non-fluent variant PPA (nfvPPA; Gorno-Tempini et al., 2011) and primary progressive apraxia of speech (PPAOS; Josephs et al., 2012) Beyond syndromic classification, MSI also suggests an underlying tauopathy (Deramecourt et al., 2010; Josephs, Duffy, et al., 2006; Josephs, Petersen, et al., 2006; Santos-Santos et al., 2016; Grossman, 2010, 2012) Thus, measurement of MSI in PPA is important for both assessment of clinical syndrome and prediction of likely neuropathology.

Despite its importance, assessment of MSI is challenging even for experienced clinicians, who rely largely on subjective ratings of speech features (Strand et al., 2014). The critical need for improved diagnostic and longitudinal speech markers has motivated research into quantitative measures of MSI. Much of the research aiming to develop quantitative measures of MSI in PPA has focused on reduced speech rate (Ash et al., 2013, 2009; Fraser et al., 2014; Sajjadi et al., 2012; Wilson et al., 2010), a core diagnostic feature of AOS and dysarthria (Duffy, 2013; Strand et al., 2014). However, speech rate is influenced by both motor (i.e., speed of articulator movement) and language (i.e., word-finding pauses) factors (Nip & Green, 2013), introducing a potential confound in a population with comorbid motor speech and aphasic deficits. By contrast, articulation rate—a measure of speaking rate exclusive of pauses—captures only motor-dependent factors, and may thus be a better indicator of MSI, but has received little study in PPA (Poole et al., 2017; Wilson et al., 2010).

In this study, we investigated whether articulation rate (1) sensitively detects MSI in mild PPA, (2) captures changes in MSI over time, and (3) correlates with cortical thickness in ROIs predicted to subserve motor speech function based on the Directions Into Velocities of Articulators (DIVA) model (Tourville & Guenther, 2011) of speech motor control.

## Methods

***Patients*.** Sixty-four patients meeting criteria for PPA were recruited from the Massachusetts General Hospital Frontotemporal Disorders (MGH FTD) Unit's PPA Longitudinal Cohort. Baseline clinical speech and language assessments were used to characterize patients and to subgroup them into non-fluent (nfvPPA; N=22), logopenic (lvPPA; N=23) and semantic (svPPA; N=19) variants, according to current consensus criteria (Gorno-Tempini et al., 2011). The Progressive Aphasia Severity Scale (PASS; Sapolsky et al., 2010)—an instrument used by clinicians to rate degree of impairment (0-3 interval scale) across ten primary speech and language domains—was used to index severity of impairment in specific speech/language domains (e.g., fluency, lexical retrieval, etc.). Overall severity of speech/language impairment was indexed using the Clinical Dementia Rating (CDR) supplemental Language box score (Morris, 1997). An individual's CDR Language score was then used to group patients into 'very mild' (CDR Language score = 0.5) and 'mild/moderate' (CDR Language score = 1, 2) severity subgroups for cross-sectional analyses. Baseline speech/language characteristics per PPA participant are reported in Supplementary Table A-1 (see Appendix). For longitudinal analyses, a subset (N=39; 15 nfvPPA, 14 lvPPA, 10 svPPA) of the sixty-four PPA patients was followed from initial visit to a reassessment approximately one-year after the initial visit.

MSI was assessed clinically for all patients and rated independently by a speech-language pathologist (MQ) and speech-language pathology clinical fellow (CC), with consensus ratings to resolve any discrepancies in individual ratings. Each rater listened to a blinded spontaneous speech sample as well as recorded diadochokinetic tasks (e.g., /puhpuhpuh/, /puhtuhkuh/), where available. Overall severity of clinical MSI was rated on a 0-3 scale (0=no impairment; 3=severe impairment). Operational definitions of clinical MSI at each severity interval are given in Supplementary Table A-2. Percentage agreement between the two raters was 91% ($\kappa = 0.91$). For patients rated by consensus as having any degree of MSI, a follow-up rating was done to characterize the type of MSI (e.g., AOS, dysarthria, unspecified) according to specified speech characteristics, (Strand et al., 2014) listed in Supplementary Table A-3. For nfvPPA patients only, overall MSI severity ratings were compared to PASS Syntax subdomain ratings to derive a

ratio indicating predominant impairment (i.e., primary motor speech impairment vs. primary agrammatism).

***Healthy controls*.** Two independent groups of age-matched healthy control participants were used for comparison to behavioral speech outcomes (i.e., articulation rate) and neuroimaging results, respectively. For the speech analyses, twenty age-matched healthy older controls were enrolled through the Speech and Feeding Disorders Lab at the MGH Institute of Health Professions (mean age = 65.6 yrs, SD = 8.3). Healthy control participants passed a hearing and cognitive screen, were native English speakers, and had no history of neurological injury or developmental speech/language disorder. For neuroimaging analyses, the healthy control sample included scans from 115 older adults who were native English speakers with no history of neurological or psychiatric disorder, recruited at MGH (mean age = 69.4 yrs, SD = 7.4).

***Standard Protocol Approvals, Registrations, and Patient Consents*.** The study was approved by the Partners Human Research Committee, the Institutional Review Board of Partners HealthCare. All participants provided written informed consent prior to being enrolled in the study.

***Speech data*.** Responses to the picnic scene picture description task of the Western Aphasia Battery – Revised (Kertesz, 2007) were collected at baseline from all 64 PPA patients, and from 20 healthy age-matched controls. Responses to the same task were also collected at each follow-up visit for the subset (N=39) of PPA patients followed longitudinally. Audio was recorded using a digital recorder (Olympus VN-702PC for PPA participants; Countryman B3P4FF05B for control participants) and processed using a MATLAB-based program, Speech Pause Analysis (SPA), which algorithmically estimates speech and pause segments in continuous speech (Green et al., 2004). Thresholds for the minimum duration of speech and pause events were set at 25 ms. and 100 ms. respectively. A manual syllable count was calculated for each spontaneous speech sample using orthographic transcription, as described previously (Cordella et al., 2017). Syllable counts and automatic SPA output regarding the frequency and duration of speech events were combined to derive articulation rate (= # syllables / total speech duration).

***Behavioral analysis*.** Cross-sectional speech data were analyzed using analysis of variance (ANOVA) tests to determine significant between-groups differences (nfvPPA, lvPPA, svPPA, HC) in baseline

articulation rate, with post-hoc tests (Tukey HSD) conducted as appropriate. Separate analyses were conducted for (1) severity collapsed across all CDR Language subscores and (2) within-groups analysis for 'very mild' (CDR Language subscore = 0.5) and 'mild/moderate' (CDR Language subscore = 1, 2) severity subgroups. Sensitivity and specificity were also calculated as measures of diagnostic accuracy of the articulation rate measure to detect motor-speech impaired nfvPPA patients, as compared to lvPPA, svPPA, and healthy controls. The *pROC* package (Robin et al., 2011) was used for sensitivity/specificity analyses, with the optimal threshold determined by the Youden statistic (Youden, 1950). To maximize interpretability of diagnostic accuracy results, the nfvPPA group was restricted to those patients with clinician-rated MSI (any severity level), necessitating the exclusion of the three nfvPPA patients that were judged by clinicians to have no MSI. Similarly, the lvPPA groups was restricted to those patients with no MSI; three lvPPA patients were excluded based on this criterion. No individuals were excluded from either the svPPA or healthy control groups.

To examine between-groups differences (PPA groups only) in longitudinal rates of change in articulation rate, linear mixed-effects models were conducted in R using the *lme4* package (Bates, Mächler, Bolker, & Walker, 2014). Articulation rate served as the dependent variable, with fixed effects of time, subgroup, and their interaction (i.e., time*subgroup). The nfvPPA group was mapped to the intercept to maximize interpretability and meaningfulness of model results. Subjects were modeled as a random effect to account for individual variability in the intercept and slope of each participant's performance. This model was chosen as the most parsimonious based on statistical comparisons of successively more complex models. An alternative model was run that included baseline severity and although severity was a significant predictor in the model overall, it did not alter significance for the primary interaction term of interest (time*subgroup); thus the more parsimonious model was selected.

***Structural MRI data analysis*.** For both patient and healthy control samples, MRI scans were collected on a 3T Magnetome Tim Trio system (Siemens Medical Systems, Erlangen, Germany), using a 20-channel phased-array head coil. 3D T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequences (repetition time/echo time/flip angle=2.5/3.5/7°, resolution=1 $mm^3$) were acquired

for all participants. All left-handed PPA participants were excluded from imaging analyses. Quantitative morphometric analysis of MRI data was performed using the *FreeSurfer* analysis software, version 6.0.(Fischl, 2004) Each structural volume underwent spatial and intensity normalization, skull stripping, and an automated segmentation of cerebral white matter (Dale, Fischl, & Sereno, 1999) to locate the gray–white boundary. Defects in the surface topology were corrected (Fischl, Liu, & Dale, 2001), and the gray–white boundary was deformed outward using an algorithm designed to obtain an explicit representation of the pial surface. Cortical thickness was then derived from the distance between the gray–white boundary and the pial surface across the entire cortical mantle (Fischl & Dale, 2000).

Based on study hypotheses, we obtained cortical thickness for motor speech related regions of interest (ROIs). ROIs were selected based on simulated predictions of the Directions Into Velocities of Articulators (DIVA) model (Tourville & Guenther, 2011), a well-established model of speech motor control that localizes speech motor processes to stereotactic regions of the brain. Because we hypothesize that our primary outcome variable—articulation rate—is a proxy measure for MSI in the PPA population, we focus on DIVA model regions associated with the two main aspects of motor speech function: motor planning/programming and motor execution of speech. These regions included the left hemisphere inferior frontal gyrus, premotor cortex, supplementary motor area, and ventral motor cortex (Bohland & Guenther, 2006; Peeva et al., 2010; Tourville & Guenther, 2011), areas shown to be associated with motor speech deficits, particularly AOS, in the broader motor speech disorders literature (Botha et al., 2018; Graff-Radford et al., 2014; Josephs et al., 2014, 2013; Utianski, Whitwell, et al., 2018). ROIs were derived using the *SpeechLabel* cortical labeling system (Cai et al., 2014), which allows for the parcellation of each cortical hemisphere into 63 ROIs, including fine-grained subdivision of motor speech-relevant regions. Twelve *SpeechLabel* ROIs were selected for analysis (Supplementary Figure A-1): dorsal pars opercularis (dIFo), ventral pars opercularis (vIFo), posterior inferior frontal sulcus (pIFs), ventral premotor cortex (vPMC), mid premotor cortex (midPMC), middle dorsal premotor cortex (mdPMC), posterior dorsal premotor cortex (pdPMC), ventral motor cortex (vMC), mid motor cortex (midMC), dorsal motor cortex (dMC), supplementary motor area (SMA), and pre-supplementary motor

area (preSMA). As a control region for non-specific effects, we selected the *SpeechLabel* occipital cortex (OC) region, which is not hypothesized to underlay motor speech impairment.

To identify overall between-group differences in cortical thickness in ROIs, we conducted a MANOVA, with univariate ANOVAs conducted as follow-up tests to determine between-groups differences per individual motor speech ROI.

***Brain-behavior analyses*.** To test whether atrophy in our hypothesized ROIs correlates with reduced articulation rate, we used Pearson correlation coefficients. For the ROIs showing overall correlational significance across all PPA subtypes, post-hoc correlations were conducted within subgroup to identify differential trends across subgroups. For all PPA participants, scan dates were matched to behavioral timepoints (mean time difference = 46 days, SD = 67).

To test the specificity of the relationship between atrophy and reduced articulation rate, post-hoc whole cortical analyses were performed. We used a generalized linear model (GLM) implemented in *FreeSurfer* to model the relationship between articulation rate and cortical thickness at each vertex point of the cortical surface. Articulation rate was modeled as the independent variable of variable of interest, with cortical thickness as the dependent variable across the whole PPA cohort. Because our primary hypothesis was unidirectional (i.e., reduced articulation rate is associated with cortical thinning in motor speech ROIs), a one-tailed GLM was performed. Given the small sample size and specific *a priori* hypotheses, a one-tailed statistical threshold of $p<.01$, uncorrected, was used for this analysis. We used this relatively liberal threshold with the consideration that if effects were found in speech motor control regions consistent with our ROI analysis but not in other cortical areas, this would provide strong support for the specificity of the effects. Results were visualized on an independent, template brain surface, smoothed at a full-width/half-maximum value of 15.

***Data Availability Statement*.** Anonymized data will be shared by request from any qualified investigator.

## Results

***Clinical results*.** Nineteen out of 22 nfvPPA patients (86%) were rated by consensus as having some degree of MSI (mean severity=1.07, SD = 1.0; Table 3.1). For 17/19 of these patients, MSI was judged to be of equal or greater predominance relative to a syntactic impairment. Of the 19 nfvPPA patients with MSI, eight were designated as having primary dysarthria, six as having primary AOS, and three as having both dysarthria and AOS; two nfvPPA patients were rated as having MSI of unspecified type, which in both cases included a mildly reduced rate and occasional sound distortions not uniquely attributable to either dysarthria or AOS. Three out of 23 lvPPA patients were also rated as having mild MSI of unspecified type, characterized in all three cases by false starts and mild articulatory groping. No svPPA patients were rated as having MSI. Diagnostic speech features used to determine the type of MSI are listed in Supplementary Table A-3, with detailed motor speech characteristics of the entire patient sample summarized in Supplementary Table A-4.

Group-level demographics and clinical characteristics are summarized in Table 3.1. No significant between-groups differences (nfvPPA, lvPPA, svPPA, HC) were observed in age, CDR language severity, sex, level of education, or mean inter-visit duration.

***Cross-sectional behavioral results*.** A 4-way ANOVA (nfvPPA, lvPPA, svPPA, HC) revealed between-groups differences ((F(3, 80)) = 29.46, $p<.001$) in baseline articulation rate, taking into account patients of all severity levels as part of a single, group-level analysis (Figure 3.1A). Specifically, articulation rate was reduced at initial visit for the nfvPPA subgroup (mean articulation rate = 2.88, SD = .81), as compared to lvPPA (mean articulation rate = 4.09, SD = .88; $p<.001$), svPPA (mean articulation rate = 4.46, SD = .66; $p<.001$), and HC (mean articulation rate = 4.9, SD = .49; $p<.001$). Baseline articulation rate also differentiated the lvPPA group from HC ($p<.01$).

In a second-level analysis in which patients were subgrouped by severity level, ANOVA results revealed between-groups differences (nfvPPA, lvPPA, svPPA) in baseline articulation rate within both 'very mild' (CDR Language subscore = 0.5; (F(3, 49)) = 20.68, $p<.001$) and 'mild/moderate' (CDR Language subscore = 1, 2; (F(3, 47)) = 34.04, $p<.001$) severity subgroups (Figure 3.1B). Within the 'very

mild' severity subgroup, nfvPPA patients had lower baseline articulation rate (mean = 3.29, SD = .61) as compared to lvPPA (mean articulation rate = 4.28, SD = .81; $p$=.001) and svPPA (mean articulation rate = 4.86, SD = .53; $p$<.001). Within the 'mild/moderate' severity subgroup, baseline articulation rate for nfvPPA (mean = 2.16, SD = .63) was likewise reduced relative to both lvPPA (mean articulation rate = 3.84, SD = .94; $p$<.001) and svPPA (mean articulation rate = 4.27, SD = .65; $p$<.001). There were no significant differences between lvPPA and svPPA groups within either 'very mild' or 'mild/moderate' severity subgroups. Both nfvPPA and lvPPA groups were significantly differentiable from healthy controls in 'very mild' (NC vs. nfvPPA: $p$<.001; NC vs. lvPPA: $p$=.03) and 'mild/moderate' (NC vs. nfvPPA: $p$<.001; NC vs. lvPPA: $p$<.001) severity subgroups. The svPPA group was differentiable, though only marginally so, from healthy controls in the 'mild/moderate' severity subgroup ($p$=.05); svPPA and HC groups were not significantly differentiable in the 'very mild' subgroup.

*Table 3.1. Summary demographic and clinical characteristics.*

| | PPA (N=64) | | | Healthy controls (HC) (N=20) |
|---|---|---|---|---|
| *Demographics* | **nfvPPA (N=22)** | **lvPPA (N=23)** | **svPPA (N=19)** | |
| Age at baseline, years (SD) | 68.5 (8.9) | 70.1 (6.8) | 67.3 (7.7) | 65.6 (8.3) |
| Female, n (%) | 12 (55) | 7 (30) | 13 (68) | 11 (55) |
| Education, years (SD) | 16.0 (2.9) | 16.6 (2.2) | 16.5 (1.9) | 15.7 (0.7) |
| Handedness (R:L), n | 21:1 | 20:3 | 15:4 | 16:4 |
| Mean disease duration[d], years (SD) | 1.3 (1.7) | 1.0 (1.7) | 0.75 (1.7) | -- |
| Patients with ≥ 2 visits, n (%) | 15 (68) | 14 (61) | 10 (53) | -- |
| Mean duration between first and last visit, days (SD) | 259 (87) | 280 (74) | 307 (98) | -- |
| | | | | |
| *Clinical characteristics* | | | | |
| Mean CDR Language subscore (SD) | 0.82 (0.5) | 0.80 (0.5) | 0.89 (0.4) | -- |
| n per CDR Language subscore (0.5; 1; 2) | 14;5;3 | 13;8;2 | 6;12;1 | -- |
| Mean PASS subdomain scores (SD) | | | | |
| Articulation | 0.93 (0.8)[b,c] | 0.02 (0.1)[a] | 0.00 (0.0)[a] | -- |
| Fluency | 0.84 (0.6)[b,c] | 0.48 (0.4)[a,c] | 0.08 (0.2)[a,b] | -- |
| Syntax | 0.73 (0.5)[c] | 0.50 (0.3) | 0.24 (0.3)[a] | -- |
| Word Retrieval | 0.55 (0.2)[b,c] | 0.98 (0.5)[a] | 0.87 (0.23)[a] | -- |
| Repetition | 0.40 (0.3)[b] | 0.87 (0.5)[a,c] | 0.28 (0.4)[b] | -- |
| Auditory Comprehension | 0.34 (0.4)[b] | 0.65 (0.3)[a] | 0.45 (0.5) | -- |
| Single Word Comprehension | 0.05 (0.2)[c] | 0.20 (0.3)[c] | 0.76 (0.3)[a,b] | -- |
| Reading | 0.39 (0.49)[c] | 0.74 (0.74) | 1.21 (1.05)[a] | -- |
| Writing | 0.73 (0.67) | 1.15 (0.9) | 0.97 (0.75) | -- |
| Functional Communication | 0.68 (0.50) | 0.67 (0.32) | 0.76 (0.59) | -- |
| Mean MSI severity score (SD) | 1.07 (1.0)[a,b] | 0.07 (0.2)[a] | 0.00 (0)[a] | -- |
| n per MSI severity score (0;0.5;1;2;3) | 3;9;4;3;3 | 20, 3, 0, 0, 0 | 19, 0, 0, 0, 0 | -- |
| MSI designation (AOS; Dysarthria; Comorbid AOS + Dysarthria; Unspecified)[e], n (%) | 9 (47); 11 (58); 3 (16); 2 (11) | 0;0;0;3 (13) | 0;0;0;0 | -- |
| Predominant impairment[f] ($ag^+$; $MSI^+$; ag=MSI), n (%) | 5 (23); 9 (41); 8 (36) | -- | -- | -- |

**CDR** = Clinical Dementia Rating; **PASS** = Progressive Aphasia Severity Score; **MSI** = Motor Speech Impairment. CDR Language subscore, PASS subdomain scores, and MSI severity scores are all clinician-rated measures scored on a common interval scale: 0 (no impairment), 0.5 (very mild impairment), 1 (mild impairment), 2 (moderate impairment), 3 (severe impairment).

Superscript letters denote post-hoc significance relative to the [a]nfvPPA [b]lvPPA, and [c]svPPA at $p<0.05$.

[d]Mean disease duration is calculated as the time (in years) between diagnosis date and initial study visit.

[e]Patients may be rated as having AOS, Dysarthria, or both (Comorbid AOS + Dysarthria). The same patient may therefore be included in multiple categories.

[f]Predominant impairment, rated for nfvPPA only, is derived from a ratio of MSI severity score: PASS Syntax subdomain score. **$ag^+$** (MSI < Syntax) indicates a predominant agrammatism; **$MSI^+$** (MSI > Syntax) indicates a predominant motor speech impairment; **ag=MSI** indicates impairments of equal predominance.

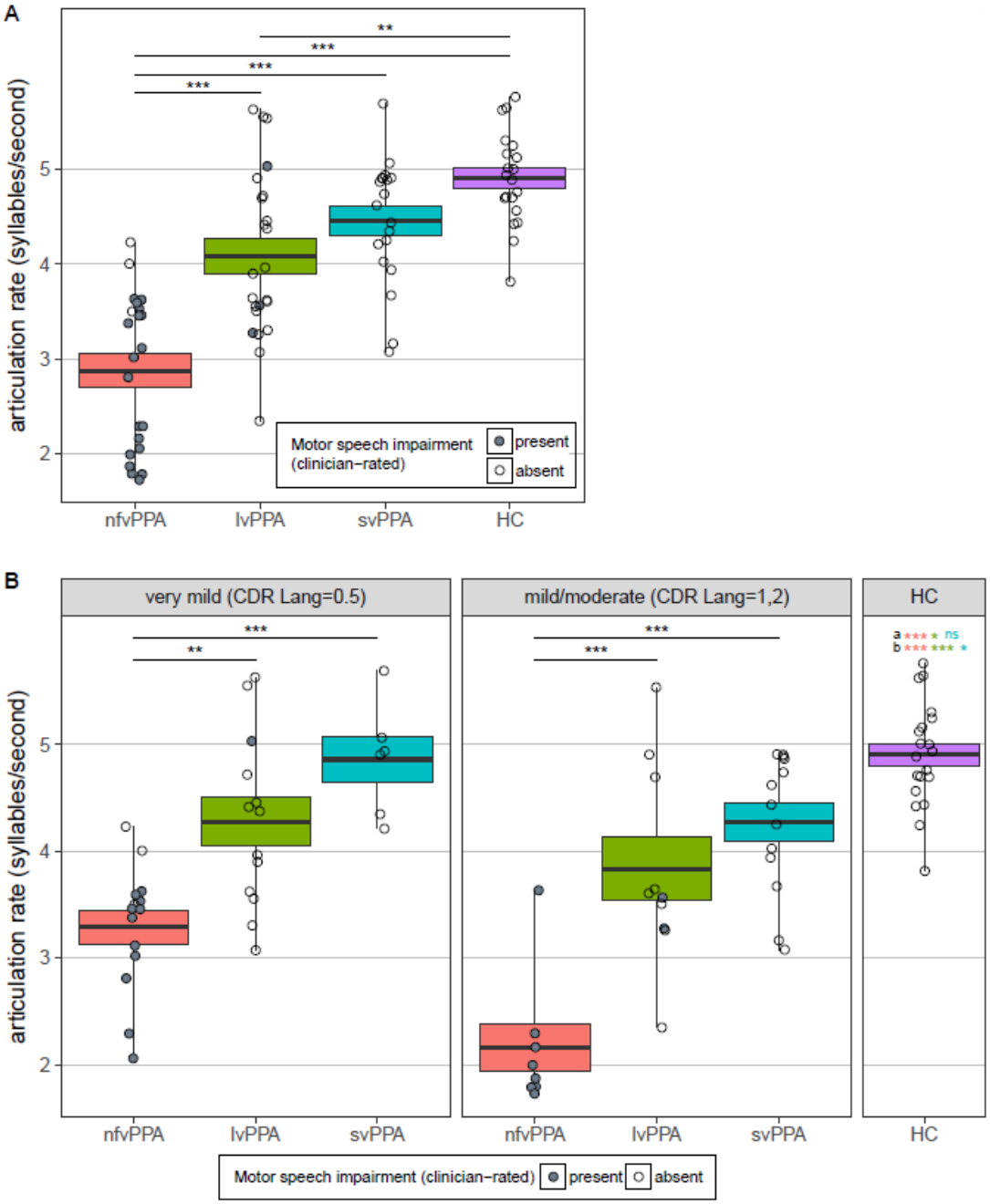



*Figure 3.1. Baseline articulation rate is reduced for nfvPPA patients*

**(A)** Articulation rate (AR) at baseline is significantly lower for nfvPPA compared to healthy controls (HC) and all other PPA subtypes. AR is also reduced for lvPPA compared to HC. Patients of all severity levels are included in this analysis. **(B)** Among patients of 'very mild' disease severity, AR at baseline is significantly lower for nfvPPA compared other PPA subtypes. AR is even more significantly reduced for patients of 'mild/moderate' severity. [a]Significant between-groups difference between HC, PPA subgroups in 'very mild' severity subgroup. Color-coding denotes significance for specific between-groups comparisons (pink=HC v. nfvPPA, green=HC v. lvPPA, teal= HC v. svPPA). [b]Significant between-groups difference between HC, PPA subgroups in 'mild/moderate' severity subgroup. Color-coding denotes significance for specific between-groups comparisons. ** p<.01, ***p<.001. Thick line = mean; boxes = SEM.

The sensitivity of the articulation rate measure for identifying nfvPPA relative to the pooled lvPPA, svPPA, and HC samples was 100% (95% CI 95, 100). The specificity of the articulation rate measure for that same comparison was 85% (95% CI 75, 93). The sensitivity and specificity of articulation rate for identifying nfvPPA within the 'very mild' severity subgroup (plus HC) were 100% (95% CI 91, 100) and 92% (95% CI 82, 100), respectively, indicating excellent overall diagnostic accuracy even in early stages of disease progression. Diagnostic accuracy measures—including binary subgroups comparisons (i.e., nfvPPA vs. lvPPA, nfvPPA vs. svPPA, nfvPPA vs. HC) per severity subgroup—are reported in full in Table 3.2.

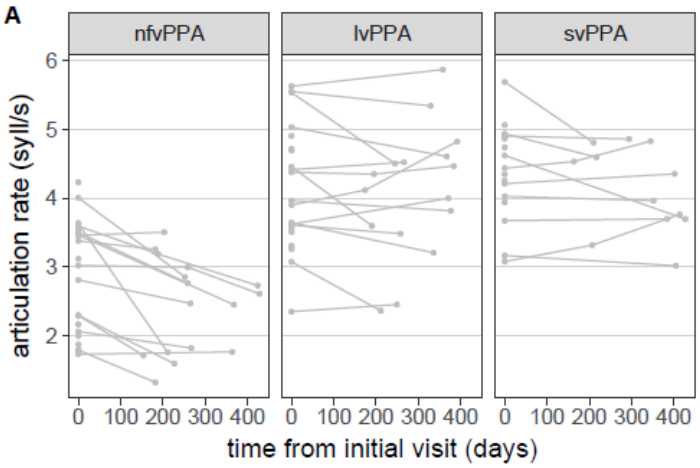
*Table 3.2. Diagnostic accuracy (sensitivity, specificity) of articulation rate measure*

| | Groups Comparison | | Sensitivity % (95% CI) | Specificity % (95% CI) | AR Threshold (syll/sec) |
|---|---|---|---|---|---|
| All severity subgroups (N=78) | nfvPPA[a] | all (lvPPA[b], svPPA, HC) | 100 (95, 100) | 85 (75, 93) | 3.64 |
| | nfvPPA[a] | lvPPA[b] | 95 (58, 100) | 85 (74, 92) | 3.60 |
| | | svPPA | 100 (100, 100) | 89 (74, 100) | 3.65 |
| | | NC | 100 (100, 100) | 100 (100, 100) | 3.73 |
| Very mild (CDR Lang=0.5) (N=46) | nfvPPA[a] | all (lvPPA[b], svPPA, HC) | 100 (91, 100) | 92 (82, 100) | 3.72 |
| | nfvPPA[a] | lvPPA[b] | 100 (73, 100) | 75 (50, 100) | 3.72 |
| | | svPPA | 100 (100, 100) | 100 (100, 100) | 3.92 |
| | | NC | 100 (100, 100) | 100 (100, 100) | 3.72 |
| Mild/moderate (CDR Lang=1,2) (N=49) | nfvPPA[a] | all (lvPPA[b], svPPA, HC) | 100 (88, 100) | 100 (78, 100) | 2.69 |
| | nfvPPA[a] | lvPPA[b] | 88 (63, 100) | 100 (75, 100) | 2.32 |
| | | svPPA | 100 (75, 100) | 100 (77, 100) | 2.73 |
| | | NC | 100 (100, 100) | 100 (100, 100) | 3.73 |

**Sensitivity** = True Positive (TP)/(TP +False Negative (FN)), **Specificity** = True Negative (TN)/(TN + False Positive (FP)). Articulation rate thresholds were calculated using Youden "best method" in pROC package (Robin et al., 2011).
[a]Excludes three nfvPPA participants who were rated by clinicians as not having any motor speech impairment.
[b]Excludes three lvPPA participants who were rated by clinicians as having motor speech impairment.

***Longitudinal behavioral results*.** LME results revealed a significant overall linear trend in articulation rate over time ($p$<.001) within the pooled PPA sample; fixed effect estimates for the time*subgroup interaction revealed differential rates of change in articulation rate within each of the PPA subgroups. Specifically, the linear decline in articulation rate over time was greater for the nfvPPA group compared to both the lvPPA ($p$=.004) and svPPA ($p$=.015) groups. The average annual rate of change in AR was –0.69 (95% CI –1.03, –0.38) among nfvPPA patients, –0.04 (95% CI –0.80, 0.72) for lvPPA patients, and

–0.14 (95% CI –0.92, 0.63) for svPPA patients. Figure 3.2 shows individual linear trends in AR, grouped by diagnostic subgroup (2A), averaged linear trends in AR per subgroup (2B), and LME model parameter estimates (2C).




**C**

| Parameter | Estimate | SE | *t* | *p* |
|---|---|---|---|---|
| *Articulation rate* | | | | |
| Intercept | 2.863 | 0.163 | 17.611 | <.0001 |
| lvPPA subgroup | 1.191 | 0.228 | 5.233 | <.0001 |
| svPPA subgroup | 1.582 | 0.239 | 6.620 | <.0001 |
| time | -0.002 | 0.0004 | -4.355 | <.0001 |
| lvPPA x time | 0.002 | 0.0006 | 3.042 | .004 |
| svPPA x time | 0.002 | 0.0006 | 2.530 | .015 |

*Figure 3.2. Articulation rate declines more rapidly for nfvPPA patients over a one-year period*

Longitudinal data collected for a subset (N=39) of PPA patients reveals a significantly more rapid decline in articulation rate for nfvPPA compared to lvPPA, svPPA. **(A)** Individual data points at baseline and (where available) at follow-up visit, separated by subgroup. Connected lines show individual trends. **(B)** Subgroup trends in articulation rate as a function of time, based on LME model output. Solid line = mean group slope; dashed line = 95% CI of mean group slope. **(C)** LME results demonstrate significant main effects of subgroup, time and time*subgroup interaction.

***Imaging results.*** MANOVA results revealed between groups (nfvPPA, lvPPA, svPPA, HC) differences in cortical thickness in hypothesis-driven ROIs ($F(3,148) = 2.35$, $p<.001$). Compared to healthy controls, the nfvPPA group exhibited thinner cortex for a majority of motor speech ROIs, specifically regions of the premotor cortex (vPMC, midPMC, pdPMC, mdPMC), supplementary motor area (SMA, pre-SMA), inferior frontal gyrus (vIFo, dIFo, pIFs), and a single subregion of the motor cortex (midMC). There were no significant group differences in cortical thicknesses of ventral and dorsal motor cortex (vMC, dMC) ROIs, or in the control region selected from the occipital cortex (OC). Between-groups comparisons across all groups for each ROI are reported in Table 3.3.

*Table 3.3. Cortical thickness by subgroup in each motor speech ROI*

| ROI | *p* | nfvPPA (N=15) | lvPPA (N=10) | svPPA (N=12) | HC (N=115) |
|---|---|---|---|---|---|
| *Left premotor cortex* | | | | | |
| vPMC | **<.001** | 2.29 ± 0.18[d] | 2.31 ± 0.14[d] | 2.43 ± 0.19 | 2.49 ± 0.15[a,b] |
| midPMC | **<.001** | 2.03 ± 0.26[c,d] | 2.02 ± 0.13[c,d] | 2.28 ± 0.24[a,b] | 2.33 ± 0.16[a,b] |
| pdPMC | **<.001** | 2.33 ± 0.24[d] | 2.30 ± 0.20[d] | 2.43 ± 0.21 | 2.50 ± 0.17[a,b] |
| mdPMC | **<.001** | 2.30 ± 0.22[d] | 2.31 ± 0.20[d] | 2.50 ± 0.28 | 2.59 ± 0.17[a,b] |
| *Supplementary motor area (SMA)* | | | | | |
| SMA | **<.001** | 2.39 ± 0.16[d] | 2.39 ± 0.23[d] | 2.55 ± 0.24 | 2.58 ± 0.19[a,b] |
| pre-SMA | **<.001** | 2.32 ± 0.16[c,d] | 2.45 ± 0.17 | 2.55 ± 0.23[a] | 2.59 ± 0.21[a] |
| *Left motor cortex* | | | | | |
| vMC | .164 | 2.38 ± 0.25 | 2.36 ± 0.26 | 2.45 ± 0.14 | 2.48 ± 0.22 |
| midMC | **<.001** | 2.17 ± 0.30[d] | 2.14 ± 0.21[d] | 2.29 ± 0.23 | 2.37 ± 0.20[a,b] |
| dMC | **.029** | 2.25 ± 0.24 | 2.18 ± 0.32 | 2.27 ± 0.24 | 2.35 ± 0.19 |
| *Left inferior frontal gyrus* | | | | | |
| vIFo | **<.001** | 2.19 ± 0.24[d] | 2.35 ± 0.22 | 2.28 ± 0.22 | 2.42 ± 0.17[a] |
| dIFo | **<.001** | 2.26 ± 0.23[d] | 2.36 ± 0.18 | 2.42 ± 0.20 | 2.48 ± 0.18[a] |
| pIFs | **<.001** | 2.06 ± 0.23[d] | 2.09 ± 0.12[d] | 2.20 ± 0.11 | 2.23 ± 0.14[a,b] |
| *Occipital cortex* (control region) | **.213** | 2.01 ± 0.10 | 1.94 ± 0.11 | 2.01 ± 0.11 | 1.96 ± 0.12 |

**HC** = Healthy controls. *p*-value refers to overall between-groups significance in articulation rate per ROI. Superscript letters denote post-hoc significance relative to the [a]nfvPPA [b]lvPPA [c]svPPA and [d]NC at $p<0.05$.

Brain-behavior analyses showed that atrophy in motor speech ROIs correlated with reduced articulation rate. Specifically, articulation rate correlated with cortical thickness in vPMC ($r(35)=.384$, $p=.019$), midPMC ($r(35)=.389$, $p=.017$), mdPMC ($r(35)=.340$, $p=.039$), SMA ($r(35)=.375$, $p=.022$), and pre-SMA ($r(35)=.504$, $p=.001$). Correlations between articulation rate and cortical thickness in the remaining hypothesized motor speech ROIs—including the pdPMC, vMC, midMC, dMC, vIFo, dIFo,

and pIFs— were also positive, but did not reach the threshold for statistical significance. There was no relationship between articulation rate and cortical thickness in the occipital cortex region employed as a control ROI (r(35)=.011, *p*=.950). Figure 3.3 depicts the strength of correlation between articulation rate and the *a priori* motor speech ROIs (3.3A). Figure 3.3B shows articulation rate plotted against cortical thickness for each ROI showing overall significance, using pooled subject data (nfvPPA, lvPPA, svPPA). Additional correlation analyses (following up on overall pooled subjects results) show within-group trends that mirror trends of pooled subject data (3.3C), particularly for the nfvPPA group, although small sample sizes within each subgroup limit these analyses and the likelihood of detecting statistical significance.

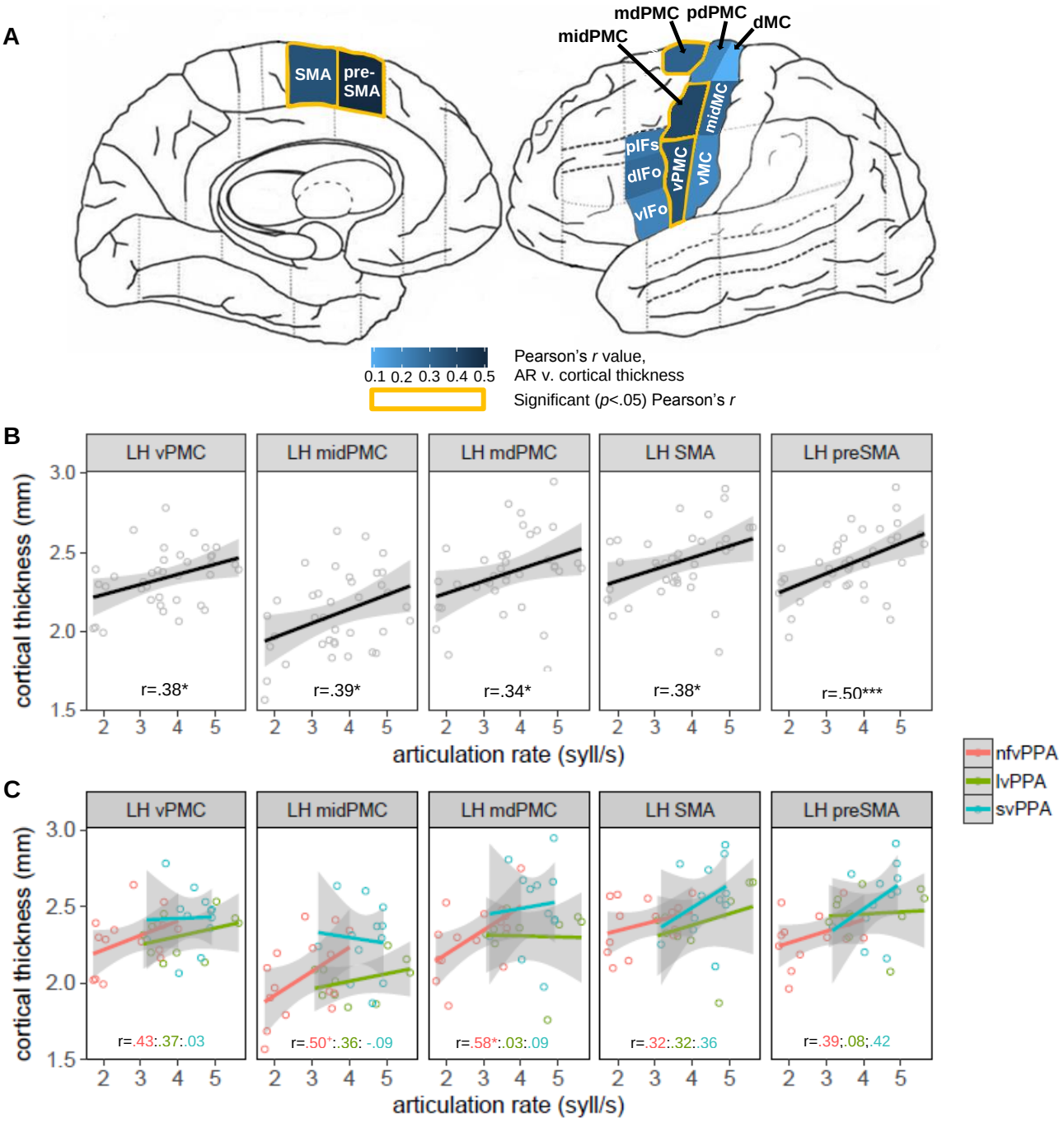



*Figure 3.3. Slower articulation rate is correlated with thinner cortex in select motor speech ROIs*

Strength of correlations between articulation rate and supplementary motor and premotor ROIs is greater than with inferior frontal or motor cortex ROIs. **(A)** Pearson's r values are shown per ROI, along with significant (p<.05) correlations. **(B)** Scatterplot showing relationship between articulation rate and cortical thickness using pooled subgroup data for each ROI returning overall group significance. **(C)** Scatterplot showing relationship between articulation rate and cortical thickness using separate subgroup (nfvPPA, lvPPA, svPPA) data for each ROI returning overall group significance. For **(B)** and **(C)**, open dots denote individual data, solid lines = linear group/subgroup trend, gray shaded region = 95% CI. *p<.05, **p<.01. +p<.1

A final set of analyses characterized the anatomical and behavioral specificity of these findings. Results of the whole-cortex GLM analysis revealed an association ($p$<.01) between reduced articulation rate at baseline and cortical atrophy with a left-lateralized, regionally specific localization that included the premotor and middle motor cortex, and medially in the supplementary motor area. A similar, weaker association was observed in corresponding right-hemisphere regions. Crucially, the whole-cortex GLM revealed no significant association between reduced articulation rate and cortical thinning in any regions outside premotor and supplementary motor areas and an isolated portion of the motor cortex, suggesting a high degree of regional specificity for the articulation rate measure (Figure 3.4).

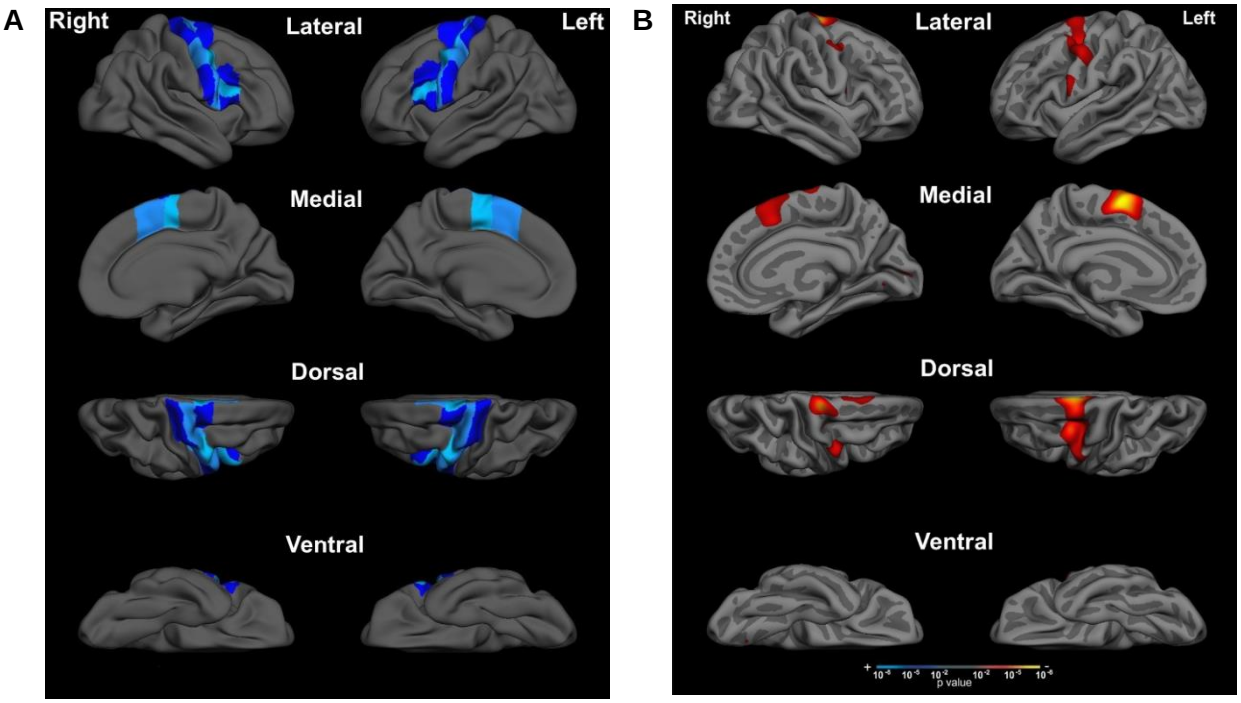



*Figure 3.4. Reduced articulation rate is associated with premotor and supplementary motor cortical atrophy*

**(A)** Motor speech ROIs mapped onto a template brain surface, for comparison to whole cortical surface results **(B)** Whole cortical surface GLM analysis demonstrates an association with cortical thinning in premotor and supplementary motor areas and reduced articulation rate at baseline within the pooled group of PPA patients. This association was stronger in left-hemisphere regions, as compared to corresponding right-hemisphere regions. A $p$<0.01, one-tailed significance threshold was used for this analysis. Results are visualized on an independent, template brain surface, smoothed at a full-width/half-maximum value of 15.

## Discussion

We found that articulation rate is an effective quantitative behavioral marker of MSI in PPA, both in measuring baseline MSI in mild stages of disease as well as in measuring decline in motor speech function over time. Reduced articulation rate is associated with cortical atrophy in specific hypothesized regions predicted to subserve motor speech based on the DIVA model of motor speech control, reinforcing the biological validity of this model and of this quantitative behavioral speech measure.

### *Articulation rate as an objective and effective measure of MSI*

Although MSI is widely discussed in the PPA literature in terms of its importance in determining diagnostic subgroups (Croot et al., 2012; Gorno-Tempini et al., 2011; Josephs et al., 2012), there remains little guidance on how to effectively assess MSI. Several recent studies focused on the predictive value of motor speech characteristics have acknowledged the need for objective, quantifiable measures of MSI (Santos-Santos et al., 2016). Results from the current study suggest that articulation rate could be one such proxy for a variety of types of MSI in a PPA population. Specifically, the articulation rate measure differentiated a motor speech impaired nfvPPA group from non-motor speech impaired subgroups in even the mildest stages of disease. Reduced speaking rate is a core diagnostic feature for both AOS and dysarthria, and is also a core feature of the newly defined prosodic subtype of PPAOS (Utianski, Duffy, et al., 2018). Thus, the reliable quantification of reduced rate of speech, and its ability to sensitively detect even very mild MSI, holds promise for improved diagnosis of motor speech subtypes in PPA.

Besides diagnostic utility, results of the current study suggest that the articulation rate measure may be responsive to change and, thus, useful for clinical monitoring. In a group of nfvPPA patients whose motor speech function is known clinically to decline over time (Whitwell, Weigand, et al., 2017), the articulation rate measure provided quantitative substantiation of motor speech decline—significantly different from trajectories of non-motor speech impaired subgroups—within a relatively short period of one year. This result adds to the emerging body of literature that has used baseline motor speech characteristics to track and predict the rate of decline in a PPA population (Whitwell, Weigand, et al., 2017). Reliable monitoring of subtle declines in motor speech function holds great clinical value for

providers seeking to advise their patients on topics such as advance planning for augmentative and alternative communication (AAC). The ability to detect subtle changes in motor speech function is also likely to become increasingly important as more tauopathy-focused clinical trials emerge that require reliable behavioral endpoints to measures clinically meaningful effects of therapeutic agents on motor speech function.

*Improved anatomic localization of MSI using the articulation rate measure*

Oftentimes, a single behavioral speech or language measure can in fact reflect multiple, related cognitive and/or motor processes. In the speech domain, rate is one such measure that reflects not only motor speech function (i.e., speed/displacement of articulators) but also higher-level language and cognitive processes. Articulation rate, by contrast, is a more specific proxy for MSI alone. Imaging results from the current study support the regional specificity of the articulation measure: reduced articulation rate was associated with cortical thinning in regions important for speech motor planning and programming, including the pre-motor cortex (PMC) and supplementary motor area (SMA). The associations we found between MSI and the anatomical integrity of the PMC and SMA are highly consistent with previously published results (Basilakos, Rorden, Bonilha, Moser, & Fridriksson, 2015; Utianski, Whitwell, et al., 2018; Whitwell et al., 2013); however, additional regions found to be anatomic correlates of MSI in several of these prior studies—for instance the posterior inferior frontal lobe (Rohrer, Rossor, & Warren, 2010), supramarginal gyrus (Wilson et al., 2010), and anterior insula (Ogar et al., 2007)—were not found to be significantly correlated with reduced articulation rate in the current study. We hypothesize that this result of regional specificity for the AR measure reflects the fact that it is a more direct proxy of motor speech impairment, not confounded by higher-level language contributions. This finding is in line with results from a prior study in the post-stroke literature showing a dissociation between motor speech-specific, as compared to language-specific, lesion patterns (Basilakos et al., 2015). In the progressive aphasia literature, a similar dissociation in atrophy patterns has also been demonstrated, primarily with regard to PPAOS (Josephs, Duffy, et al., 2006; Utianski, Whitwell, et al., 2018; Whitwell, Duffy, et al., 2017).

*Anatomic localization of MSI provides confirmatory evidence for theoretical model of speech motor control*

In this study, application of a theoretically-grounded model of speech motor control—the DIVA model—allowed for a selection of ROIs that the model predicts to be associated with specific sub-processes of speech motor control, including motor planning/programming as well as motor execution. In the DIVA model, early planning/programming of syllables is localized to left premotor cortex, with later stage execution of the motor plan localized to ventral motor cortex; left supplementary motor area is involved with speech initiation and is therefore also crucial for speech motor control.

The DIVA model also offers a framework in which to interpret results of the current study. Specifically, we conclude that because reduced articulation rate correlates with thinning in premotor and supplementary motor cortices, more so than primary motor cortex, reduced rate in nfvPPA likely reflects a predominant motor planning/programming (cf. motor execution) disorder. This interpretation is consistent with recent meta-analyses that have reported a higher incidence of AOS (a motor planning/programming disorder) compared to dysarthria (a motor execution disorder) in nfvPPA and PPAOS (Poole et al., 2017). Relating observed anatomic abnormalities to underlying mechanisms of impairment, as predicted by a powerful model of motor speech control, is useful not only for interpreting structural imaging results as reported in this study, but also for functional imaging and tau-PET imaging that together, will provide a clearer elucidation of motor speech impairment in PPA.

*Limitations of the current study*

An important limitation of the current study centers on the grouping of nfvPPA participants. In line with current consensus criteria, we opted for a maximally inclusive nfvPPA group that includes individuals with either syntactic deficits or motor speech impairment. Although clinician ratings demonstrated that the vast majority (86%) of individuals in the nfvPPA group had some degree of motor speech impairment, it is possible that separating the group based on predominant impairment (motor speech vs. syntactic) may reveal differential subgroup patterns for the articulation rate measure; this type of follow-up analysis should be considered for future studies with larger sample sizes.

A second limitation of the current study is that our brain-behavior analyses were focused only on cortical thickness as a preliminary test of select DIVA model predictions. We did not investigate either subcortical structures or white matter degeneration, both of which have been shown in prior work to be affected in motor speech impaired populations (Josephs et al., 2014; Santos-Santos et al., 2016). The limiting of imaging analyses to cortical grey matter may be one reason we found imaging evidence for a primary planning/programming disorder despite clinical characterizations of several nfvPPA patients as primarily dysarthric. It is possible that more detailed investigation of subcortical structures as well as white matter tracts would reveal a more widespread atrophy pattern that would better account for the motor execution, in addition to planning/programming, deficits.

**Chapter 4.** Acoustic and kinematic assessment of motor speech impairment in patients with suspected 4-Repeat (4R) tauopathies: A pilot study[4]

[4] This chapter is currently in prep: Cordella, C., Eshghi, M., Getchell, K., Jakkam, R., Dickerson, B. C., & Green, J. R. (2018). Acoustic and kinematic assessment of motor speech impairment in patients with suspected 4-Repeat (4R) tauopathies: A pilot study.

Contributions of respective authors are as follows: Design and conceptualization of study (CC, JG); acquisition of data (CC, KG); analysis and interpretation of data (CC, ME, RJ, KG), drafting of manuscript for intellectual content (CC, JG), editing of manuscript for intellectual content (BCD, JG).

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## Abstract

***Objective*:** To use acoustic and kinematic speech measures to characterize type of motor speech impairment—AOS versus dysarthria—in individuals with 4R tauopathy-associated syndromes, including non-fluent variant primary progressive aphasia (nfvPPA), corticobasal syndrome (CBS) and progressive supranuclear palsy syndrome (PSP-S).

***Methods*:** Thirteen patient participants were recruited and stratified into two groups: (1) a motor-speech impaired group of individuals with nfvPPA, CBS, or PSP and suspected 4RT pathology ("MSI+") and (2) a non-motor-speech impaired group of individuals with lvPPA ("MSI−"). Ten healthy, age-matched controls also participated in the study. Participants completed a battery of speech tasks, including diadochokinesis (DDK), maximum phonation, CVC and multisyllabic word repetition, and picture description. Fifteen acoustic and kinematic measures were derived, and individual scores were Z-transformed. Quantitative speech measures were grouped into feature categories ("AOS features", "dysarthria features", "shared features"). A principal components analysis was conducted to investigate the relative contributions of quantitative features. In addition to quantitative speech measures, two certified speech-language pathologists (SLPs) made independent ratings of motor speech impairment and a standardized measure of intelligibility was also obtained.

***Results*:** Quantitative speech measures were generally in concordance with independent clinician ratings of motor speech impairment severity, and higher quantitative speech Z-scores (i.e., more disordered) were associated with reduced intelligibility. Hypothesis-driven groupings of quantitative measures differentiated predominantly apraxic from predominantly dysarthric presentations within the MSI+ group. PCA results provided additional evidence for differential profiles of motor speech impairment in the MSI+ group; heterogeneity across individuals is explained in large part by varying levels of overall severity—captured by the shared feature variable group—and degree of apraxia severity, as measured by the AOS feature variable group.

***Conclusions*:** Quantitative features appeared to capture the heterogeneity of MSI in the 4RT group in terms of both overall severity and subtype of MSI. Results also suggest the potential for better specificity of quantitative measures compared to clinician ratings. Taken together, our findings motivate further investigation into quantitative measures as a way to differentiate between AOS and dysarthria, as well to capture comorbidity.

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## Introduction

Four-repeat tauopathies (4RT) are a subclass of tauopathies characterized by the accumulation of a type of abnormal tau protein containing four repeats in the microtubule binding domain (Dickson, Kouri, Murray, & Josephs, 2011). Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are the most common of the 4RT pathologies (Josephs et al., 2011). The clinical syndromes that are associated with the 4RT pathologies are complex (Josephs et al., 2011; Kouri, Whitwell, Josephs, Rademakers, & Dickson, 2011). CBD and PSP pathology, for example, can manifest as a variety of clinical syndromes including corticobasal syndrome (CBS), progressive supranuclear palsy syndrome (PSP-S), non-fluent variant primary progressive aphasia (nfvPPA), or primary progressive apraxia of speech (PPAOS; Josephs et al., 2006; Olney, Spina, & Miller, 2017). Moreover, research has shown that CBS is a common clinical presentation of PSP pathology (Ling et al., 2010), as is PSP syndrome in the case of underlying CBD pathology (Dickson et al., 2011). Associative links between pathology and syndrome have been particularly difficult to establish for nfvPPA because the clinical syndrome is associated with multiple tauopathies: CBD, PSP, as well as Pick's disease (a 3-Repeat tauopathy) (Grossman, 2012; Rohrer et al., 2010). Therefore, for all tauopathy-associated syndromes—but perhaps in particular for the nfvPPA group—it is valuable to identify specific clinical signs that may relate more reliably to one underlying pathology or the other. Behavioral phenotyping based on clinical signs remains the primary means of pre-mortem diagnosis of 4RT-associated syndromes since pathological diagnoses can only be confirmed at autopsy. This diagnostic challenge makes research into reliable, potentially diagnostic clinical signs critical in this population, especially as targeted, protein-specific clinical trials emerge.

Motor speech impairment is one clinical sign that has been cited in previous literature to be an early indicator of tau-positive pathology, and of 4RT specifically (Josephs, 2008; Montembeault, Brambati, Gorno-Tempini, & Migliaccio, 2018; Ogar, Dronkers, Brambati, Miller, & Gorno-Tempini, 2007; Santos-Santos et al., 2016). In clinical settings, motor speech impairments are often dichotomously classified as an apraxia of speech (AOS) or a dysarthria, with the former characterized by speech

symptoms consistent with problems with planning or programming of speech movements and the latter by speech symptoms consistent with weakness, dyscoordination or paresis of the speech musculature. Prior research suggests that the type of motor speech impairment may vary depending on the presenting tau-associated syndrome. There is, for example, overwhelming evidence for the salience of apraxia of speech in nfvPPA—indeed, it is one of two diagnostic inclusion criteria (Gorno-Tempini et al., 2011)—as well as mounting evidence of dysarthria and comorbid AOS/dysarthria presentations in the nfvPPA population (Caso et al., 2014; Duffy et al., 2014; Poole et al., 2017). Relatively less is known about motor speech impairments in CBS or PSP-S, although extant literature suggests AOS and orobuccal apraxia to be more common in CBS compared to PSP-S, whereas dysarthria is very common is PSP-S (Duffy et al., 2014).

Emerging research suggests that differentiating between the different motor speech subtypes will be informative for improving predictions of underlying pathology. A recent study looking at a group of nfvPPA patients with a post-mortem pathological diagnosis of PSP (nfv-PSP) or corticobasal degeneration (nfv-CBD) found early dysarthric features to be one factor useful for identifying nfv-PSP as compared nfv-CBD (Santos-Santos et al., 2016). This finding extends prior work associating motor speech impairment with tauopathies generally (Deramecourt et al., 2010; Duffy et al., 2014; Josephs et al., 2006), and suggests that specific motor speech impairments may be associated with different underlying pathologies within the 4RT family.

Despite the emerging evidence demonstrating the importance of more granular classification of motor speech impairments in 4RT-associated syndromes, differentiating AOS from dysarthria has been a long-standing scientific and clinical challenge (Weismer & Green, 2015). Perhaps the most significant barrier to differential diagnosis is the degree of overlap of diagnostic features. Although apraxia of speech and dysarthria appear to be associated with lesions or atrophy at different cortical and subcortical locations (Weismer & Green, 2015), surface speech features often cannot be attributed uniquely to a motor planning/ programming versus motor execution deficit (Maassen, Kent, Peters, & Lieshout, 2007). For instance, reduced rate of speech and sound distortions are the two most commonly cited diagnostic

inclusion features for AOS, as determined in a recent review of AOS-related research studies since 2007 (Allison et al., *in prep*). These same features, however, are also widely cited in the dysarthria literature as being common characteristics of most types of dysarthria (Clark et al., 2014; Darley, Aronson, & Brown, 1969; Duffy, 2013; Mefferd, Pattee, & Green, 2014; Rong, Yunusova, Wang, & Green, 2015). There is, therefore, a critical need to identify speech features that can be more reliably mapped to either apraxia of speech or dysarthria.

Another major barrier to differential diagnosis of motor speech impairment subtypes is the reliance on perceptual judgment of speech features. Diagnosis of motor speech impairment remains largely dependent on clinician judgment, which can be time-consuming, requires extensive rater training, and most importantly, is not always reliable (Kent, 1996). Prior research has demonstrated added value for quantitative speech measures for identification of motor speech impairment (Allison et al., 2017; Cordella et al., 2017; Green et al., 2018). Quantitative measures have included speech and articulation rate (Ash et al., 2013; Sajjadi et al., 2012; Wilson et al., 2009), pairwise variability for vowel duration (Ballard et al., 2014), vowel space metrics (Turner, Tjaden, & Weismer, 1995; Whitfield & Goberman, 2014), as well as kinematic measures of articulator movement (Green, Yunusova, et al., 2013; Rong, Loucks, Kim, & Hasegawa-Johnson, 2012; Yunusova et al., 2010). However, most prior work has focused on identifying motor speech impairment (cf. phonological or other higher-level language impairment), and not on distinguishing between motor speech subtypes. It remains unclear the extent to which quantitative features could be useful for characterizing AOS-specific versus dysarthria-specific impairments. It is also crucial to investigate whether diagnostic models based on hypothesis-driven groupings of quantitative speech measures (e.g., *a priori* multivariate models) may more accurately distinguish apraxia from dysarthria than do models based on a single quantitative speech measure.

In this pilot study, we focus on characterizing the type(s) of motor speech impairment as it occurs in 4RT-associated syndromes. We aim to (1) identify acoustic and kinematic markers of motor speech impairment in individuals with nfvPPA, CBS, and PSP, and compare these with clinician-rated measures for the same individuals, and (2) use these acoustic/kinematic measures to better characterize the type of

motor speech impairment (i.e., AOS, dysarthria), specifically by deriving individual profiles of motor speech impairment. We predict that the results will demonstrate heterogenous profiles of motor speech impairment within the 4RT syndrome group, wherein both apraxic and dysarthric features are present and characterizable using a combination of acoustic and kinematic measures.

## Methods

***Patients*.** Thirteen patient participants were recruited from the Massachusetts General Hospital Frontotemporal Disorders (MGH FTD) Unit. Patients met published diagnostic criteria for one of three conditions: primary progressive aphasia (Gorno-Tempini et al., 2011), corticobasal syndrome (CBS; Armstrong et al., 2013), or progressive supranuclear palsy (PSP; Höglinger et al., 2017). Patients diagnosed with primary progressive aphasia were subgrouped into non-fluent (nfvPPA) or logopenic (lvPPA) variants, according to current consensus criteria; semantic variant PPA (svPPA) patients were excluded from the current study. In accordance with study aims and hypotheses, patients diagnosed with nfvPPA, CBS, or PSP were grouped together to form an umbrella 4RT group. Patients in the 4RT group additionally had to show evidence of at least a mild motor speech impairment of any type, as determined by clinical speech assessment. The lvPPA group served as a disease control group, wherein patients demonstrated language, but not speech, impairment; additionally, the most common underlying pathology for this group of patients is Alzheimer's disease (AD) and not a tau-positive pathology. Thus, following patient stratification based on phenotype diagnosis and clinically-determined presence/absence of motor speech impairment, we had two resultant subgroups: (1) a motor-speech impaired group of individuals with nfvPPA, CBS, or PSP and suspected 4RT pathology (hereafter "MSI+") and (2) a non-motor-speech impaired group of individuals with lvPPA and suspected AD pathology (hereafter "MSI−").

All patient participants completed a short battery of standardized assessments aimed at characterizing general cognitive/language abilities. These assessments included the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) and Western Aphasia Battery-Revised (WAB-R; Kertesz, 2007). A reading screen (including the WAB Word-Picture Choice Matching and Boston Diagnostic

Aphasia Examination (BDAE) Basic Oral Word Reading) was administered to ensure patients' ability to comply with the experimental protocol. Demographic information is given for all participants in Table 4.1.

Additional information was collected to provide a more complete clinical characterization of the MSI+ group, including detailed information about clinical phenotype (e.g., PSP, CBS subtype), phenotype-specific rating scales, neurological exam results, and depression (Table 4.2).

*Table 4.1. Summary demographic and clinical characteristics*

| Group | Case | Clinical phenotype | Age (yrs) | Age of onset (yrs) | Gender | Education (yrs) | CDR | MoCA | WAB AQ |
|---|---|---|---|---|---|---|---|---|---|
| MSI– | 1 | lvPPA | 71 | 65-69 | F | 14 | 0.5 | 21 | 86.2 |
| | 2 | lvPPA | 68 | 65-69 | F | 12 | 0 | 23 | 83 |
| | 3 | lvPPA | 73 | 60-64 | M | 16 | 0.5 | 15 | 81.1 |
| | 4 | lvPPA | 71 | 65-69 | M | 16 | 0.5 | 19 | 81.4 |
| | 5 | lvPPA | 69 | 60-64 | M | 16 | 0.5 | 13 | 75.2 |
| | 6 | lvPPA | 72 | 65-69 | M | 12 | -- | 12 | 78.1 |
| MSI+ | 7 | nfvPPA | 70 | 65-69 | M | 19 | 0.5 | 26 | 96.6 |
| | 8 | nfvPPA | 70 | 65-69 | F | 14 | 0 | 22 | 81.2 |
| | 9 | CBS | 51 | 45-49 | F | 14 | 0.5 | 25 | 86.4 |
| | 10 | PSP | 61 | 55-59 | F | 14 | 0.5 | 22 | 93.8 |
| | 11 | nfvPPA | 76 | 70-74 | F | 16 | 0 | 25 | 89.1 |
| | 12 | PSP | 70 | 65-69 | M | 16 | 1 | 16 | 86.4 |
| | 13 | nfvPPA | 72 | 65-69 | F | 18 | 0.5 | 6 | 54.4 |

**MSI** = Motor Speech Impairment**; CDR** = (Global) Clinical Dementia Rating; **MoCA** = Montreal Cognitive Assessment, score range = 0 (worst) – 30 (best); WAB AQ = Western Aphasia Battery Aphasia Quotient, a weighted summary score indicating overall aphasia severity, score range = 0 (severe aphasia) – 100 (no aphasia). CDR is scored on a common interval scale: 0 (no impairment), 0.5 (very mild impairment), 1 (mild impairment), 2 (moderate impairment), 3 (severe impairment).

*Table 4.2. Detailed clinical characteristics for MSI+ group*

| Case | Clinical phenotype | Confidence in Phenotype dx (%) | CBD-FS Total | PSPRS Total | Depressed Mood (NACC B9) | Neuro Exam Findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cranial Nerves | Motor | Coord-ination | Reflex-es | Gait |
| 7 | nfvPPA | 90 | 4 | 2 | 0 | 0 | 1 | 1 | 1 | 1 |
| 8 | nfvPPA | 90 | 4 | 2 | 0 | 0 | 1 | 1 | 1 | 1 |
| 9 | CBS | 90 | 6 | 7 | 0 | 0 | 0 | 0 | 1 | 1 |
| 10 | PSP | 100 | 13 | 22 | 1 | 0 | 0 | 1 | 1 | 0 |
| 12 | PSP | 100 | 51 | 31 | 0 | 0 | 0 | 0 | 1 | 0 |
| 13 | nfvPPA | 90 | 16 | 15 | 1 | 0 | 0 | 0 | 1 | 1 |

**CBD-FS** = Corticobasal Degeneration Functional Rating Scale, score range 0 (no impairment) – 100 (severe impairment); **PSPRS** = Progressive Supranuclear Palsy Rating Scale, score range 0 (no impairment) – 100 (severe impairment). Depressed mood is indicated present (1) or absent (0), based on patient self-report as captured by the NACC B9 Form. For all neurological exam findings, 1=normal, 0=abnormal.
NB: Case 11 is not included in this summary because detailed clinical charactersitics were unavailable for this patient.

***Healthy controls*.** Ten healthy, age-matched control participants were recruited through the Massachusetts General Hospital Speech and Feeding Disorders Laboratory. All control participants spoke American English as their primary language, passed a hearing screen, and reported no history of neurological disorder.

***Speech tasks and elicitation procedure*.** All study participants participated in a standardized data collection protocol that included (a) a diadochokinesis (DDK) task in which participants were asked to produce maximum alternating motion rates (AMR, e.g., /bʌbʌbʌ/) and sequential motion rates (SMR, e.g., /bʌdʌgʌ/), (b) a maximum phonation task in which participants were asked to produce the sustained vowel /ah/ for as long as possible on a single breath, (c) a CVC repetition task in which participants are asked to produce 3 repetitions each of the tokens /bit/, /bæt/, and /but/, (d) a multisyllabic word repetition task—taken from the Sydney Language Battery (SYDBAT; Savage et al., 2013)—in which participants are asked to produce 2 repetitions each of a set of 5 words with a weak-strong stress pattern (<banana>, <computer>, <potato>, <pagoda>, <thermometer>) and 5 words with strong-weak stress pattern (<stethoscope>, <butterfly>, <bicycle>, <dinosaur>, <caterpillar>), (e) a passage reading task in which participants read the Bamboo Passage, and (e) a picture description task in which participants were asked to describe the WAB picnic scene.

For all tasks, participants interacted with a computerized platform (E-Prime; Psychology Software Tools) that visually presented each token (English orthography) and cued repetition of that token with a "go" light. For real-word tokens (e.g., CVC task), an accompanying picture was presented to facilitate repetition. For all tokens, prerecorded audio from a male speaker of American English was also played upon stimulus presentation, prior to initiation of the "go" signal. The time between token presentation and the "go" cue varied randomly from 800-1700 ms. Token order was randomized per trial block for tasks with multiple blocks (CVC, multisyllable word repetition). Participants' responses were recorded using a head-mounted microphone positioned approximately 5 cm from the mouth.

In addition to audio recording, speech biomechanic data was continuously recorded for all tasks using a 3D electromagnetic articulography (EMA) device (Wave, Northern Digital, Inc.). A sampling rate

of 100 Hz was used. Sensors were placed on the forehead center, middle jaw, upper lip, and lower lip using medical tape. Two additional sensors were placed on the tongue (midline): one on the tongue blade (1 cm posterior from tongue tip) and one on the tongue body (4 cm posterior from tongue tip). Tongue sensors were adhered using periodontal glue (PeriAcryl® High Viscosity; Figure 4.1). The head sensor was a 6-DOF sensor, while all remaining sensors were 5-DOF. To remove movement of the head, the articulatory positional data was expressed relative to the 6-DOF head sensor. The other sensors were only 5DOF.

*Figure 4.1. Experimental setup for data collection using electromagnetic articulography (EMA)*

***Acoustic data analysis.*** Acoustic analyses were conducted using *Praat* software. Six acoustically-derived measures were extracted from participants' speech samples, including (a) duration of sustained vowel, measured in ms from the maximum phonation task, (b) smoothed cepstral peak prominence, measured using a *Praat* script (Maryn & Weenink, 2015) run on audio from both the maximum phonation (middle 3 seconds) and passage reading tasks (first two sentences), (c) formant centralization ratio, measured using the formula given by Sapir et al. (Sapir, Ramig, Spielman, & Fox, 2010), (d) pairwise variability index for vowel duration, calculated by comparing the first versus second vowel durations of words tokens from the multisyllabic word repetition task, and (e) articulation rate, calculated as the number of syllables over duration of speaking time in the picture description task (Cordella et al., 2017). Detailed derivations—including relevant formulae—for each measure are listed in Table 4.3.

***Kinematic data analysis.*** Articulatory kinematic data was pre-processed using a custom MATLAB-based program, Speech Movement Analysis for Speech and Hearing research (SMASH; Green, Wang, &

Wilson, 2013). Files were trimmed to exclude all extraneous movement of articulators before or after task performance. For all kinematic analyses of this study, we focused exclusively on lip movement, as measured by the 3D Euclidean distance between the upper lip and lower lip. Five kinematic measures were derived, including (a) total duration, measured for both the AMR and SMR DDK tasks, (b) # cycles, for both AMR and SMR tasks, (c) rate, calculated as # cycles/duration, for AMR and SMR tasks, (d) spatiotemporal index (i.e., variability in movement trajectory across individual cycles), measured for the SMR task only, and (e) maximum velocity, measured for the AMR task only (Table 4.3). All kinematic measures were extracted using a MATLAB-based algorithmic approach developed by Rong and colleagues (Rong, Yunusova, Richburg, & Green, 2018). The algorithm first uses automatic peak detection to identify individual cycles, and then automatically extracts 21 lip movement features, including the five selected for analysis in this study.

*Table 4.3. Speech tasks and resultant quantitative speech measures*

| Task | Tokens | Measure | Abbrev. | Acoustic v. Kinematic | Derivation |
|---|---|---|---|---|---|
| DDK | AMR: /bʌbʌbʌ/ SMR: /bʌdʌgʌ/ | duration, AMR | dur_AMR | kinematic | Auto-extract all variables (Rong et al., 2018) |
| | | duration, SMR | dur_SMR | | |
| | | # cycles, AMR | ncyc_AMR | kinematic | |
| | | # cycles, SMR | ncyc_SMR | | |
| | | maximum velocity, AMR | vel_AMR | kinematic | |
| | | spatiotemporal index, SMR | sti_SMR | kinematic | |
| | | rate, AMR | rate_AMR | kinematic | Formula: $\frac{\#\ cycles}{total\ duration\ (s)}$ |
| | | rate, SMR | rate_SMR | | |
| | | rate, AMR v. SMR | rate_AMR.SMR | | Formula: $\frac{rate_{AMR}\ (cyc/s)}{rate_{SMR}\ (cyc/s)}$ |
| Maximum phonation | /ah/ | duration | dur_ah | acoustic | Auto-extract *duration* following manual TextGrid parsing (Podgornik, 2011) |
| | | cepstral peak prominence | cpp | acoustic | Auto-extract *cpps* (Maryn & Weenink, 2015) |
| CVC repetition | /bit/, /bæt/, /but/ (x3, randomized) | formant centralization ratio | fcr | acoustic | Auto-extract *F1*, *F2* following manual TextGrid parsing (McCloy, 2012/2018)<br>Formula: $\frac{F2_u + F2_{æ} + F1_i + F1_u}{F2_i + F1_{æ}}$ |
| Multisyllabic word repetition | Weak-strong: <banana>, <computer>, <potato>, <pagoda>, <thermometer> (x2, randomized) | pairwise variability index, weak-strong | pvi_ws | acoustic | Auto-extract *duration* following manual TextGrid parsing of first (V1), second vowel (V2) (Podgornik, 2011)<br>Formula: $\frac{duration_{V1}\ (ms)}{duration_{V2}\ (ms)}$ |
| | Strong-weak: <stethoscope>, <butterfly>, <bicycle>, <dinosaur>, <caterpillar> (x2, randomized) | pairwise variability index, strong-weak | pvi_sw | | |
| Picture description | WAB picnic scene picture | articulation rate | articrate | acoustic | Auto-extract *total speech duration*. Manual syllable count. (Green et al., 2004)<br>Formula: $\frac{\#\ syllables}{total\ speech\ duration\ (ms)}$ |

***Clinician ratings of motor speech impairment.*** Two certified speech-language pathologists (SLPs) made independent ratings of motor speech impairment for each study participant using an online survey created in RedCap (Harris et al., 2009). As part of the survey, raters completed a brief training module in which they listened to researcher-selected speech samples chosen to exemplify (a) apraxia of speech (AOS), (b) dysarthria, and (c) co-morbid AOS and dysarthria. Two exemplars were chosen per category, one representing a mild severity presentation and the second representing a moderate/severe presentation. Definitions of AOS and dysarthria (Duffy, 2013) were also provided as part of the training.

After completing the training, raters listened to blinded speech samples for each participant, including the picture description and DDK (AMR + SMR) tasks. Raters were asked to rate overall impairment on a 0-3 scale (0=no impairment; 0.5=questionable/very mild; 1=mild; 2=moderate; 3=severe), with operation definitions provided per severity category (Supplementary Table A-2). For any participants rated $\geq 0.5$, SLPs were asked to provide follow-up ratings indicating the type of motor speech impairment (apraxia of speech, dysarthria, co-morbid, other) and severity (questionable/very mild, mild, moderate, severe). SLPs also estimated intelligibility (0-100 using a visual analog scale) and indicated which speech features—selected from a researcher-provided list of common apraxia and dysarthria features—were most salient for that participant. Supplementary Figure A-2 shows the RedCap survey as it appeared to raters. Supplementary Figure A-3 shows the embedded branching logic in the survey. To address potential confounds of rater fatigue, participant order was randomized per rater. Inter- and intrarater reliability was also measured using a weighted Cohen's kappa statistic. To derive intrarater reliability, clinicians re-did ratings for four out of 23 total ratings (including both patients and healthy controls). Interrater agreement between the two raters was good for overall motor speech severity (weighted Cohen's $\kappa = 0.82$) and fair for AOS severity ($\kappa = 0.64$) and dysarthria severity ($\kappa = 0.60$). Intra-rater agreement was excellent overall (Rater 1 $\kappa = 0.89, 0.86, 1.00$, Rater 2 $\kappa = 1.00, 0.86, 1.00$ for overall motor speech, AOS, and dysarthria severity respectively).

In addition to clinician ratings of motor speech impairment, a standardized assessment of speech intelligibility, the Sentence Intelligibility Test (SIT; Yorkston, Beukelman, & Hakel, 2007), was also

administered to all study participants. The SIT consists of eleven randomly-generated, minimally contextually predictable sentences ranging from 5 to 15 words per sentence. A naïve listener (research assistant) listened to the recorded audio of the SIT and transcribed what she heard using English orthography. Scores on the SIT were then derived, expressed as a percentage of words correct.

***Variable grouping and analyses.*** Because we hypothesize heterogenous profiles of motor speech impairment in the MSI+ group, and in consideration of the small N pilot sample, our analyses focused on characterizing individual patients. We first grouped the fifteen individual quantitative variables according to whether they capture speech deficits specific to AOS ("AOS features"), dysarthria ("dysarthria features"), or could plausibly reflect either ("shared features"). AOS features include those related to equal/excess stress patterns, movement variability, or difficulty with sound sequencing. Dysarthria features include those related to vowel space reduction, abnormal vocal quality, reduced articulator speed, or respiratory insufficiency. Shared features included more general indicators of motor speech impairment (e.g., slowed articulatory rate) not uniquely attributable to either AOS or dysarthria. Figure 4.2 illustrates the grouping schema for all quantitative variables.

All patients' individual scores were converted to Z-scores with reference to the healthy control mean and standard deviation (SD), for each of the fifteen variables. For variables known to vary significantly by gender, including formant and voice-related measures, the Z-score reference was the gender-matched healthy control mean/SD. All Z-scores were expressed as an absolute value in order to equate deviations from normal in either direction. For each individual, a |Z| mean was calculated per category (i.e., AOS, dysarthria, shared) by averaging |Z| scores of the component variables in that category. A mean |Z| score > 2—reflecting extreme ends (±2.5%) of the normal distribution—was the cutoff score used to determine presence/absence of overall motor speech impairment for each individual. The mean |Z| score for the shared feature category was correlated (Spearman's rho) with SIT intelligibility scores to assess the validity of the quantitative measures to capture overall severity of motor speech impairment. Clinician ratings of overall motor speech impairment were also correlated with SIT intelligibility scores for comparison.

In addition to deriving individual profiles of motor speech impairment, we used a data-driven approach, principal components analysis (PCA), to investigate the relative contributions of each quantitative feature toward explaining variance of speech performance in the heterogeneous MSI+ group. Individual raw scores per quantitative speech variable were entered into a PCA, implemented in R. Individual scores were standardized and centered as part of the PCA analysis, and individual orthogonal components were extracted. Factors with eigenvalues < 1 were excluded from results. Sample size adequacy was assessed using both Bartlett's test of sphericity and the Kaiser-Meyer-Olkin (KMO) measure.

**A**

| Measure | Abbrev. | Category |
|---|---|---|
| duration, AMR | dur_AMR | shared |
| duration, SMR | dur_SMR | shared |
| # cycles, AMR | ncyc_AMR | shared |
| # cycles, SMR | ncyc_SMR | shared |
| maximum velocity, AMR | vel_AMR | dysarthria |
| spatiotemporal index, SMR | sti_SMR | AOS |
| rate, AMR | rate_AMR | shared |
| rate, SMR | rate_SMR | shared |
| rate, AMR v. SMR | rate_AMR.SMR | AOS |
| duration | dur_ah | dysarthria |
| cepstral peak prominence | cpp | dysarthria |
| formant centralization ratio | fcr | dysarthria |
| pairwise variability index, weak-strong | pvi_ws | AOS |
| pairwise variability index, strong-weak | pvi_sw | AOS |
| articulation rate | articrate | shared |

**B**

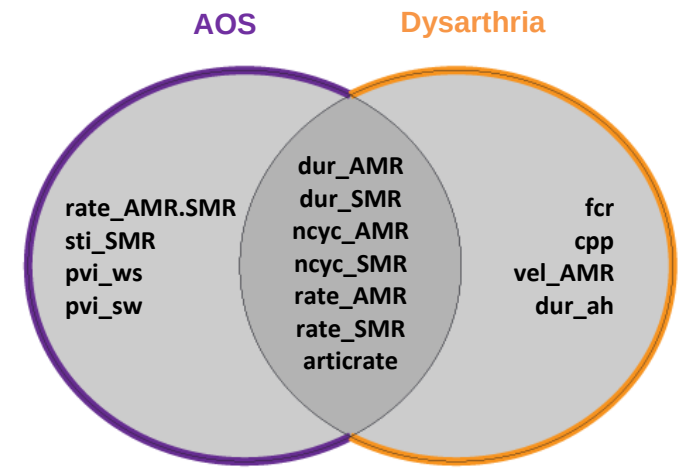


*Figure 4.2. Classification and grouping schema for quantitative speech measures*

## Results

***Clinician rating results.*** All seven patients in the MSI+ group were rated as having some degree of overall motor speech impairment based on the averaged scores of the two SLPs raters (mean severity = 1.61, range = 0.25-3, SD = 1.11). Six out of seven (86%) patients were designated as having some degree of AOS (mean severity = 0.93, range = 0-2, SD = 0.75); six out of seven (86%) were also identified as

having some degree of dysarthria (mean severity = 1.1, range = 0-3, SD = 1.31). Of the seven MSI+ patients, four were designated as having primary AOS (i.e., mean AOS severity > dysarthria severity) and three were designated as having primary dysarthria (i.e., mean dysarthria severity > AOS severity). In the primary AOS subgroup, the most commonly noted motor speech features were slowed rate (3/4 patients), inconsistent sound distortions (3/4 of patients), and syllable segmentation (3/4 patients). In the primary dysarthria group, the most commonly noted features were slowed rate, consistent sound distortions, and prosodic abnormalities (e.g., monopitch).

All seven patients in the MSI− group were also rated by clinicians as having some degree of overall motor speech impairment (mean severity = 0.58, range = .25-1, SD = 0.38). All seven patients in this groups were designated as apraxic (mean severity = 0.71, range = .25-1, SD = 0.53), primarily owing to clinician observation of sequencing difficulty (4/6 patients), speech initiation difficulty (3/6 patients), and inconsistent sound distortions (3/6 patients), and syllable segregation (3/6 patients). Additionally, two individuals in the MSI− were rated as questionably dysarthric.

Sentence Intelligibility Test (SIT) scores revealed reduced overall intelligibility, and considerable variability in intelligibility, for the MSI+ group (mean intelligibility = 65%, range = 2-97, SD = 42.79) as compared to the MSI− group (mean intelligibility = 98%, range = 95-100, SD = 1.86), whose overall intelligibility fell within normal limits. SIT scores and clinician-rated speech characteristics are reported in full per individual and group in Table 4.4.

*Table 4.4. Summary of clinician ratings of motor speech impairment*

| Group | Case | Clinical phenotype | SIT score (%) | Overall MSI severity | AOS severity | Dysarthria severity | (MSI+ only) AOS$^+$, Dys$^+$ | Salient motor speech features |
|---|---|---|---|---|---|---|---|---|
| MSI− | 1 | lvPPA | 100 | 0.75 | 1 | 0 | -- | slowed rate, syllable segregation, sequencing difficulty, speech initiation difficulty |
| | 2 | lvPPA | 99 | 0.25 | 0.25 | 0 | -- | syllable segregation |
| | 3 | lvPPA | 98 | 0.25 | 0.25 | 0 | -- | slowed rate, speech initiation difficulty |
| | 4 | lvPPA | 95 | 1 | 1 | 0.5 | -- | inconsistent sound distortions, sequencing difficulty |
| | 5 | lvPPA | 98 | 1 | 1.5 | 0.5 | -- | inconsistent sound distortions, sequencing difficulty, syllable segregation |
| | 6 | lvPPA | 96 | 0.25 | 0.25 | 0 | -- | inconsistent sound distortions, sequencing difficulty, speech initiation difficulty |
| Group Mean, MSI− | | | 98 | 0.58 | .71 | .17 | -- | Top features: **sequencing difficulty, speech initiation difficulty, inconsistent sound distortions, syllable segregation** |
| MSI+ | 7 | nfvPPA | 91 | 0.75 | 0.5 | 0.75 | Dys$^+$ | slowed rate, consistent sound distortions consistent, insufficient breath support, prosodic abnormalities |
| | 8 | nfvPPA | 94 | 1.5 | 1.5 | 0.5 | AOS$^+$ | slowed rate, inconsistent sound distortions, syllable segregation |
| | 9 | CBS | 71 | 2 | 2 | 0.25 | AOS$^+$ | slowed rate, inconsistent sound distortions, speech initiation difficulty, syllable segregation |
| | 10 | PSP | 97 | 0.25 | 0.25 | 0 | AOS$^+$ | sequencing difficulty, syllable segregation |
| | 11 | nfvPPA | 94 | 0.75 | 0.75 | 0.25 | AOS$^+$ | slowed rate, inconsistent sound distortions, speech initiation difficulty, voice quality |
| | 12 | PSP | 5 | 3 | 0 | 3 | Dys$^+$ | slowed rate, speech initiation difficulty, prosodic abnormalities |
| | 13 | nfvPPA | 2 | 3 | 1.5 | 3 | Dys$^+$ | slowed rate, consistent sound distortions, nasality, syllable segregation |
| Group Mean, MSI+ | | | 65 | 1.61 | .93 | 1.1 | -- | Top features: **slowed rate**, **sound distortions (inconsistent > consistent)** |

***Quantitative speech results.*** Analysis of the Z-score transformed quantitative speech measures (which were grouped into "shared", "AOS", and "dysarthria" features, as described in Methods) suggest greater levels of motor speech impairment—as measured by the mean |Z| of shared features—in the MSI+ group (mean |Z| = 2.85, range = 1.26-4.98, SD = 1.31) than in the MSI− group (mean |Z| = 1.26, range = 0.55-2.51, SD = 0.80). Six out seven patients in the MSI+ group were identified as being motor speech impaired, defined as having |Z| mean > 2 in the any feature category. AOS was the predominant impairment (i.e., mean |Z| AOS > mean |Z| dysarthria) for three of these patients, with syndromic diagnoses of nfvPPA (2 patients) and CBS (1 patient). Dysarthria was the predominant impairment for the remaining three patients, who had syndromic diagnoses of nfvPPA (2 patients) and PSP (1 patient). Within the MSI− group, only one patient was identified as being motor speech impaired. Table 4.5 summarizes the quantitative speech results per individual and group.

*Table 4.5. Summary of quantitative acoustic and kinematic speech measures*

| **Group** | **Case** | **Clinical phenotype** | **Mean \|Z\|, shared features** | **Mean \|Z\|, AOS features** | **Mean \|Z\|, dysarthria features** | **(MSI+ only)[a] $AOS^+$, $Dys^+$** |
|---|---|---|---|---|---|---|
| MSI− | 1 | lvPPA | 0.56 | 0.68 | 0.87 | -- |
| | 2 | lvPPA | 0.55 | 1.05 | 0.72 | -- |
| | 3 | lvPPA | 1.94 | 0.78 | 0.34 | -- |
| | 4 | lvPPA | 2.51 | 1.47 | 0.43 | -- |
| | 5 | lvPPA | 0.87 | 1.04 | 0.89 | -- |
| | 6 | lvPPA | 1.13 | 0.46 | 0.48 | -- |
| Group Mean, MSI− | | | 1.26 | 0.91 | 0.62 | -- |
| MSI+ | 7 | nfvPPA | 2.64 | 0.16 | 1.08 | $Dys^+$ |
| | 8 | nfvPPA | 3.34 | 2.67 | 2.23 | $AOS^+$ |
| | 9 | CBS | 1.31 | 3.43 | 1.98 | $AOS^+$ |
| | 10 | PSP | 1.26 | 0.32 | 1.20 | -- |
| | 11 | nfvPPA | 2.76 | 1.40 | 1.18 | $AOS^+$ |
| | 12 | PSP | 3.63 | 0.68 | 1.43 | $Dys^+$ |
| | 13 | nfvPPA | 4.98 | 3.18 | 8.38 | $Dys^+$ |
| Group Mean, MSI+ | | | 2.85 | 1.69 | 2.49 | -- |

[a]Predominant impairment, rated for the MSI+ group only, is derived from a ratio of Mean |Z|, AOS features: Mean |Z|, dysarthria features. **$AOS^+$** ($|Z|_{AOS} > |Z|_{dys}$) indicates predominant apraxic impairment; **$Dys^+$** ($|Z|_{dys} > |Z|_{AOS}$) indicates predominant dysarthric impairment.

***Comparing clinician ratings and quantitative results*.** There was strong agreement in predominant impairment as determined separately by clinician rating and quantitative feature Z-scores: six out of seven patients in the MSI+ group were classified into the same predominant impairment category (e.g., $AOS^{+}$, $Dys^{+}$) using these two different approaches. Within the MSI− group, only one patient was identified as being motor speech impaired using the quantitative feature approach, compared with seven patients identified by clinicians as having motor speech impairment. Individual motor speech profiles are shown in Figure 4.3, with summary clinician ratings superimposed per individual for comparison.

When clinician ratings and quantitative feature Z-scores (specifically mean |Z| for the shared feature category) were compared individually to standardized intelligibility scores from the SIT (Figure 4.4), results revealed a strong inverse relation to intelligibility for both measures ($r=-0.73$, $p < .001$ and -0.85 respectively, $p = .005$; Figure 4.4).

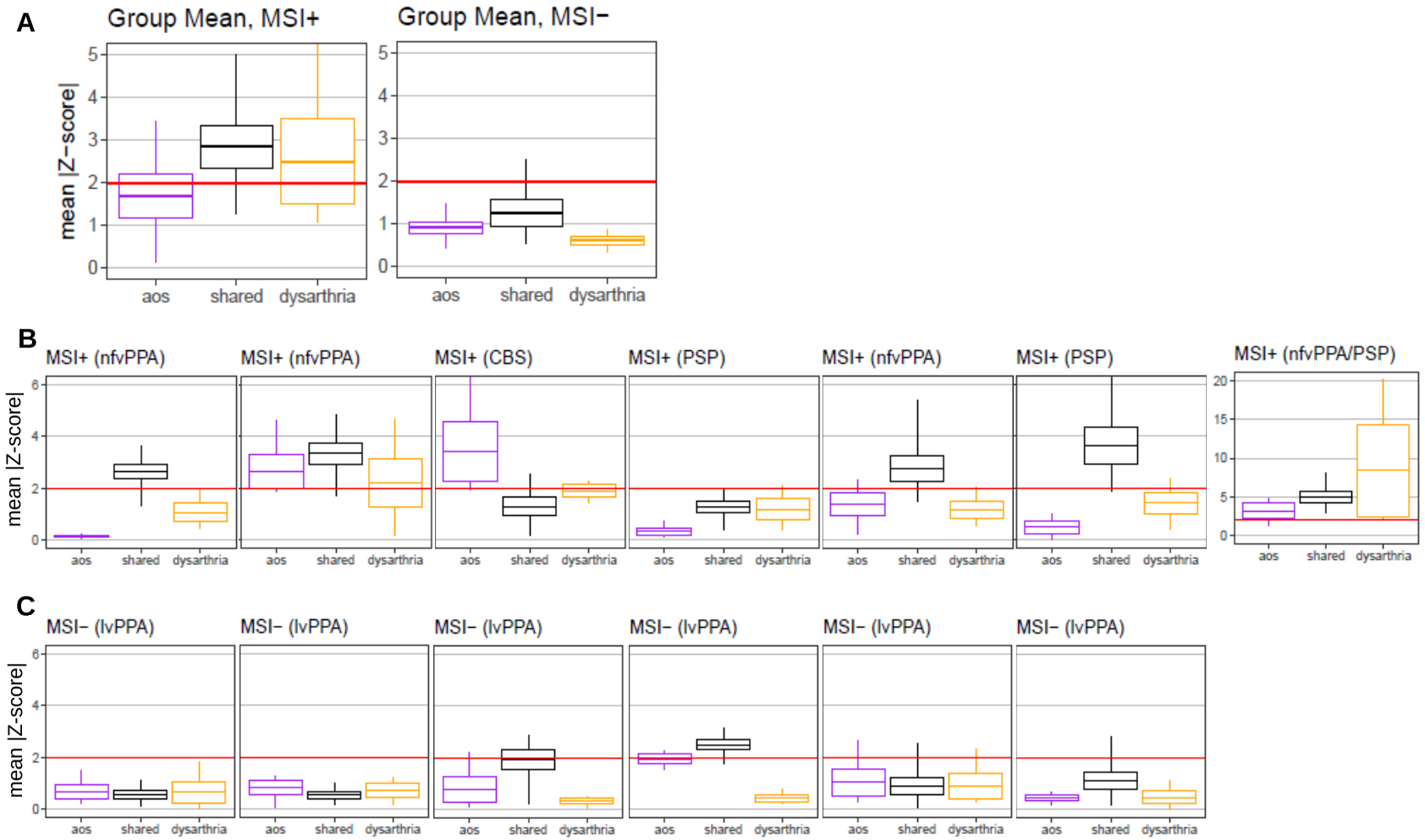


*Figure 4.3. Individual quantitative profiles of motor speech impairment show heterogeneity in MSI+ group, validate absence of impairment in MSI− group*

Individual profiles of motor speech impairment show dissociation between predominantly apraxic v. predominantly dysarthric presentation s in the MSI+ group. **(A)** Comparison of group means across different feature categories **(B)** Individual profiles, MSI+ group **(C)** Individual profiles, MSI− group. Solid red line drawn at |Z|=2 to indicate a cutoff for extreme values. Thick line = mean; boxes = SEM.

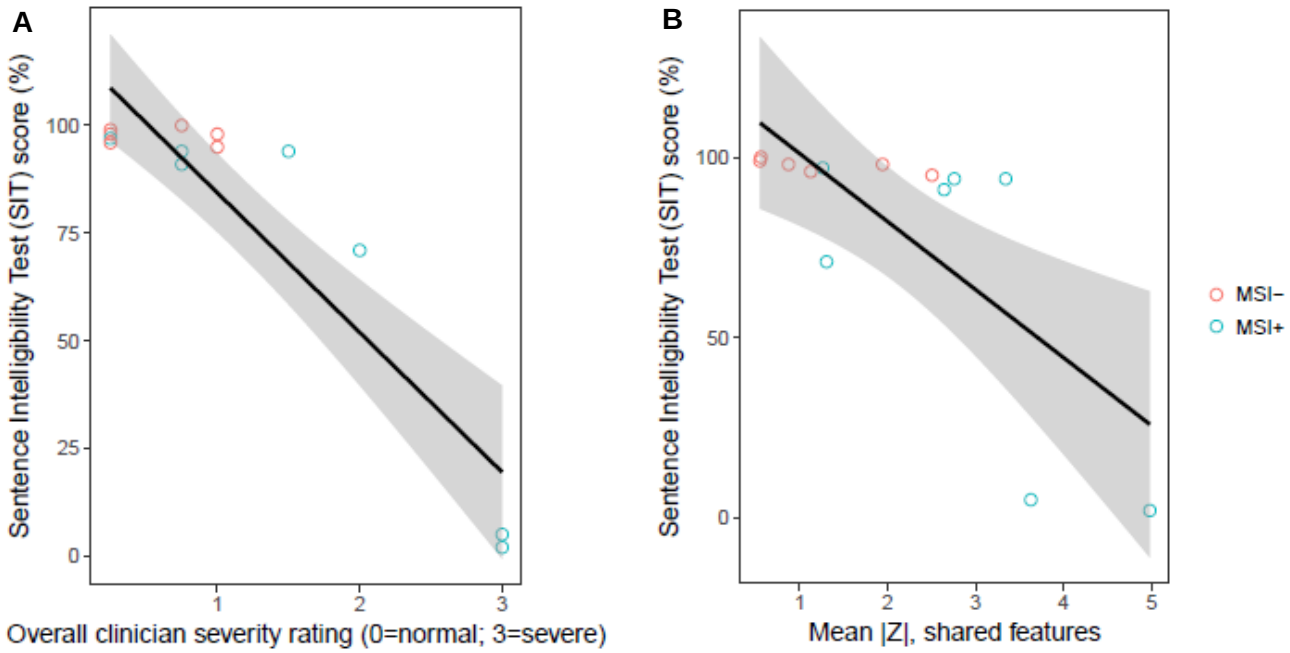


*Figure 4.4. Quantitative measures and clinician ratings of motor speech impairment are inversely correlated with intelligibility*

**(A)** Scatterplot showing relationship between clinician rating of overall motor speech severity and Sentence Intelligibility Test (SIT) score (%) using pooled subgroup data, **(B)** Scatterplot showing relationship between mean |Z| of shared quantitative features and SIT score (%) using pooled subgroup data. For **(A)** and **(B)**, open dots denote individual data, solid lines = linear group/subgroup trend, gray shaded region = 95% CI.

***Principal components analysis (PCA) results***. Statistical analysis of sample adequacy for PCA analysis revealed correlations between individual measures to be sufficient (Bartlett's test = 353.7, $p$ <.001), but the overall sample size to borderline adequate for PCA analysis (Keiser-Meyer-Olkin = 0.55). Therefore, we consider the following results exploratory. Following exclusion of PCA component factors with eigenvalues <1, four individual component factors resulted from PCA analysis, that together accounted for 78% of the total variance (Component 1: 49.55%, Component 2: 12.94%, Component 3: 7.99%, Component 4: 7.49%). We focus our analysis on the first two component factors (explaining 62.49% of the variance), as shown in Figure 4.5, with group and SIT intelligibility scores superimposed. For patients in the MSI+ group, case number is also displayed. We further investigate the loading onto each of these two component factors as a way of interpreting which of the quantitative measures are driving dispersion in the data. Figure 4.6 shows the top five measures that load onto Component 1 and 2, respectively. For Component 1 (C1), measures that load heavily are all shared features of motor speech impairment, and

thus we consider C1 to capture 'Overall Severity.' For Component 2 (C2), heavy loading measures include all four of the AOS features, as well as articulation rate (a shared feature). We thus consider C2 to capture 'AOS Severity.' In line with this interpretation of these two components, individuals with high Component 1 (e.g., Case 12) are the most severely motor speech impaired. Individuals with high Component 2 scores (e.g., Case 9) are the most severely apraxic, while those with low scores (e.g., Case 12) are severely dysarthric in the relative absence of apraxic features.

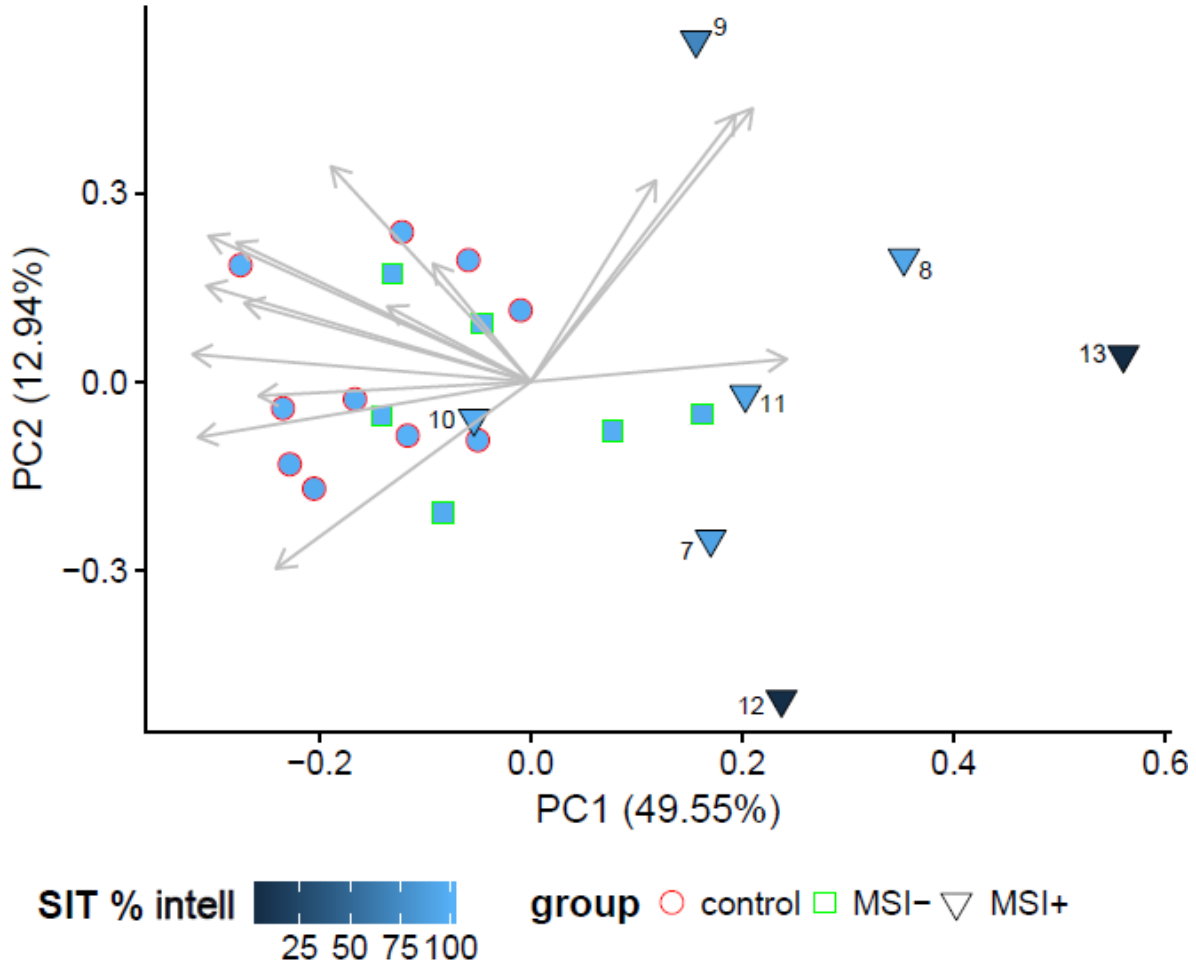


*Figure 4.5. PCA results show stratification of MSI+ patients and reflect within group heterogeneity in severity and speech features*

**PC1** = Component 1 (% Variance Explained); **PC2** = Component 2 (% Variance Explained). Gray arrows indicate individual loadings for each quantitative variable. Group membership connoted by shape and outline color, fill shaded based on Sentence Intelligibility Test (SIT) scores (%). For MSI+ group only, individual patients are indicated with Case # for cross-referencing purposes.

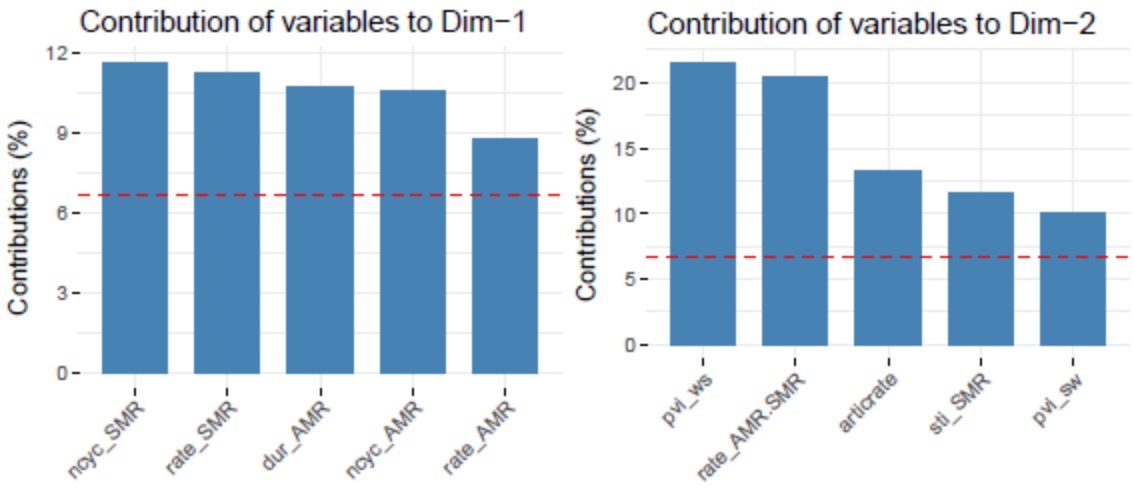


*Figure 4.6. Individual speech measures load differentially on Components 1 and 2, reflecting 'Overall Severity' (C1) and 'AOS Severity' (C2)*

**Dim-1** = Component 1; **Dim-2** = Component 2. Reference dashed red line indicates expected value (%) if all variable contributions were uniform.

## Discussion

In this exploratory study, we profiled quantitative and clinician-rated features of motor speech impairment in a 4RT, MSI+ group. Quantitative speech measures were generally in concordance with independent clinician ratings of motor speech impairment severity, and higher quantitative speech Z-scores (i.e., more disordered) were associated with reduced intelligibility. Moreover, results indicate that hypothesis-driven groupings of quantitative measures can effectively differentiate predominantly apraxic from predominantly dysarthric presentations within the MSI+ group. Results from an exploratory PCA analysis provide additional evidence for differential profiles of motor speech impairment in the MSI+ group; heterogeneity across individuals is explained in large part by varying levels of overall severity—captured by the shared feature variable group—and degree of apraxia severity, as measured by the AOS feature variable group.

*Quantitative speech measures differentiate speech from language impairment*.

Differentiating speech impairment from language impairment is a longstanding clinical challenge in populations with comorbid impairments, including many 4RT-associated syndromes (Josephs et al., 2012). Prior work in the PPA literature specifically has identified the challenge in differentiating

phonological impairment common in the lvPPA subgroup from apraxia of speech common in the nfvPPA subgroup because these two impairment types share common speech features (e.g., inconsistent sound distortions, difficulty sequencing sounds).

The clinician ratings findings further illustrate this challenge, as all six patients in the MSI− group were rated as being mildly motor speech impaired, and further subclassified as mildly apraxic by two experienced clinicians. By contrast, using a standard Z-score cutpoint ($Z \geq 2$) for the quantitative speech measures, only one of the six patients in the MSI− group was identified as motor speech impaired. This patient (Case 4) was also rated by clinicians as the most severely speech-impaired individual in the MSI− group, raising the possibility of a mixed lvPPA phenotype.

Both clinician ratings and quantitative speech measures appeared to effectively identify motor speech impairment in the MSI+ group. The presence of motor speech impairment was questionable for one of the seven MSI+ patients (Case 10) based on both the quantitative and clinician-based measures. For this patient, quantitative scores did not pass the threshold to constitute motor speech impairment. In addition, one of the SLPs assigned a normal speech rating. Overall, results suggest that both clinician speech ratings and quantitative speech measures have potential for high sensitivity in identifying motor speech impairment, but that quantitative measures appear more promising in terms of specificity (cf. phonological impairment).

*Acoustic and kinematic speech measures capture motor speech impairment severity*

Besides identifying the presence of motor speech impairment, it is important for a candidate measure to reliably capture the severity of that impairment in order to be useful for clinical staging or monitoring of disease progression. Results of the current study show that quantitative speech measures are related to independently-derived intelligibility scores (used here as a proxy for motor speech impairment severity) such that more extreme quantitative scores are correlated with reduced intelligibility. Though not unexpected, this result provides confirmatory evidence that quantitative measures of motor speech impairment are meaningfully and reliably related to a well-established perceptual construct of severity, namely intelligibility.

It is also interesting to note, however, the MSI+ individuals whose quantitative speech scores did not correlate well with intelligibility (i.e., outliers to the general trend). These cases appeared to follow two patterns where either (1) shared quantitative features did not capture the patients' specific and unique motor speech deficits, or (2) the patient was perceptibly motor speech impaired but highly intelligible. Case 9 is a good example of the first pattern, where quantitative measures revealed only a mild impairment based on shared features, but a moderate-severe impairment based on AOS-specific features. This finding suggests that although the shared features used in this study reflect impairments across a broad range of motor speech impairments including AOS and many dysarthria subtypes, they are not universal and may not account fully for atypical motor speech presentations. The clinician ratings shed light on Case 9: at least one rater indicated the possibility of a fluency disorder appearing alongside a more traditional AOS presentation, which has been previously documented in individuals with CBS (Silbergleit, Feit, & Silbergleit, 2009). Cases 7 and 11 are good examples of the second pattern wherein motor-speech impaired individuals are maintaining intelligibility. In both cases, clinician ratings agreed with quantitative results that motor speech impairment was present, although quantitative features identified a greater severity of motor speech impairment compared to clinician ratings. This finding supports the efficacy of quantitative speech measures for detecting speech changes prior to declines in intelligibility. It also suggests that the relationship between motor speech severity and intelligibility is likely not linear, and that small changes in severity may have little impact on intelligibility in mild stages but large effects in moderate-severe stages (Rong et al., 2015).

*Quantitative feature groupings dissociate to reveal heterogeneity in motor speech subtypes within the 4RT group*

A major aim of the current study was to profile the range of motor speech impairments in 4RT-associated syndromes to identify and distinguish between AOS and dysarthria. Results suggest that, within our small sample of patients, quantitative feature groupings (i.e., "shared", "AOS", "dysarthria") do reveal differential profiles of motor speech impairment, and can give clear indication of whether a particular patient is primarily apraxic versus dysarthric. For six out of seven patients, the designation of

predominant impairment agreed with clinician designation. For the remaining patient (Case 10), the disagreement was likely due to the fact that the motor speech impairment was very mild and therefore, difficult to subtype.

Results from the exploratory PCA analysis suggest that a data-driven approach—based on quantitative speech features and free of assumptions about group membership (i.e. MSI−, MSI+)—can capture heterogeneity of motor speech impairment in MSI+ group. Results also shed light on which specific features are accounting for such heterogeneity. We identified that the shared feature group appears to be a reliable proxy of overall severity, which explains much of the variability in our small sample. Moreover, AOS features further differentiate among MSI+ individuals, separating out individuals with more and less prominent apraxia features; those with less prominent apraxic features tend to be those with prominent dysarthria. Dysarthria-specific features do not dissociate as robustly and specifically, there appears to be overlap between the dysarthria and shared feature groupings. This likely reflects the fact that dysarthria subtypes are more varied and it is thus more difficult to identify a limited number of individual quantitative measures that capture the full range of dysarthric presentations. Additional work is required to elucidate the presence and characteristics of dysarthria in 4RT.

At this time, the literature on motor speech impairment in 4RT-associated syndromes is primarily focused on nfvPPA, with much less attention given to PSP-S and CBS. In the PPA literature, a separate subtype has been suggested to classify patients with sole or primary apraxia of speech (i.e., primary progressive apraxia of speech; PPAOS) and more recently, even subtypes of PPAOS have been introduced (Utianski, Duffy, et al., 2018). Therefore, our preliminary results identifying individuals as primarily apraxic or dysarthric—based on a clearly defined set of features—are potentially useful for better diagnostic subgrouping within motor speech phenotypes. They are also informative in terms of evaluating the limits of these predefined diagnostic categories, a point best illustrated by Case 7. Case 7 is an individual diagnosed with nfvPPA according to consensus criteria (Gorno-Tempini et al., 2011) but who could also be reasonably considered to have a motor speech only, and not aphasic (WAB AQ=96.6) presentation, thus making him eligible for a PPAOS diagnosis (Josephs et al., 2012). However, a look at

Case 7's individual motor speech profile, which is in agreement with clinician ratings, shows that he has dysarthria, and no evidence of apraxia. An open question remains then of how best to account for progressive motor speech prominent presentations that are characterized by primary dysarthria rather than AOS. In any case, fine-grained characterization of motor speech impairment is likely to be of considerable value toward the goal of more reliable motor speech phenotyping.

*Limitations*

The current study is only an exploratory pilot analysis of motor speech impairment subtypes across 4RT-associated syndromes. Our inclusion of individuals with varying syndrome diagnoses (i.e., nfvPPA, CBS, PSP-S), while allowing us the opportunity to explore heterogeneity in tau-related motor speech impairment, prevents us from making more definitive conclusions about which subtypes of motor speech impairment are more likely to occur in each of these syndromes. We are therefore restricted to analyses at the individual level. In the same vein, our data-driven analysis of quantitative measures is informative as a proof-of-concept of the potential for quantitative measures to differentiate among individuals with different types of motor speech impairment, but still requires validation of results with a much larger sample size for results to be considered more generalizable. Lastly, the addition of imaging or other biomarkers could provide evidence of biological validity of the hypothesis that there are different subtypes of motor speech impairment across 4RT-associated syndromes.

# **Chapter 5.** Discussion

In this dissertation, we have presented results from three studies that, together, demonstrate the added value of quantitative speech measures for identifying, monitoring and characterizing motor speech impairment in PPA and related 4 Repeat tauopathy-associated syndromes. Results from this dissertation suggest that quantitative measures can help differentiate speech from language impairment in a population with co-morbid deficits and furthermore, that these quantitative measures may be able to help differentiate between different types of motor speech impairment. Summary of the specific results of each of the three studies is summarized below (Table 5.1), followed by a general thematic discussion of results and their clinical relevance.

*Table 5.1. Research questions, aims and hypotheses for each study comprising the dissertation*

| | |
|---|---|
| **Chapter 2** | *Slowed articulation rate is a sensitive diagnostic marker for identifying non-fluent variant primary progressive aphasia*<br><br>*Research Question*: Can quantitative measures of speech fluency—specifically subcomponent measures of speech rate—differentiate PPA subtypes?<br><br>*Study Aims*: (1a) Compare diagnostic accuracy of quantitative v. clinician-rated measures of speech fluency; (1b) Identify quantitative measures of speech rate that best differentiate PPA subtypes, especially the non-fluent group (nfvPPA) from the more fluent groups (lvPPA, svPPA).<br><br>*Study Results*: Quantitative rate measures have higher diagnostic accuracy for identifying nfvPPA as compared to clinician-rated measures. Diagnostic accuracy was greatest for the articulation rate (AR) measure, suggesting that AR may be an effective indicator of motor speech impairment (MSI) in the nfvPPA population. |
| **Chapter 3** | *Quantification of motor speech impairment and its anatomic basis in primary progressive aphasia*<br><br>*Research Question*: Does the AR measure have potential for early identification and monitoring of motor speech impairment in PPA, and is it a biologically valid measure?<br><br>*Study Aims*: Assess in a PPA population whether the AR measure (2a) sensitively detects MSI in very mild stages of disease, (2b) captures changes in MSI over time, and (2c) correlates with cortical thickness in motor speech ROIs.<br><br>*Study Results*: The AR measure detects MSI with excellent sensitivity and good specificity, even in very mild disease stages, suggesting utility of the AR measure for early identification of MSI. The rate of decline in AR is significantly greater for the nfvPPA group over a one-year period, suggesting utility of AR for monitoring of disease progression. Reduced AR is associated with cortical thinning in motor speech ROIs—including the left premotor and supplementary motor cortices—suggesting biological validity of AR measure. |
| **Chapter 4** | *Acoustic and kinematic assessment of motor speech impairment in patients with suspected 4-Repeat (4R) tauopathies: A pilot study*<br><br>*Research Question*: Can a broader range of quantitative speech measures be combined to differentiate subtypes of MSI (AOS, dysarthria)?<br><br>*Study Aims*: (3a) Identify acoustic and kinematic markers (beyond articulation rate) of MSI in individuals with 4R tauopathy-associated syndromes (nfvPPA, CBS, PSP); (3b) characterize type of motor speech impairment (AOS, dysarthria) using acoustic/ kinematic measures to derive quantitative motor speech impairment profiles.<br><br>*Study Results*: Quantitative features capture the heterogeneity of MSI in the 4RT group in terms of both overall severity and subtype of MSI. Hypothesis-driven groupings of acoustic and kinematic speech measures effectively differentiate predominantly apraxic versus predominantly dysarthric presentations in the motor speech impaired (MSI+) 4RT group, suggesting potential for quantitative measures to differentiate between AOS and dysarthria, as well to capture comorbidity. |

*Quantitative measures differentiate speech from language impairment*

Differentiating speech and language impairment is crucial in a population with co-morbid deficits, particularly when subtype diagnoses depend on unique identification. Additionally, in the case of PPA and related syndromes, early identification of a motor speech impairment can predict underlying tauopathy (Josephs, Duffy, et al., 2006; Santos-Santos et al., 2016). Results from this dissertation add to the existing body of literature that suggests that quantitative measures may be useful for identifying motor speech impairment, particularly when this distinction is perceptually subtle and clinically challenging, as is the case in differentiating motor speech impairment in nfvPPA and phonological impairment in lvPPA. In this dissertation, we tested the diagnostic efficacy of quantitative speech measures. In the first two studies, we found that a measure of articulation rate (AR) was a more effective diagnostic marker for separating a motor speech impaired PPA subgroup (i.e., nfvPPA) from a language-impaired PPA subgroups (lvPPA, svPPA), and that it does so more accurately than did a clinician-based rating scale of speech fluency. We also demonstrate that AR was responsive to longitudinal declines in motor speech impairment in the nfvPPA group and provide anatomical imaging evidence for the observed dissociation between speech and language impairment. Specifically, reduced AR was correlated with cortical thinning in motor speech regions (e.g., premotor cortex, supplementary motor area, but not with regions associated with more general language function (e.g., Broca's area). Results of the third study, although preliminary, further support the use of quantitative features to uniquely identify motor speech impairment. This study showed that a broader range of quantitative speech features can be used to generate individual motor speech profiles that differ between motor speech impaired and non-motor speech impaired individuals; compared to clinician-ratings of motor speech impairment, quantitative measures were less likely to identify lvPPA individuals as motor speech impaired, whereas this was a common confusion for clinician raters owing to shared surface speech features (e.g., difficulty sequencing, inconsistent sound distortions).

*Quantitative speech measures have potential for differentiating types of motor speech impairment*

A secondary aim of the dissertation was to determine if quantitative features could be useful for identifying subtypes of motor speech impairment, namely AOS versus dysarthria. This is an important

distinction to be made in PPA and other 4RT-associated syndromes because of the evidence in the literature suggesting that specific, early-emerging speech symptoms may help to more reliably predict underlying pathology (Santos-Santos et al., 2016; Utianski, Duffy, et al., 2018). Results from the third study of the dissertation indicate that hypothesis-driven groupings of quantitative speech measures—representing "shared," "AOS," and "dysarthria" feature categories—can differentiate between individuals who have predominantly apraxic versus predominantly dysarthric speech symptoms. Data-driven exploratory results from this study suggest that shared features and AOS-specific features are particularly useful for explaining the heterogeneity of motor speech impairment in the group of individuals with 4RT-associated syndromes. Dysarthria-specific features appeared less robust for characterizing motor speech impairment in our analyses. This may be because our limited number of measures failed to capture the full range of dysarthric impairment in the MSI+ group; prior literature has noted the occurrence of different dysarthria subtypes (e.g., hypokinetic, flaccid) as well as mixed dysarthric subtypes in 4RT-associated syndromes (Duffy et al., 2014). Taken together, results from the third study suggest that quantitative speech measures may be useful for improved diagnostic subgrouping within motor speech phenotypes.

*Implications for assessment, monitoring and measurement of outcomes*

The reliable measurement of motor speech impairment using quantitative features has implications for diagnostic assessment and subtyping, clinical monitoring of progression, and development of speech motor outcome measures. In this dissertation, we have identified select quantitative speech features that can more objectively and reliably index motor speech impairment in PPA, and have demonstrated the added value of these quantitative features relative to clinician ratings. Such quantitative measures show promise for lessening the current reliance on clinician judgment as the diagnostic gold standard for motor speech impairment. We have also begun to identify which specific measures may be particularly robust for detecting both overall motor speech impairment as well as the specific type of motor speech impairment. Results can thus serve as a starting point for clinicians and researchers looking to operationalize the

measurement of motor speech impairment in a population with comorbid speech and language deficits.

Quantitative measures of motor speech impairment are useful not only for differential diagnosis of motor speech phenotypes but also for clinical monitoring of disease progression within motor speech impaired subgroups. Articulation rate is one such measure that has been explored in depth in this dissertation, with promising results. Identification of candidate measures provides a first step toward collecting more standardized, population-level information about clinical milestones to motor speech decline. Knowledge about population-level trajectories of decline is crucial for intervention planning on the part of clinicians and patients, including the introduction of alternative and augmentative communication. It is also critical to understand these typical trajectories in order to meaningfully interpret effects of speech therapy or drug intervention. Relatedly, as research into behavioral and pharmaceutical interventions grows, objective outcome measures of speech function are increasingly necessary to index intervention-related changes (Dickerson, 2011).

*Future directions*

Results of the current dissertation motivate further research into the use of quantitative speech features for the measurement of motor speech impairment. There appears to be particular value in relating objective speech features to autopsy-confirmed pathological diagnoses, such that more definitive conclusions can be reached regarding the relationship of early speech features to underlying histopathology. There is also a need for more rigorous evaluation of the candidate quantitative measures proposed in this dissertation. The diagnostic utility of these measures should be evaluated using data-driven approaches on a larger sample of individuals, with the aim of identifying a parsimonious set of tasks and measures that could serve as the basis of an objective motor speech assessment battery. Lastly, in order to make quantitative assessment of motor speech more clinically feasible, future research should attempt to maximize automation of speech measures and wherever possible, directly compare automated results with manual measurements.

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# Appendix

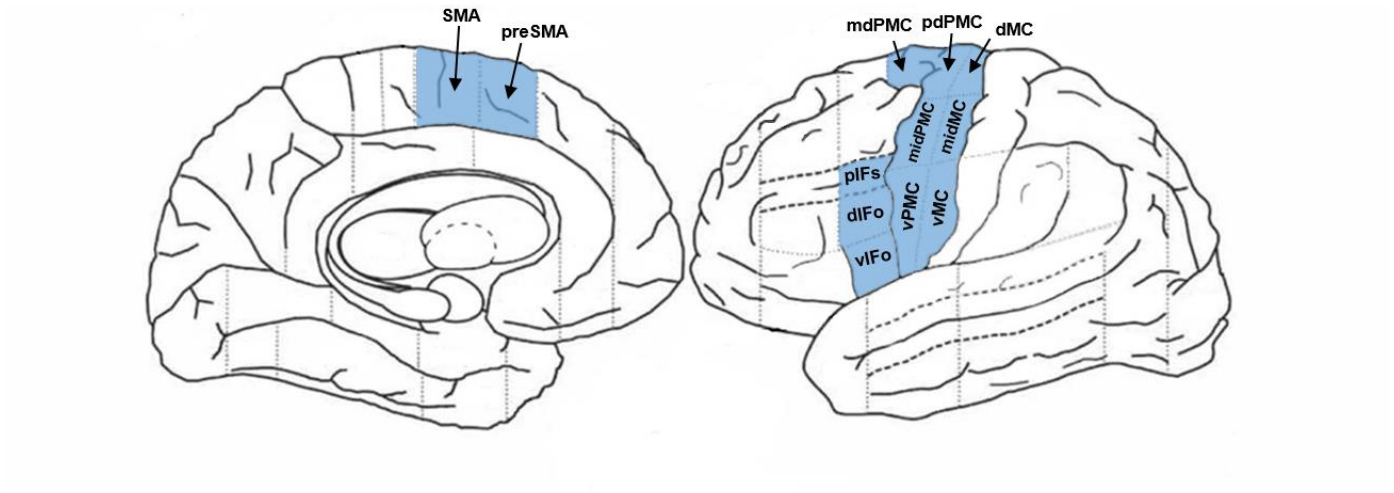


*Figure A-1. Motor speech regions of interest using SpeechLabel parcellation paradigm*

SMA = supplementary motor area, preSMA = pre-supplementary motor area, vIFo = ventral pars opercularis, dIFo = dorsal pars opercularis, pIFs = posterior inferior frontal sulcus, vPMC = ventral premotor cortex, midPMC = mid premotor cortex, mdPMC = middle dorsal premotor cortex, pdPMC = posterior dorsal premotor cortex, vMC = ventral motor cortex, midMC = mid motor cortex, dMC = dorsal motor cortex. *Figure adapted from Cai et al., 2013.*

*Table A-1. Baseline speech/language characteristics per patient*

| Subject ID | Subtype dx | CDR language score (0-3; 3 = worst) | PASS subdomain scores (0-3; 3 = worst) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Artic. | Fluency | Syntax | Word Ret. | Rep. | Aud. Comp. | Single Word Comp. | Read -ing | Writ -ing | Funct. Comm |
| PPA1 | lvPPA | 1 | 0 | 0.5 | 0.5 | 1 | 2 | 1 | 0.5 | 1 | 1 | 1 |
| PPA2 | lvPPA | 0.5 | 0 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 0.5 | 0.5 |
| PPA3 | lvPPA | 1 | 0 | 1 | 0 | 1 | 0.5 | 0.5 | 0 | 0.5 | 0.5 | 1 |
| PPA4 | lvPPA | 0.5 | 0 | 0.5 | 0 | 1 | 1 | 1 | 0 | 1 | 2 | 0.5 |
| PPA5 | lvPPA | 2 | 0 | 1 | 1 | 2 | 1 | 1 | 0.5 | 3 | 3 | 1 |
| PPA6 | lvPPA | 0.5 | 0 | 0.5 | 0 | 0.5 | 1 | 0 | 0 | 0.5 | 0.5 | 0 |
| PPA7 | lvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 1 | 0.5 | 0 | 0 | 0.5 | 0.5 |
| PPA8 | lvPPA | 0.5 | 0 | 0 | 0.5 | 1 | 0.5 | 0.5 | 0 | 0.5 | 0.5 | 0.5 |
| PPA9 | lvPPA | 2 | 0 | 1 | 0.5 | 2 | 2 | 1 | 0.5 | 2 | 3 | 1 |
| PPA10 | lvPPA | 0.5 | 0 | 0.5 | 0.5 | 1 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0.5 |
| PPA11 | lvPPA | 1 | 0 | 0.5 | 0.5 | 1 | 1 | 0.5 | 0.5 | 2 | 2 | 1 |
| PPA12 | lvPPA | 0.5 | 0 | 0 | 0 | 1 | 0.5 | 0.5 | 0 | 0 | 0 | 0.5 |
| PPA13 | lvPPA | 0.5 | 0 | 0 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 0.5 | 0.5 |
| PPA14 | lvPPA | 1 | 0 | 0.5 | 0.5 | 0.5 | 1 | 1 | 0.5 | 1 | 1 | 1 |
| PPA15 | lvPPA | 1 | 0 | 1 | 0.5 | 1 | 1 | 1 | 0 | 1 | 2 | 1 |
| PPA16 | lvPPA | 1 | 0 | 0 | 0.5 | 1 | 1 | 1 | 0 | 0.5 | 1 | 1 |
| PPA17 | lvPPA | 0.5 | 0 | 0.5 | 0.5 | 0.5 | 1 | 0.5 | 0 | 0.5 | 1 | 0.5 |
| PPA18 | lvPPA | 0.5 | 0 | 0 | 0.5 | 0.5 | 0 | 0 | 0 | 0 | 0.5 | 0.5 |
| PPA19 | lvPPA | 0.5 | 0 | 0.5 | 0.5 | 1 | 0.5 | 0.5 | 0 | 0 | 0.5 | 0 |
| PPA20 | lvPPA | 1 | 0 | 0.5 | 1 | 1 | 1 | 1 | 0.5 | 0.5 | 1 | 1 |
| PPA21 | lvPPA | 0.5 | 0 | 0 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0 | 0.5 | 0.5 |
| PPA22 | lvPPA | 0.5 | 0 | 0.5 | 1 | 1 | 1 | 0.5 | 0.5 | 0.5 | 1 | 0.5 |
| PPA23 | lvPPA | 1 | 0 | 0.5 | 0.5 | 1 | 2 | 1 | 0.5 | 1 | 3 | 1 |
| PPA24 | nfvPPA | 0.5 | 0 | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 0 | 0.5 | 0.5 | 0.5 |
| PPA25 | nfvPPA | 1 | 3 | 2 | 1 | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 1 | 1 |
| PPA26 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0 | 0 | 0.5 | 0.5 |
| PPA27 | nfvPPA | 2 | 2 | 2 | 2 | 0.5 | 0.5 | 1 | 0 | 1 | 3 | 2 |
| PPA28 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 0.5 | 1 |
| PPA29 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0 | 0.5 | 0.5 | 0.5 |
| PPA30 | nfvPPA | 2 | 2 | 2 | 2 | 1 | 1 | 0.5 | 0 | 2 | 2 | 1 |
| PPA31 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0 | 0 | 0.5 | 0.5 |
| PPA32 | nfvPPA | 1 | 2 | 1 | 0.5 | 0.5 | 0 | 0.5 | 0 | 0 | 0.5 | 0.5 |
| PPA33 | nfvPPA | 2 | 2 | 2 | 1 | 0.5 | na | 0 | 0 | 0.5 | 1 | 2 |
| PPA34 | nfvPPA | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 0 | 0 | 0 | 0 | 0.5 | 0 |
| PPA35 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0 | 0 | 0.5 | 0.5 | 0.5 |
| PPA36 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0 | 0 | 0.5 | 0.5 |
| PPA37 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 1 | 0.5 |
| PPA38 | nfvPPA | 0.5 | 1 | 0.5 | 1 | 0.5 | 0.5 | 0 | 0 | 0.5 | 0.5 | 0.5 |
| PPA39 | nfvPPA | 1 | 1 | 1 | 1 | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 1 | 0.5 |
| PPA40 | nfvPPA | 1 | 0.5 | 1 | 1 | 1 | 1 | 1 | 0.5 | 0 | 0.5 | 0.5 |
| PPA41 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 0.5 | 0.5 |
| PPA42 | nfvPPA | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 |
| PPA43 | nfvPPA | 1 | 1 | 0.5 | 1 | 0.5 | 0.5 | 0 | 0 | 0 | 0.5 | 0.5 |
| PPA44 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0 | 0 | 0 | 0.5 |
| PPA45 | nfvPPA | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0 | 0.5 | 0 | 0 | 0 | 0.5 |

*Table A-1. (Continued)*

| Subject ID | Subtype dx | CDR language score (0-3; 3 = worst) | PASS subdomain scores (0-3; 3 = worst) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Artic. | Fluency | Syntax | Word Ret. | Rep. | Aud. Comp. | Single Word Comp. | Read -ing | Writ -ing | Funct. Comm |
| PPA46 | svPPA | 1 | 0 | 0 | 0.5 | 1 | 0.5 | 1 | 1 | 2 | 0.5 | 1 |
| PPA47 | svPPA | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0.5 | 0.5 | 0 |
| PPA48 | svPPA | 2 | 0 | 0.5 | 0.5 | 1 | na | 2 | 1 | 3 | 2 | 2 |
| PPA49 | svPPA | 0.5 | 0 | 0 | 0.5 | 0.5 | 0 | 0 | 0.5 | 0.5 | 0.5 | 0.5 |
| PPA50 | svPPA | 0.5 | 0 | 0 | 0 | 0.5 | 0 | 0.5 | 0.5 | 0 | 0.5 | 0.5 |
| PPA51 | svPPA | 1 | 0 | 0 | 0 | 1 | 1 | 0.5 | 1 | 1 | 1 | 1 |
| PPA52 | svPPA | 1 | 0 | 0 | 0.5 | 1 | 0 | 0.5 | 0.5 | 1 | 1 | 1 |
| PPA53 | svPPA | 1 | 0 | 0 | 0 | 1 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 1 |
| PPA54 | svPPA | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0.5 | 0.5 | 0.5 |
| PPA55 | svPPA | 1 | 0 | 0 | 0.5 | 1 | 0.5 | 0.5 | 1 | 2 | 1 | 1 |
| PPA56 | svPPA | 0.5 | 0 | 0 | 0 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 |
| PPA57 | svPPA | 0.5 | 0 | 0 | 0.5 | 1 | 1 | 0.5 | 0.5 | 1 | 2 | 1 |
| PPA58 | svPPA | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 3 | 1 | 1 |
| PPA59 | svPPA | 0.5 | 0 | 0 | 0.5 | 1 | 0.5 | 0 | 0.5 | 0.5 | 1 | 0.5 |
| PPA60 | svPPA | 1 | 0 | 0 | 0 | 1 | 0 | 0.5 | 1 | 2 | 0.5 | 1 |
| PPA61 | svPPA | 1 | 0 | 0.5 | 0.5 | 1 | 0.5 | 0.5 | 1 | 2 | 2 | 2 |
| PPA62 | svPPA | 0.5 | 0 | 0 | 0 | 0.5 | 0 | 0 | 0.5 | 0 | 0.5 | 0 |
| PPA63 | svPPA | 1 | 0 | 0.5 | 0.5 | 1 | 0.5 | 0 | 1 | 0.5 | 0.5 | 0.5 |
| PPA64 | svPPA | 1 | 0 | 0 | 0 | 0.5 | 0 | 0.5 | 1 | 3 | 3 | 0 |

**CDR** = Clinical Dementia Rating; **PASS** = Progressive Aphasia Severity Score. CDR Language subscore and PASS subdomain scores are clinician-rated measures scored on a common interval scale: 0 (no impairment), 0.5 (very mild impairment), 1 (mild impairment), 2 (moderate impairment), 3 (severe impairment). Artic. = Articulation; Word Ret. = Word Retrieval; Rep. = Repetition; Aud. Comp. = Auditory Comprehension; Single Word Comp. = Single Word Comprehension; Funct. Comm. = Functional Communication.

*Table A-2. Operational guidelines for motor speech severity ratings*

| | **normal** | **questionable/very mild impairment** | **mild impairment** | **moderate impairment** | **severe impairment** |
|---|---|---|---|---|---|
| **MOTOR SPEECH: Ability to plan, program, coordinate, and execute speech production** | Speech is natural-sounding, fluent, and effortless. Normal articulation, pitch, loudness, voice quality, resonance, prosody (incl. rate), and respiration. | Occasional misarticulation and/or effortful or halting speech (not due to word-finding); very mild or inconsistent impairment in pitch, loudness, voice quality, resonance, prosody (incl. rate), or respiration. | Mild and consistent impairment in articulation, pitch, loudness, voice quality, resonance, prosody (incl. rate), or respiration. May exhibit occasional unintelligible words or utterances. | Moderate impairment in articulation, pitch, loudness, voice quality, resonance, prosody (incl. rate), or respiration. Frequent unintelligible words or utterances. | Severe impairments in articulation, pitch, loudness, voice quality, resonance, prosody (incl. rate), or respiration. The majority of words or phrases are unintelligible. |

*Table A-3. Motor speech features and criteria for diagnosing AOS, Dysarthria*

| AOS characteristics | Dysarthria characteristics | Shared AOS/Dys characteristics |
|---|---|---|
| ▪ Distorted sound substitutions/sound additions<br>▪ Inconsistent articulatory errors<br>▪ Increased errors with increased utterance length/articulatory complexity/rate<br>▪ Articulatory groping; speech initiation difficulty; false starts/restarts<br>▪ Reduced words per breath group relative to maximum vowel duration<br>▪ Inaccurate speech AMRs<br>▪ Decrement in speech performance for SMRs as compared to speech AMRs<br>¥ Non-verbal oral apraxia | ▪ Impairments across multiple speech subsystems beyond articulation & prosody (i.e., phonation, resonance, respiration)<br>- Phonation: deviant vocal quality, monopitch, low pitch, pitch breaks<br>- Resonance: hyper-/hyponasality<br>- Respiration: stridor, speaking on inhalation<br>▪ Consistent deviant speech characteristics<br>¥ Reduced range of motion of articulators, tongue atrophy/fasciculations/weakness; dysphagia, drooling, hyper-/hypoactive gag | ▪ Slow overall speech rate<br>▪ Sound distortions<br>▪ Syllable segmentation within multisyllabic words/across words in phrases/sentences<br>▪ Lengthened vowel &/or consonant segments<br>▪ Lengthened intersegment durations (between sounds, syllables, words, or phrases; possibly filled, including intrusive schwa) |

¥ = non-speech oral mechanism finding

*Adapted from Strand et al., 2014*

Rating instructions:

- Diagnosis of **AOS** requires ≥3 unique AOS characteristic OR ≥2 shared characteristic + supportive AOS oral mech finding
- Diagnosis of **dysarthria** requires ≥3 unique Dys characteristic OR ≥2 shared characteristic + supportive Dys oral mech finding
- Rate as **nonspecific** if 0-2 unique AOS/Dys characteristics

*Table A-4. Motor speech characterizations (consensus ratings) per patient*

| | Subtype dx | Motor Speech Impairment (MSI) rating (0-3; 3 = worst) | AOS | Dysarthria | Unspecified | Predominant impairment[a] ($MSI^+$, $ag^+$, ag=MSI) |
|---|---|---|---|---|---|---|
| PPA1 | lvPPA | 0 | | | | |
| PPA2 | lvPPA | 0 | | | | |
| PPA3 | lvPPA | 0.5 | | | ✓ | |
| PPA4 | lvPPA | 0 | | | | |
| PPA5 | lvPPA | 0 | | | | |
| PPA6 | lvPPA | 0 | | | | |
| PPA7 | lvPPA | 0 | | | | |
| PPA8 | lvPPA | 0 | | | | |
| PPA9 | lvPPA | 0.5 | | | ✓ | |
| PPA10 | lvPPA | 0 | | | | |
| PPA11 | lvPPA | 0 | | | | |
| PPA12 | lvPPA | 0 | | | | |
| PPA13 | lvPPA | 0 | | | | |
| PPA14 | lvPPA | 0 | | | | |
| PPA15 | lvPPA | 0 | | | | |
| PPA16 | lvPPA | 0 | | | | |
| PPA17 | lvPPA | 0 | | | | |
| PPA18 | lvPPA | 0 | | | | |
| PPA19 | lvPPA | 0 | | | | |
| PPA20 | lvPPA | 0.5 | | | ✓ | |
| PPA21 | lvPPA | 0 | | | | |
| PPA22 | lvPPA | 0 | | | | |
| PPA23 | lvPPA | 0 | | | | |
| PPA24 | nfvPPA | 0 | | | | **$ag^+$** |
| PPA25 | nfvPPA | 3 | ✓ | ✓ | | **$MSI^+$** |
| PPA26 | nfvPPA | 0 | | | | **$ag^+$** |
| PPA27 | nfvPPA | 3 | | ✓ | | **$MSI^+$** |
| PPA28 | nfvPPA | 0.5 | | | ✓ | **=** |
| PPA29 | nfvPPA | 0.5 | ✓ | | | **=** |
| PPA30 | nfvPPA | 1 | | ✓ | | **$ag^+$** |
| PPA31 | nfvPPA | 0 | | | | **$ag^+$** |
| PPA32 | nfvPPA | 2 | ✓ | ✓ | | **$MSI^+$** |
| PPA33 | nfvPPA | 3 | | ✓ | | **$MSI^+$** |
| PPA34 | nfvPPA | 0.5 | ✓ | | | **$MSI^+$** |
| PPA35 | nfvPPA | 1 | | ✓ | | **$MSI^+$** |
| PPA36 | nfvPPA | 0.5 | ✓ | ✓ | | **=** |
| PPA37 | nfvPPA | 0.5 | ✓ | | | **=** |
| PPA38 | nfvPPA | 2 | | ✓ | | **$MSI^+$** |
| PPA39 | nfvPPA | 2 | | ✓ | | **=** |
| PPA40 | nfvPPA | 1 | ✓ | | | **=** |
| PPA41 | nfvPPA | 0.5 | ✓ | | | **=** |

*Table A-4. (Continued)*

| | Subtype dx | Motor Speech Impairment (MSI) rating (0-3; 3 = worst) | AOS | Dysarthria | Unspecified | Predominant impairment[a] (MSI$^+$, ag$^+$, ag=MSI) |
|---|---|---|---|---|---|---|
| PPA42 | nfvPPA | 0.5 | ✓ | | | **MSI$^+$** |
| PPA43 | nfvPPA | 0.5 | | ✓ | | **ag$^+$** |
| PPA44 | nfvPPA | 0.5 | | | ✓ | **=** |
| PPA45 | nfvPPA | 1 | | ✓ | | **MSI$^+$** |
| PPA46 | svPPA | 0 | | | | |
| PPA47 | svPPA | 0 | | | | |
| PPA48 | svPPA | 0 | | | | |
| PPA49 | svPPA | 0 | | | | |
| PPA50 | svPPA | 0 | | | | |
| PPA51 | svPPA | 0 | | | | |
| PPA52 | svPPA | 0 | | | | |
| PPA53 | svPPA | 0 | | | | |
| PPA54 | svPPA | 0 | | | | |
| PPA55 | svPPA | 0 | | | | |
| PPA56 | svPPA | 0 | | | | |
| PPA57 | svPPA | 0 | | | | |
| PPA58 | svPPA | 0 | | | | |
| PPA59 | svPPA | 0 | | | | |
| PPA60 | svPPA | 0 | | | | |
| PPA61 | svPPA | 0 | | | | |
| PPA62 | svPPA | 0 | | | | |
| PPA63 | svPPA | 0 | | | | |
| PPA64 | svPPA | 0 | | | | |

[a]Predominant impairment, rated for nfvPPA only, is derived from a ratio of MSI severity score: PASS Syntax subdomain score. **ag$^+$** (MSI < Syntax) indicates a predominant agrammatisms; **MSI$^+$** (MSI > Syntax) indicates a predominant motor speech impairment; **ag=MSI** indicates impairments of equal predominance.

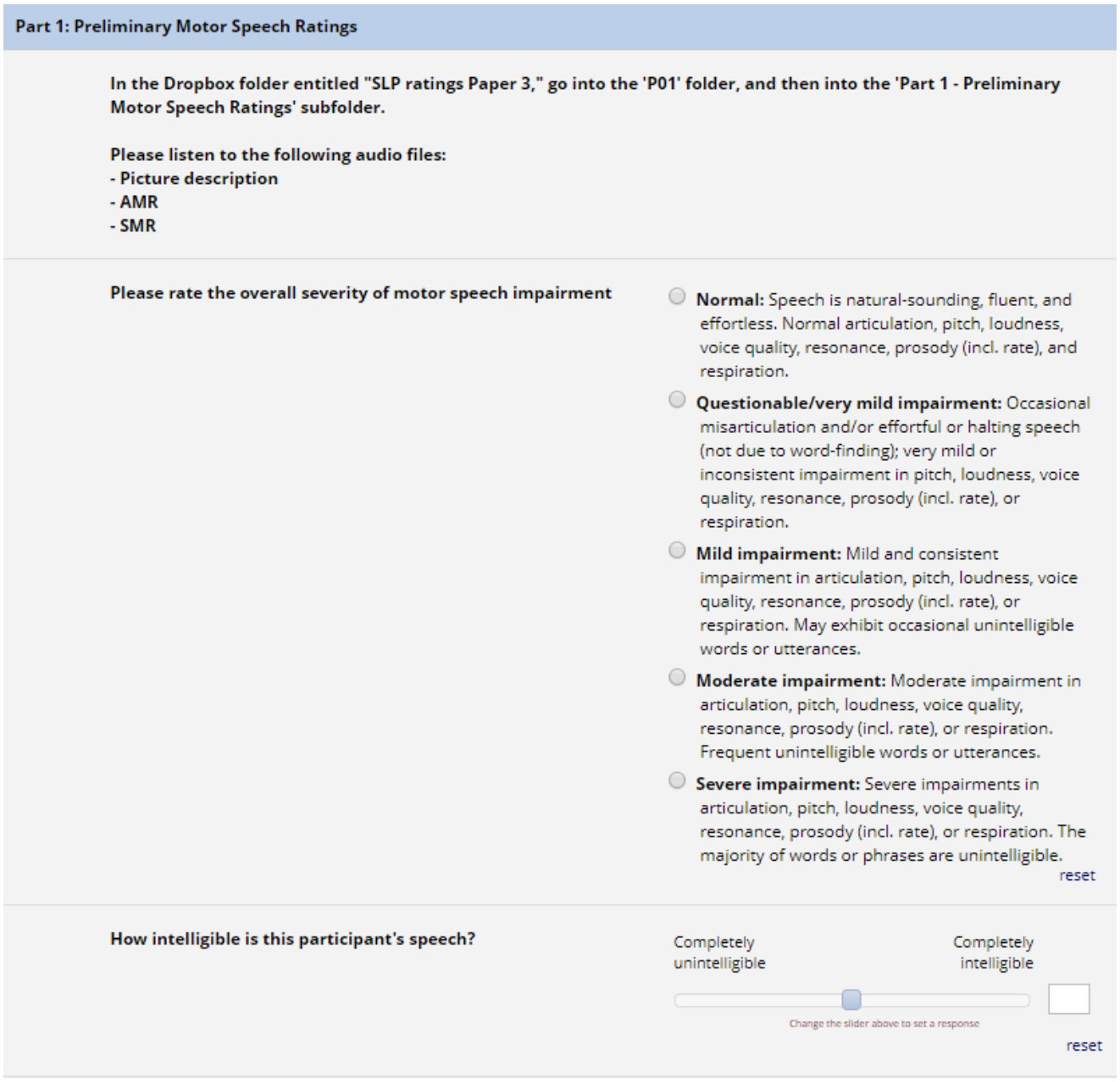


*Figure A-2. RedCap clinician rating survey of motor speech impairment*

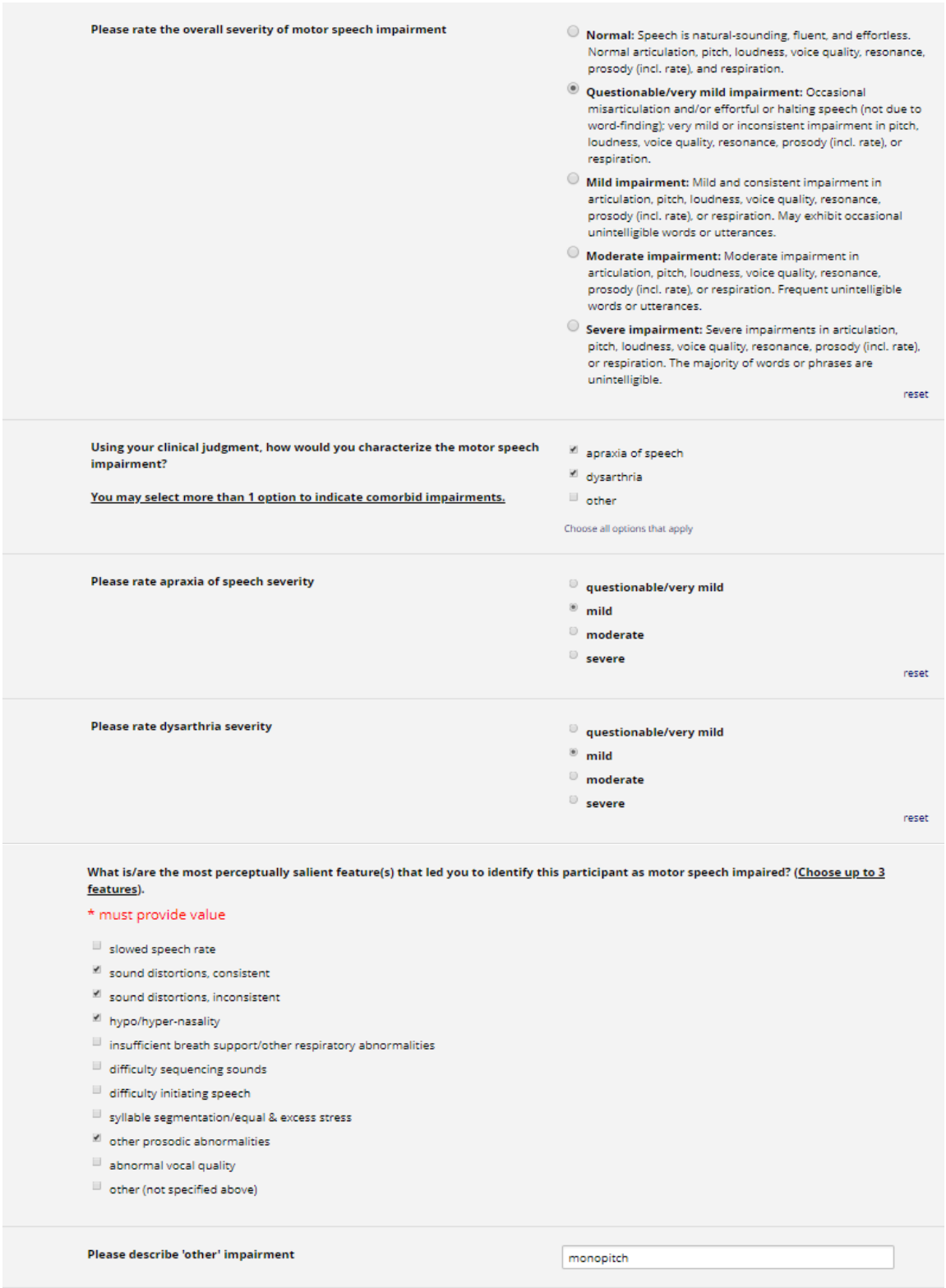


*Figure A-3. Example branching logic in RedCap clinician survey*