Quantification of motor speech in primary progressive aphasia and frontotemporal dementia

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Abstract

Frontotemporal dementia (FTD) and primary progressive aphasia (PPA) are two groups of related disorders which are classified into the behavioural (bvFTD), semantic (svPPA), nonfluent/agrammatic (nfvPPA) and logopaenic (lvPPA) variants. Each variant presents with characteristic impairments of communication or behaviour, and the defining features of the syndromes are under ongoing debate in the literature. Researchers and clinicians usually assess speech with listener-based rating scales, which pose a challenge for identifying subtle changes to speech. Objective measures of speech may therefore improve characterisation of speech impairments in the literature and assist in clinical diagnosis and management.

In this study, speech samples were taken from 43 people with PPA or FTD (8 svPPA, 4 nfvPPA, 9 lvPPA, 22 bvFTD) and 24 healthy controls. Speech was analysed perceptually using a 5-point rating scale across all speech subsystems. Speech was objectively quantified with measures of lexical stress (the pairwise variability index, PVI), vowel production, timing, voice quality and diadochokinetic (DDK) speech rate. The ability of speech measures to predict regions of neurodegeneration was assessed by comparison of speech to calculations of cortical thickness and subcortical volume derived from participants' clinical magnetic resonance imaging (MRI) scans. Longitudinal speech investigations were conducted for a subgroup of participants to investigate the capacity of the measures to track disease progression.

Group comparisons indicated that several speech measures differentiate pathological groups from controls, including measures of speech timing, DDK rate, and PVI. PVI and DDK also differentiated the nfvPPA group from other subtypes. Case studies of longitudinal data highlight measures which reflect motor speech changes in a case of bvFTD progressing to motor neurone disease (MND), and in two cases of nfvPPA.

Findings add to the documentation of speech production in PPA and FTD by establishing acoustic correlates which differ from the healthy population. Longitudinal case studies demonstrate the potential for these measures to be used clinically to improve monitoring of disease progression.

Declaration

This is to certify that:

- The thesis comprises only my original work towards the PhD except where indicated in the Preface
- Due acknowledgement has been made in the text to all other material used
- The thesis is fewer than 100,000 words in length, exclusive of tables, bibliographies and appendices

Matthew Poole

Preface

During my candidature I was supported by an NHMRC Postgraduate Scholarship (GNT1093182).

My supervisors, Associate Professor Adam Vogel and Associate Professor Amy Brodtmann assisted with the analysis and interpretation of data throughout the thesis. A/Prof Vogel and A/Prof Brodtmann, alongside Associate Professor David Darby provided revisions to the publication presented in Chapter Two. In addition, Hugh Pemberton and Essie Low collected pilot data which was incorporated into analyses in Chapters Four and Five, and constituted initial time point data in the longitudinal analysis of Chapter Seven. Frederique Boonstra provided cortical thickness and subcortical volume calculations for Chapter Five. I received statistical advice from Professor Ian Gordon at the University of Melbourne Statistical Consulting Centre while planning the statistical analysis of the studies.

All research procedures were approved by the Eastern Health and University of Melbourne Human Research Ethics Committee.

Thesis with publication

This thesis includes one publication:

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Submitted with this thesis are the co-author authorisation forms of Associate Professor Adam Vogel, Associate Professor Amy Brodtmann, and Associate Professor David Darby.

Matthew L. Poole designed the study, analysed and interpreted the data, and drafted the manuscript; Amy Brodtmann interpreted the data and revised the manuscript; David Darby interpreted the data and revised the manuscript; and Adam P. Vogel designed and conceptualised the study, analysed and interpreted the data, and revised the manuscript.

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Abbreviations

AAT	Aachener Aphasia Test
ABA	Apraxia Battery for Adults
ACC	anterior cingulate cortex
ACE-R	Addenbrooke's Cognitive Examination - Revised
AD	Alzheimer's disease
AF	arcuate fasciculus
agPPA	agrammatic primary progressive aphasia
ALS	amyotrophic lateral sclerosis
AMR	alternating motion rates
ANOVA	analysis of variance
ANT	anterior
AOS	apraxia of speech
APV	Adam P Vogel
ASRS	Apraxia of Speech Rating Scale
AUC	area under curve
BA	Brodtmann area
BDAE	Boston Diagnostic Aphasia Examination
BOLD	blood-oxygen-level dependent
C9orf72	hexanucleotide expansion repeats in chromosome 9
CAT	Comprehensive Aphasia Test
Cau	caudate
cMFG	caudal middle frontal gyrus
CBD	corticobasal degeneration
CBS	corticobasal syndrome
CI	confidence interval
CNS	central nervous system
CoV	coefficient of variation
dBSPL	decibel of sound pressure level
DDK	diadochokinesis
DIVA	directions into velocities of articulators
DRA	Diadochokinetic Rate Analysis
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
ECDC	Eastern Cognitive Disorders Clinic
f0	fundamental frequency
FA	fractional anisotropy
FCR	formant centralisation ratio
FDG-PET	fluorodeoxyglucose positron emission tomography
fMRI	functional magnetic resonance imaging
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration

FTD-MND	frontotemporal dementia with motor neurone disease
GM	grey matter
GRN	granulin
GWAS	genome wide association study
HC	healthy controls
HLA	human leucocyte antigen
HNR	harmonics-to-noise ratio
HSD	honest significant difference
IBM	International Business Machines Corporation
ICC	international consensus criteria
IFG	inferior frontal gyrus
ILF	inferior longitudinal fasciculus
INF	inferior
Ins	insula
IPL	inferior parietal lobe
LAT	lateral
lvPPA	logopenic variant primary progressive aphasia
MAPT	microtubule-associated protein tau
MED	medial
MEG	magnetoencephalography
MFG	middle frontal gyrus
MLP	Matthew L Poole
MMSE	Mini-Mental State Examination
MND	motor neurone disease
MND-FTD	motor neurone disease with frontotemporal dementia
MPRAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MRI	magnetic resonance imaging
MSD	motor speech disorder
MSE	Motor Speech Evaluation
naPPA	nonfluent/agrammatic primary progressive aphasia
NC	not classifiable
nfvPPA	Nonfluent/agrammatic variant primary progressive aphasia
NJ	New Jersey
NVOA	non-verbal oral apraxia
PALS	Progressive Aphasia Language Scale
PAOS	progressive apraxia of speech
PASS	Progressive Aphasia Severity Scale
PCG	precentral gyrus
PDA	progressive dynamic aphasia
PFA	progressive fluent aphasia
PMC	premotor cortex
Pop	pars opercularis
Por	pars orbitalis

POS	posterior
PPA	primary progressive aphasia
PPAOS	primary progressive apraxia of speech
PSP	progressive supranuclear palsy
pSTG	posterior superior temporal gyrus
PT	pars triangularis
PVI	pairwise variability index
RD	radial diffusivity
ROC	receiver operating characteristic
ROI	region of interest
SCA	spinocerebellar ataxia
SD	standard deviation
SLF	superior longitudinal fasciculus
SMA	supplementary motor area
SMG	supramarginal gyrus
SMR	sequential motion rate
SNP	single nucleotide polymorphism
SPECT	Single-photon emission computed tomography
SPSS	Statistical Package for the Social Science
STC	superior temporal cortex
STG	superior temporal gyrus
SUP	superior
svPPA	semantic variant primary progressive aphasia
SW	strong-weak
TDP-43	TAR DNA-binding protein 43
TMEM106B	Transmembrane protein 106B
TP	temporal pole
UMN	upper motor neuron
UPDRS	Unified Parkinson's Disease Rating Scale
USA	United States of America
VBM	voxel based morphometry
VSA	vowel space area
WAB	Western Aphasia Battery
WFD	word finding difficulties
WM	white matter
WS	weak-strong

Peer reviewed publications and presentations

Published work arising from thesis:

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Dodd, B. & **Poole, M.** (2017). A case of inconsistent phonological disorder: A three year follow up. In B. Dodd & A. Morgan (Eds.), *Intervention Case Studies of Child Speech Impairment* (pp. 227-247). London, UK: J&R Press.

Poole, M. L., Wee, J., Folker, J. E., Corben, L. A., Delatycki, M.B., Vogel, A. P. (2015). Nasality in Friedreich ataxia. Clinical Linguistics & Phonetics, 2014; Early Online: 1–13. doi:10.3109/02699206.2014.954734

Vogel A. P., Folker J., **Poole M. L.** (2014) Treatment for speech disorder in Friedreich ataxia and other hereditary ataxia syndromes. Cochrane Database of Systematic Reviews, Issue 10. Art. No.: CD008953. DOI:10.1002/14651858.CD008953.pub2.

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Poole M. L., Brodtmann A, Darby D., and Vogel A. P. (2015). 'Objective monitoring of dysarthria in FTD-MND: a case study' presented at the Seventh Annual Meeting of the Society for the Neurobiology of Language, Chicago, USA.

Poole M, Brodtmann A, Pemberton H, Low E, Darby D and Vogel A (2015). Motor speech deficits in behavioural variant frontotemporal dementia. Front. Hum. Neurosci. Conference Abstract: XII International Conference on Cognitive Neuroscience (ICON-XII). doi:10.3389/conf.fnhum.2015.217.00396

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Outline of thesis

Evaluation of speech is important in the management of frontotemporal dementia (FTD) and primary progressive aphasia (PPA) for several reasons. Speech is often central to the classification of PPA, and accurate classification informs therapy targets, prognosis, and pathology. Furthermore, monitoring of speech is required in FTD and PPA for the emergence of motor impairments associated with corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), and motor neurone disease (MND).

Description of the differing speech features of PPA variants has developed significantly since the term was coined in the 1980s. Current diagnosis is based on International Consensus Criteria which were establish in 2011. While these have allowed for some consistency between different research groups, the criteria do not prescribe specific tools for evaluation of speech features, and there is inconsistency of speech measures in the literature. Further, there is debate about the most important features for classification, as well as the best way to conceptualise syndromes which do not fit into the classification system. The development of objective measures of speech production is therefore worthwhile in order to establish consistency of the characterisation and severity of speech features within the literature. Large proportions of people with bvFTD have been reported to have abnormalities of speech production; however, comprehensive descriptions of speech in bvFTD are lacking. Investigation of speech production in bvFTD will allow for clarification of the speech phenotype, and the potential to identify deviations of motor speech production indicative of the development of parkinsonian syndromes or MND. In the clinical setting, evaluation of speech production in PPA and FTD is performed with subjective listener-based assessment. While easily implemented, this approach may be limited by lack of sensitivity for tracking progression, and inability to directly compare ratings between assessors.

The aims of this thesis are therefore to clarify characterisations of speech production in PPA and FTD using speech acoustic methods alongside perceptual (listener-based) evaluations. A secondary aim of the thesis is to investigate any associations between speech features and known regions of atrophy in PPA and FTD, by measuring cortical thickness and subcortical volume from participants' magnetic resonance imaging (MRI) scans. In doing so it aims to establish objective measures which can be used to clarify clinical syndromes for research and clinical purposes, to predict regions of neurodegeneration, and assist with disease monitoring by providing sensitive and quantifiable metrics.

Chapter One: General Introduction

In Chapter One, I introduce the syndromes of PPA and FTD, including clinical features, genetics, pathology and neurological changes. I provide a theoretical discussion of speech production and explore the contributions of cognition, language and motor control to verbal expression, including how these can be differentially affected by various disease processes. The limitations of the international consensus criteria for PPA classification are discussed, in particular the lack of speech measures consistently applied between research groups. The aims and justifications of the thesis are outlined.

Chapter Two: Systematic Review – Motor speech phenotypes of frontotemporal dementia, primary progressive aphasia, and progressive apraxia of speech

Chapter Two comprises a published article which provided a systematic review of the motor speech impairments of FTD, PPA and progressive apraxia of speech (PAOS). A meta-analysis of subtype differences was conducted for measures that were used consistently in multiple studies. There was consistency within the literature regarding the presence of prominent motor speech disorder in some PPA subtypes and preservation of motor speech in others. Neural correlates of motor speech disorders were identified in the motor speech regions of the frontal lobe, particularly the left hemisphere, whereas hesitancy of speech was associated with a range of left posterior perisylvian cortical regions. Results of the meta-analysis indicate that several quantitative measures have the potential to assist in diagnosis of clinical variant.

Chapter Three: Methodology

In Chapter Three, I outline the methods used in each of the studies. This chapter includes a description of recruitment and data collection procedures. I describe the language assessments conducted and protocol for eliciting speech stimuli. A description and rationale of each of the acoustic measures and perceptual evaluation is provided. These measures are the basis of analysis in Chapters Four to Seven.

Chapter Four: Subgroup comparison of speech in FTD and PPA

Chapter Four includes a characterisation of each of the PPA subtypes and behavioural variant FTD (bvFTD) using both acoustic and perceptual methods. Comparisons are conducted to identify features which differentiate the variants. Measures of speech timing, diadochokinetic

productions and lexical stress demonstrate capacity to differentiate PPA subtypes in research and clinical settings. Results of this chapter also indicate subtle motor speech deterioration in bvFTD, thereby clarifying the phenotype of this syndrome.

Chapter Five: Neural correlates of speech in FTD and PPA

Chapter Five expands upon earlier investigations of the relationship between quantified speech metrics and cortical regions of atrophy in order to examine specific speech measures which may provide prediction of aetiology. Measures of cortical thickness and subcortical volume were taken from participants' clinical magnetic resonance imaging scans. I discuss a DDK metric which was associated with the left superior temporal gyrus and rating of hypernasality with the right precentral gyrus. Findings in this chapter support using acoustic measures of speech in larger studies in future.

Chapter Six: Monitoring progression of speech decline in two cases of nonfluent/agrammatic primary progressive aphasia

In Chapter Six, I describe longitudinal speech data for two cases of the nonfluent variant of PPA (nfvPPA) in order to provide a proof of concept for using acoustic measures to quantify speech decline. Two distinct rates of change were seen consistently across the acoustic measures of speech production, highlighting the more rapid progression for one participant. Importantly, the acoustic measures were able to demonstrate decline over a six-month period, whereas perceptual evaluation required a 12-month period in order to unequivocally establish speech decline. These findings support the notion of using acoustic measures of speech to support perceptual assessment in clinical management, and in longitudinal research studies of progression and treatment.

Chapter Seven: Objective monitoring of dysarthria in FTD-MND

In support of Chapter Six, this chapter provides an additional proof of concept for the use of acoustic measures in tracking disease trajectory. In this case series, four participants with bvFTD are assessed at two time points to examine speech decline. One of the four participants presents with concomitant dysarthria associated with MND. Findings of this chapter highlight two speech metrics which are sensitive to motor speech deterioration, despite occurring in the presence of abnormalities associated with the behavioural and cognitive changes of bvFTD.

Chapter Eight: Summary, limitations, and future directions

In Chapter Eight, I provide a summary of the findings presented in the thesis, with consideration of the four results chapters and how these contribute to our understanding of the FTD and PPA speech phenotypes. Further, acoustic measures are discussed in consideration of their capacity to differentiate subtypes, predict regions of brain atrophy, and monitor progression in nfvPPA and bvFTD. Clinical implications of the research are discussed, and future directions for speech acoustic research in FTD and PPA are suggested.

1 General Introduction

1.1 Frontotemporal dementia and primary progressive aphasia

Frontotemporal dementia (FTD) and primary progressive aphasia (PPA) are related disorders that cause prominent disturbances of speech and communication (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Each group of disorders can be divided into subtypes based on clinical features, and these features are often evident in speech production (Ash et al., 2013; Wilson et al., 2010). In PPA, aphasia or motor speech disorder are the primary impairments, which may be characterised by effortful speech, agrammatism, word retrieval deficits and dysfluency. Speech abnormalities in behavioural variant FTD (bvFTD) are more commonly considered to have a behavioural and/or cognitive origin, and may include aspontaneity and impaired pragmatic use of language (Neary et al., 1998).

The prevalence of FTD is estimated to be 15 per 100,000 in the 45-64 year age group (Ratnavalli, Brayne, Dawson, & Hodges, 2002). There are three clinical syndromes of FTD, which are bvFTD, progressive nonfluent aphasia and semantic dementia (Neary et al., 1998). Progressive nonfluent aphasia and semantic dementia are language onset forms of the disorder and are therefore also considered subtypes of primary progressive aphasia (PPA). PPA is a clinical syndrome; a concept introduced by Mesulam in his seminal paper (1982). He used the term to describe a group of patients who presented with gradually progressing language impairment. Mesulam's group defined this syndrome as a primary language impairment with preservation of other cognitive domains, such as memory and executive function, during the early stages of the disease (Weintraub, Rubin, & Mesulam, 1990). This had to be an isolated impairment of language for a minimum of two years, and semantic impairment was not a prominent feature of these syndromes (Mesulam, 1982; Weintraub et al., 1990).

Around the same time as Mesulam's initial description of PPA (1982), Warrington (1975) described three cases of dementia characterised by word and object agnosia with preserved attention and visual acuity, which suggested an impairment of semantic memory. These syndromes did not have any deficits of articulation or syntactic comprehension (Warrington, 1975). The term 'semantic dementia' was introduced by Snowden, Goulding, and Neary

(1989) to describe three additional cases of language onset dementia affecting semantic memory. Hodges and colleagues (1992) clarified the syndrome, by describing features of anomia, impaired single-word comprehension and surface dyslexia, with sparing of syntax and phonology. Hodges (1992) used the term progressive nonfluent aphasia to distinguish between semantic dementia and what is now also termed non-fluent variant PPA (nfvPPA). These terms are still used in the literature (Poole, Brodtmann, Darby, & Vogel, 2017).

Later a third variant, termed logopaenic variant primary progressive aphasia (lvPPA), was recognised as a distinct syndrome (Gorno-Tempini, Dronkers, et al., 2004). Gorno-Tempini and colleagues (2004) described lvPPA as a syndrome with slow rate and word finding pauses, which met the general criteria for PPA, but did not have agrammatism or articulatory deficits. Subsequently, further characterisation of lvPPA highlighted phonemic paraphasias and impaired repetition, and the syndrome was suggested to be caused by a deficit of the phonological loop (Gorno-Tempini et al., 2008). Early investigations suggested that lvPPA was an atypical form of Alzheimer's disease (Gorno-Tempini, Dronkers, et al., 2004), and this has been supported by larger studies (Chare et al., 2014; Josephs et al., 2008). These three variants: progressive nonfluent aphasia, semantic dementia and lvPPA, have been labelled by international consensus as the nonfluent/agrammatic PPA (nfvPPA), semantic variant PPA (svPPA) and logopaenic variants of PPA (lvPPA; Gorno-Tempini et al., 2011). While each of these subtypes is associated with a distinct aphasia, and therefore characteristic impairments of speech production, clinical overlap occurs. An additional syndrome, primary progressive apraxia of speech (PPAOS), has been proposed as a progressive communication disorder. Patients with this condition have profound apraxia of speech rather than aphasia, and therefore do not meet initial criteria for PPA (Josephs et al., 2012). PAOS has considerable overlap with nfvPPA, and the international consensus criteria (ICC) suggest a classification of nfvPPA can be made for patients presenting with apraxia of speech (AOS) without agrammatism (Gorno-Tempini et al., 2011). Josephs and colleagues (2013) propose a two-tier classification system to highlight the relative severity of aphasia and/or AOS when classifying patients. Some patients who initially present with PAOS later develop features of corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP; Josephs & Duffy, 2008; Josephs et al., 2006).

1.2 Impaired verbal expression: Language, cognition and motor control

Before describing the speech of FTD and PPA, it is necessary to discuss the cognitive and motor processes involved in speech production. Levelt's (1989) model of information processing provides a way of conceptualising verbal expression based upon the error patterns of healthy people, and has been applied to word finding difficulty in PPA (Rohrer, Knight, et al., 2008). The model divides the process of verbal expression into conceptualisation, formulation and articulation (see Figure 1-1; Levelt, 1989). The conceptualisation level is considered to be preverbal, and represents the speakers' need to conceive of their intended message, including selection of the relevant information, and consideration of information that has already been expressed in the conversation (Levelt, 1989). These concepts are then converted into a linguistic structure in the 'formulator'. This process is multifaceted and can be subdivided into functional and positional processing (Bock & Levelt, 1994). Functional processing involves selection of lexical (word) meanings and some grammatical information such as form class (noun, verb, etc.) and function (e.g., subject, object, agent). It is important to note that during the grammatical encoding process, the lexical items are not yet linked with their component sounds (phonemes). The second component of grammatical encoding is positional processing, which places the lexical items into the correct order (syntax) within an utterance and provides inflectional affixes, such as plural 's', and past tense 'ed' (Bock & Levelt, 1994). Grammatical encoding is followed by phonological encoding, which retrieves the phonological form of words including number of syllables, stress patterns and phonemes (speech sounds). Finally, the phonological codes are converted into a motoric program or phonetic plan for motor speech movement, which is then realized at the articulatory level (Levelt, 1989).

Impairments of cognition, language or motor production can differentially affect this process of verbal expression (Levelt, 1989). At the conceptualisation level, impaired cognition may lead to cognitive-communication disorder, a term used to refer to a range of presentations that impact communication but are not considered primary language impairments (aphasia). This may result in speech production marked with aspontaneity, tangential utterances or disregard for social conventions. In FTD and PPA, features of cognitive-communication disorder are most likely to be observed in bvFTD (Neary et al., 1998). In contrast to the conceptualization level, breakdown at the formulation level leads to aphasia, which is the primary impairment of PPA and results in features such as agrammatism, semantic errors, and impaired

comprehension and repetition (Gorno-Tempini et al., 2011). Impairments occurring after the formulation process include the motor speech disorders of dysarthria and apraxia. Apraxia of speech (AOS) is defined as a deficit in the motor planning and programming process where the phonological codes are converted to motor plans for the speech musculature, whereas dysarthria is an impairment of the execution and control of these motor plans (Ziegler, 2008).

The dichotomy between AOS and dysarthria can be questioned due to the fact that each are motor speech disorders, and the fact that there is heterogeneity amongst the subtypes of dysarthria (Ziegler, Aichert, & Staiger, 2012). For example, there is significant difference between flaccid dysarthria resulting from impaired lower motor neuron functioning, and hyperkinetic dysarthria characterized by dystonia and chorea, and it could be argued that there are greater differences between subtypes of dysarthria than between AOS and some dysarthrias (Darley, Aronson, & Brown, 1969). Similarly, there are many overlapping features between AOS and the dysarthrias, such as imprecise consonants and reduced intelligibility (Darley et al., 1969; Strand, Duffy, Clark, & Josephs, 2014). By definition, AOS is differentiated from dysarthria because the disordered speech features do not result from weakness, slowness or incoordination of speech musculature (Darley, Aronson, & Brown, 1975; Wertz & Rosenbek, 1991; Ziegler et al., 2012). Instead, the typical speech features of hesitancy, groping for correct articulation and self-correction resemble features of limb apraxia (Goldenberg, 2008; Ziegler et al., 2012). Further evidence of a motor planning disorder are the presence of distorted speech sound substitutions, as opposed to consistent distortions of target sounds in dysarthria (Strand et al., 2014). The intermittent nature of speech impairment in AOS is additional support for the notion of a motor planning rather than execution problem, as periods of unimpaired speech which would be inconsistent with a deficit of execution (Staiger, Finger-Berg, Aichert, & Ziegler, 2012). In addition, there are notable differences in the form of brain damage which results in AOS and the dysarthrias. AOS results from focal cortical lesions of the frontal lobe, while dysarthria is commonly the result of diffuse and subcortical damage (Ziegler et al., 2012). The directions into velocities of articulators (DIVA) model of speech production suggests that the neuroanatomical correlate of the motoric plans recruited in the planning stage of speech production, and which are presumed to be poorly retrieved in AOS, lie in a focal cortical region of the premotor cortex and posterior inferior frontal gyrus in the left hemisphere (Tourville & Guenther, 2011). Damage to these regions have been observed to result in AOS in both

neurodegenerative conditions such as PAOS (Josephs et al., 2012), and vascular infarcts (Hillis et al., 2004).

Within the PPA syndromes, AOS is considered to be one of two core features of nfvPPA and the primary disturbance in PAOS (Gorno-Tempini et al., 2011; Josephs et al., 2012). However, dysarthria is observed as a secondary feature in approximately half of reported cases of nfvPPA, PAOS and PPAOS, with the most common type of dysarthria being spastic, followed by hypokinetic (Botha et al., 2015; Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014; Josephs et al., 2013; Josephs et al., 2012; Ogar, Dronkers, Brambati, Miller, & Gorno-Tempini, 2007). The defining features of spastic dysarthria, which distinguish it from AOS include a strained voice quality and slow alternating motion rates (Clark et al., 2014; Duffy, 2013). Hypokinetic dysarthria is associated with Parkinsonism, and is distinguishable by hypophonia, variable speech rate, and short rushes of speech (Darley et al., 1969; Duffy, 2013).

Dysarthria is also commonly observed in other clinical syndromes related to the FTD spectrum of disorders, namely motor neurone disease (MND), corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP; Kluin, Foster, Berent, & Gilman, 1993; Müller et al., 2001). The dysarthria observed in MND is typically mixed flaccid-spastic, owing to degradation of both upper and lower motor neurons (Tomik & Guiloff, 2010). The clinical features of this dysarthria include a strained or strangled voice quality, reduced prosodic variation, slow rate, imprecise articulation and hypernasality (Roth, Glaze, Goding, & David, 1996; Tomik & Guiloff, 2010). The dysarthria profile of PSP is most commonly spastic, and is characterised by slow rate, impaired vowel and consonant articulation and a strained voice quality (Rusz et al., 2015; Skodda, Visser, & Schlegel, 2011a). Apraxia of speech is also common in CBS (Boeve, Lang, & Litvan, 2003), however is often accompanied by hypokinetic or spastic dysarthria, characterized by poor respiratory control, articulatory imprecision, reduced rate, increased pitch and a strained voice quality (Blake, Duffy, Boeve, Ahlskog, & Maraganore, 2003; Boeve, Lang, et al., 2003). Dysarthria and apraxia of speech are rarely observed in lvPPA, or svPPA (Poole et al., 2017)

The literature on speech production in PPA makes a distinction between *phonemic* and *phonetic* errors, which can also be conceptualized within Levelt's model of processing, at the formulator and articulator levels respectively (Levelt, 1989). In this dichotomy, phonetic errors refer to speech errors caused by motor impairment, while phonemic errors are made at

the phonological encoding level of the formulation process, and are therefore considered a feature of aphasia (Ash et al., 2010; Bock & Levelt, 1994). The key perceptual difference is that phonetic errors are distortions of correctly selected phonemes, whereas phonemic errors involve clearly articulated insertions, deletions or substitutions of speech sounds into the incorrect part of the word (Ash et al., 2010). The theoretical distinction between motoric based (phonetic) and linguistically based (phonemic) speech errors as proposed by Robin and colleagues (2008) can be criticized for its arbitrariness, and for lacking clarity regarding why these functions are mutually exclusive (Ziegler et al., 2012). Nevertheless, speech errors resulting from AOS have been clinically differentiated from phonological representations of words due to the fact that people with AOS are aware of their intended utterances, and in particular the way in which it should sound, thereby indicating that phonological representations of utterances are preserved with degradation at the planning level of motoric movement (Hillis et al., 2004).

A visual representation of Levelt's model (1989) has been provided (Figure 1-1) to assist with the conceptualisation of the model. The syndromes which are the focus of this thesis have been listed alongside the model, at the point of the model which corresponds to the primary impairment that characterises the syndrome. It is important to note that each of the syndrome may affect language processing at other levels of the model; however, the figure focuses on the primary level(s) of breakdown of verbal expression as presented in the diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). For example nfvPPA may affect articulation (dysarthria), and phonological encoding, however the diagnostic criteria refer only to apraxia of speech (phonetic encoding) and agrammatism (positional processing). Therefore nfvPPA is listed in Figure 1-1 at the phonetic encoding and positional processing levels of the model only.

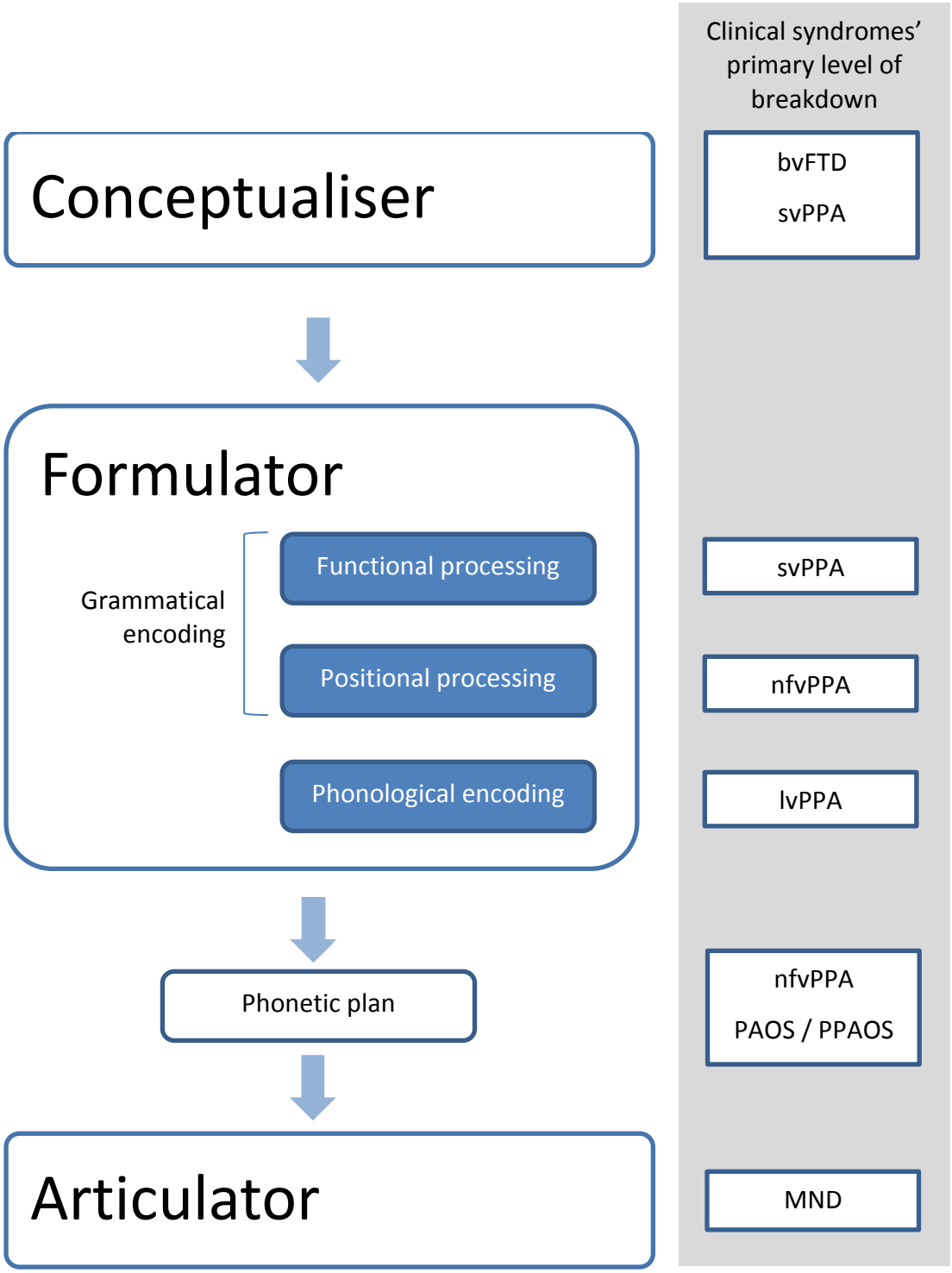

Figure 1-1. Levelt's model of information processing (left; Bock & Levelt, 1994; Levelt, 1989) adapted to include primary level of breakdown in the speech production process for each FTD, MND and PPA syndrome (right). Conditions are listed at the level corresponding to their primary level of breakdown as described in the diagnostic criteria, however each syndrome may also experience changes at other levels of the model. Communication change in bvFTD is characterised by aspontaneity and loss of social convention (Neary et al., 1998); svPPA characterised by loss of semantic memory (conceptualiser) and link to lexical items (formulator; Gorno-Tempini et al., 2011); nfvPPA by agrammatism and/or apraxia of speech (Gorno-Tempini et al., 2011); lvPPA by impaired phonological processing (Gorno-Tempini, Dronkers, et al., 2004; Gorno-Tempini et al., 2011); PAOS and PPAOS by impairment of speech motor programs (AOS; Josephs et al., 2013); and MND by impaired execution of phonetic plans (dysarthria; Tomik & Guiloff, 2010).

The terms *dysfluent* and *nonfluent* require clarification due to their reference to different speech behaviours. Fluency of speech is a key feature for the characterisation of aphasia post stroke (Goodglass, Barresi, & Kaplan, 1983), and 'nonfluent' is used to refer to forms of aphasia (e.g., Broca's) where reduced fluency is characterised by agrammatism which may co-occur with AOS (Geschwind, 1967). 'Nonfluent' was used by Mesulam (1982) when describing two of the six patients in his initial series, due to their speech profile resembling Broca's aphasia, and the term was incorporated into Neary and colleagues' (1998) diagnostic criteria of FTD to describe a progressive disorder of effortful speech, and phonological and grammatical errors (progressive nonfluent aphasia). Therefore, the terms 'nonfluent' and 'agrammatic' are often used interchangeably in descriptions of both progressive and non-progressive aphasia, with the former term often suggesting the presence of grammatical deficits (Gorno-Tempini et al., 2008; Thompson et al., 2012). In contrast, the term 'dysfluent' is used to describe reduced fluency regardless of its cause, and is inclusive of the hesitancy and pausing associated with lvPPA (Mesulam et al., 2008). Chapter Two provides a comprehensive systematic review of the speech disorders that can be present in PPA and FTD, and the ways in which these impairments are assessed.

1.3 Clinical and imaging presentations of clinical variants

A patient must first meet the criteria of primary language impairment outlined by Mesulam (2001) before they can be classified as a subtype of PPA. The patient is subsequently classified based on clinical features and neuroimaging defined by the international consensus criteria (Gorno-Tempini et al., 2011). The clinical diagnostic criteria for the three PPA syndromes are outlined in Table 1-1.

Table 1-1: Clinical features of PPA variants

	svPPA	nfvPPA	lvPPA
Spontaneous speech	Fluent, circumlocutory, empty speech, semantic errors, grammatically correct	Dysfluent, agrammatic, articulatory errors	Slow rate, word-finding pauses, phonemic paraphasias
Motor speech	Spared	Impaired	Spared
Single word comprehension	Impaired	Initially spared	Relatively spared
Grammar comprehension	Initially spared	Impaired for grammatically complex sentences	Impaired for simple and complex sentences
Sentence repetition	Spared	Possibly impaired	Impaired
Naming	Anomia (nouns>verbs)	Spared initially, anomia emerges with progression (verbs>nouns)	Impaired
Verbal fluency	Impaired (categorical>letter)	Impaired (letter>categorical)	Impaired
Reading	Surface dyslexia	Phonological dyslexia	Phonological dyslexia

*Adapted from Seelaar, Rohrer, Pijnenburg, Fox, and van Swieten (2011).

1.3.1 Nonfluent/agrammatic variant PPA

The nonfluent/agrammatic variant of PPA is a language onset form of FTD. The prominent features of nfvPPA in the ICC are apraxia of speech and agrammatism of expression, which often become evident alongside early word finding difficulties (Gorno-Tempini et al., 2011). Deficits of grammatically accurate expression are often mirrored by impaired comprehension of grammatically and syntactically complex sentences. AOS, characterised by slow and labored speech production with distorted speech sounds and impaired prosody, is well established as one of the core deficits in the nonfluent variant of PPA (Gorno-Tempini et al.,

2011). Researchers directly examining speech disorders of nfvPPA have documented bradylalia, phonetic errors and impaired prosody (Amici, Gorno-Tempini, Ogar, Dronkers, & Miller, 2006; Ash et al., 2013; Leyton et al., 2011).

Atrophy and/or hypometabolism in the left inferior frontal gyrus, insula, premotor cortex and supplementary motor area are supportive imaging features for a clinical diagnosis of nfvPPA (Gorno-Tempini, Dronkers, et al., 2004; Gorno-Tempini et al., 2011; Grossman et al., 1996; Josephs et al., 2006; Nestor et al., 2003a). Mandelli and colleagues (2016) have suggested that early atrophy in nfvPPA begins in a dorsal section of the pars opercularis in the inferior frontal gyrus. As the disease progresses, pathology spreads to neighbouring regions through the aslant tract, superior longitudinal fasciculus and arcuate fasciculus (Mahoney et al., 2013; Mandelli et al., 2016; Schwindt et al., 2013). It has been suggested that damage to the superior longitudinal fasciculus (SLF) plays a central role in the linguistic deficits of nfvPPA (Galantucci et al., 2011; Whitwell et al., 2010). Furthermore, damage to the superior tracts of the SLF may contribute to the presentation of AOS due to connections with the premotor and primary motor cortices (Makris et al., 2005). Longitudinal studies of nfvPPA indicate that degeneration spreads to the left posterior regions of the inferior, middle and superior frontal gyri, SMA, insula, striatum, inferior parietal lobe, anterior temporal lobe, fusiform gyrus and the white matter underlying these regions (Brambati et al., 2015; Mandelli et al., 2016; Rogalski, Cobia, Harrison, Wieneke, Weintraub, et al., 2011).

1.3.2 Semantic variant PPA

The semantic variant of PPA (svPPA) is another language-onset form of FTD, also referred to as PPA-semantic (Dickerson, 2010) or semantic dementia (Hodges et al., 1992). The primary deficit of this syndrome involves the semantic system, presenting primarily as impaired confrontation naming and impaired single word comprehension (Gorno-Tempini et al., 2011). Typically, these features are accompanied by loss of object knowledge, and surface dyslexia and dysgraphia are often present due to reduced access to the semantic system while reading and writing (Gorno-Tempini et al., 2011). In general, svPPA is not considered to have any form of motor speech disorder (Ash et al., 2013), and the absence of motor speech disturbance is a secondary diagnostic characteristic (Gorno-Tempini et al., 2011). Despite this, fluency of extemporaneous speech can be reduced due to word finding

difficulties in conversation and connected speech tasks (Amici, Gorno-Tempini, Ogar, Dronkers, & Miller, 2006; Ash et al., 2013).

A diagnosis of svPPA is supported by neuroimaging that indicates anterior temporal lobe atrophy, hypoperfusion or hypometabolism (Gorno-Tempini et al., 2011), in line with findings of bilateral damage in these areas, often predominantly in the left hemisphere (Gorno-Tempini, Dronkers, et al., 2004; Hodges et al., 1992; H. J. Rosen et al., 2002). Semantic memory is considered to be impaired due to damage in the anterior temporal lobe (Mummery et al., 2000). White matter degradation is observed in tracts adjacent to the anterior temporal lobe, including bilateral connections between the temporal lobe and occipital and orbitofrontal cortices (the uncinate, and inferior longitudinal fasciculi), and left sided pathways from the temporal lobe to the parietal and frontal lobes (arcuate and superior longitudinal fasciculi; Acosta-Cabronero et al., 2011; Galantucci et al., 2011; Mahoney et al., 2013; Schwindt et al., 2013). Disease progression in svPPA involves the spread of atrophy through anterior temporal, inferior frontal and orbitofrontal regions of grey matter, and adjacent white matter including fronto-occipital, uncinate and inferior longitudinal fasciculi (Brambati et al., 2015; Brambati et al., 2009; Rogalski, Cobia, Harrison, Wieneke, Weintraub, et al., 2011). The anterior progression of atrophy in svPPA is often associated with the emergence of behavioural symptoms similar to those of bvFTD such as apathy and loss of empathy (Brambati et al., 2009).

1.3.3 Logopaenic variant PPA

The logopaenic variant of PPA was introduced as a third subtype to account for a presentation of dysfluent speech production without agrammatism or apraxia of speech (Gorno-Tempini, Dronkers, et al., 2004). This syndrome is characterised by a deficit of phonological processing which manifests as reduced rate of spontaneous speech, pauses due to word finding difficulties (WFD), phonemic paraphasias, and dysfluencies in the form of hesitations and false starts (Amici et al., 2006; Ash et al., 2013; Gorno-Tempini et al., 2008; Gorno-Tempini, Dronkers, et al., 2004). The associated neuroimaging involves abnormalities in the posterior left superior or middle temporal gyri and inferior parietal lobule, and the syndrome is considered an atypical presentation of Alzheimer's disease (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2011). Associated white matter damage involves the left superior longitudinal fasciculus and arcuate fasciculus (Galantucci et al., 2011). As the

disease progresses, more widespread regions of the left hemisphere are involved, including the anterior temporal lobe, caudate and frontal cortices, and the right perisylvian region (Rohrer et al., 2013).

1.3.4 Behavioural variant FTD

Behavioural variant FTD is characterised by a progressive alteration in personality and social conduct, including disinhibition, emotional blunting and loss of insight (Neary et al., 1998). Cognitive impacts of the pathology include deficits of attention, problem solving and executive function (Neary et al., 1998). As there is no known definitive biomarker for the syndrome, bvFTD is diagnosed based on core clinical features and associated brain imaging. Initial diagnostic criteria formulated by Neary and colleagues (1998) were revised by the International Behavioural Variant FTD Criteria Consortium (Rascovsky et al., 2011; Rascovsky et al., 2007). For a possible diagnosis of bvFTD, the criteria require an insidious onset and gradual decline as well as three of the following features early in the disease course: behavioural disinhibition, apathy or inertia, loss of empathy, executive dysfunction, hyperorality, or perseverative, stereotyped or compulsive behaviour. Memory and visuospatial function should be spared in the early stages of the disease (Rascovsky et al., 2011). FTD leads to higher levels of carer burden than other forms of dementia due to these marked behavioural changes and neuropsychiatric symptoms, which often lead to early institutionalisation (Riedijk et al., 2006).

In order to meet criteria for a 'probable' diagnosis of bvFTD, a patient must present with frontal and/or anterior temporal atrophy, hypometabolism or hypoperfusion in addition to functional decline primarily due to cognitive and/or behavioural symptoms (Rascovsky et al., 2011). Findings of bilateral involvement of the frontal lobes is consistent with the role of these regions in behavioural control, executive function, and social cognition (Cummings, 1993; H. J. Rosen et al., 2005). Finally, bvFTD with definite frontotemporal lobar degeneration (FTLD) pathology can be diagnosed if a person has histopathological evidence of FTLD pathology on biopsy or has a known pathogenic mutation (Rascovsky et al., 2011).

1.3.5 Progressive apraxia of speech (PAOS) and primary progressive apraxia of speech (PPAOS)

PAOS and PPAOS are considered alongside the PPA spectrum of disorders due to their overlapping clinical features with nfvPPA. PPAOS is defined as an isolated progressive AOS without aphasia or other cognitive decline due to focal atrophy of the superior premotor cortex (Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014; Josephs et al., 2012). Cases of PAOS may present with both AOS and agrammatic aphasia, and are therefore clinically similar to nfvPPA. While a presentation of progressive AOS with minimal agrammatic aphasia can be considered to meet the ICC for nfvPPA (Gorno-Tempini et al., 2011), there is some debate as to whether this is appropriate in cases where AOS is a more prominent and early sign of degeneration (Josephs et al., 2013). Josephs and colleagues (2013) have suggested that cases of nfvPPA in which the communication impairment is predominantly AOS should be classified as PAOS as they have more features (clinical and regions of neuropathology) in common with PPAOS. Presentations of PPAOS and PAOS can develop at markedly different rates, with come cases retaining a syndrome dominated by AOS without cognitive change for many years, and others developing a PSP syndrome with a more rapid progression (Brodtmann, Pemberton, Darby, & Vogel, 2016; Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014).

1.4 Clinicopathological links to motor neurone disease, progressive supranuclear palsy and corticobasal syndrome

Clear clinical, pathological and genetic links between FTD and MND have now been established, contrary to earlier conceptions that the two were distinct disorders, and this has prompted the establishment of consensus criteria for frontotemporal dementia with motor neurone disease (FTD-MND; Devenney, Vucic, Hodges, & Kiernan, 2015; Strong et al., 2009). It has been estimated that 10-15% of people with bvFTD develop motor impairments which are sufficient to meet criteria for MND, and can therefore be considered to have the FTD-MND syndrome (Burrell, Kiernan, Vucic, & Hodges, 2011; Giordana et al., 2011). In addition to these cases, more than a third of people with FTD present with signs of motor dysfunction including weakness, muscle atrophy or fasciculations (Burrell et al., 2011) which do not meet clinical criteria for MND. At the opposite end of the continuum, up to 45% of people with MND develop executive function deficits similar to those observed in bvFTD,

and up to a quarter can be diagnosed with a dementia which is consistent with a bvFTD profile (Lillo, Savage, Mioshi, Kiernan, & Hodges, 2012; Phukan et al., 2012). In support of the overlapping clinical features, pathological and genetic links have been observed. In particular, the TDP-43 protein is the underlying cause of a majority of MND cases and significant proportion of FTD cases (Neumann et al., 2006). Furthermore, the *C9orf72* intronic repeat mutation has been identified as a strong genetic link, causing 70-80% of FTD-MND cases (DeJesus-Hernandez et al., 2011; Devenney, Vucic, et al., 2015; Renton et al., 2011; Rohrer et al., 2015).

The FTD spectrum of disorders also overlaps with the parkinsonian disorders of PSP and CBS. PSP is characterised by parkinsonism, supranuclear gaze palsy, postural instability and falls (Litvan et al., 1996). In addition to these diagnostic features, behavioural and cognitive changes impact upon quality of life (Burrell, Hodges, & Rowe, 2014; Schrag et al., 2003). As in bvFTD, these include apathy, impulsivity, executive dysfunction and impaired social cognition (Bak, Crawford, Berrios, & Hodges, 2010; Burrell et al., 2014; Ghosh, Rowe, Calder, Hodges, & Bak, 2009; O'Sullivan et al., 2010). Speech disorder is present early in the disease process and has been described most commonly as spastic dysarthria, though can present as predominantly hypokinetic or ataxic dysarthria in some cases (Kluin et al., 1993; Rusz et al., 2015; Skodda et al., 2011a). The dysarthria profile in PSP is characterized by speech dysfluencies, slow rate, impaired vowel and consonant articulation and a harsh voice quality (Rusz et al., 2015; Skodda et al., 2011a). A number of case studies and series have also identified AOS as a presenting feature of PSP (Josephs & Duffy, 2008).

Multiple diagnostic criteria have been proposed for CBS due to the variability of its clinical features, however most criteria describe asymmetric limb apraxia, parkinsonism, myoclonus, dystonia and alien limb phenomenon (Burrell et al., 2014). A significant proportion of CBS cases develop progressive nonfluent aphasia or features of bvFTD, such as apathy and disinhibition (Kertesz, Martinez-Lage, Davidson, & Munoz, 2000). Other cognitive changes include impaired executive and visuospatial functions (Pillon et al., 1995). In relation to speech production, apraxia of speech is commonly present (Boeve, Lang, et al., 2003), as well as hypokinetic or spastic dysarthria, characterized by poor respiratory control, articulatory imprecision, reduced rate, increased pitch and strained voice quality (Blake et al., 2003; Boeve, Lang, et al., 2003). Findings of AOS and nonfluent aphasia as an early feature in confirmed cases of corticobasal degeneration (CBD) and PSP highlight the overlap of these syndromes with PPA, and similarly the parkinsonian disorders may develop as a

secondary syndrome in some cases of PPA and PAOS (Josephs et al., 2005; Santos-Santos et al., 2016).

1.5 Pathology

Three types of pathology cause the majority of cases of FTD and PPA. These include two forms of frontotemporal lobar degeneration pathology (FTLD-TAU and FTLD-TDP) and Alzheimer's disease pathology. Each of the FTD and PPA subtypes can be caused by a range of pathologies, however the majority of nfvPPA cases have tau-positive pathology (including Pick bodies, corticobasal degeneration pathology and progressive supranuclear palsy pathology), and the majority of svPPA cases have TDP-43 ubiquitin-positive pathology (Chare et al., 2014; Grossman, 2010; Mesulam, 2013; Mesulam et al., 2014). Logopaenic variant PPA is most often associated with Alzheimer's disease (Chare et al., 2014; Josephs et al., 2008). The majority of bvFTD cases are caused by tau or TDP-43 pathologies (Chare et al., 2014). Accurate clinical diagnosis of the various types of PPA is therefore important in that it provides for some prediction of the nature of the pathology (Mesulam, 2013).

1.6 Genetics

Approximately 30-40% of FTD cases are familial, and about 10% are inherited in an autosomal dominant fashion (Devenney, Bartley, et al., 2015; Rohrer et al., 2009). It has been estimated from case series data that up to a third of PPA cases have a family history of PPA or other FTD related syndrome (Rohrer, 2014). Heritability differs between clinical variants. Thirty to forty percent of nfvPPA cases have a family history, whereas svPPA and lvPPA are more sporadic, with only 10-20% of cases having a family history (Goldman et al., 2005; Rohrer et al., 2009). Three genetic mutations have been associated with the majority (60%) of familial FTD cases. These are mutations in microtubule-associated protein tau (*MAPT*), granulin (*GRN*), and hexanucleotide expansion intronic repeats in chromosome 9 (C9orf72; Olszewska, Lonergan, Fallon, & Lynch, 2016).

An estimated 10-20% of familial FTD cases are caused by the *MAPT* mutation, causing accumulations of tau without amyloid deposition (Mackenzie & Neumann, 2016), which results in initial symptoms of disinhibition, social changes and hyperorality (Olszewska et al., 2016). PPA has not been associated with *MAPT* mutations in large cohort studies (Rohrer,

2014). *GRN* mutations are estimated to be the cause of 5-20% of familiar FTD cases (Olszewska et al., 2016), and are known to cause ubiquitin-positive neuronal inclusions without tau (Cruts et al., 2006; Lendon et al., 1998). The associated phenotype of *GRN* mutation is bvFTD in the majority of cases, while smaller proportions present with a progressive aphasia (16%) or CBS (6%; Le Ber et al., 2008). The *GRN* mutation has been associated with nfvPPA in a small number of cases that present with prominent anomia but without AOS (Rohrer, Crutch, Warrington, & Warren, 2010; Snowden & Neary, 2003; Snowden et al., 2008). Most cases of *C9orf72* develop bvFTD or FTD-MND syndromes (DeJesus-Hernandez et al., 2011; Renton et al., 2011). An investigation of the *C9orf72* mutation by PPA subtype found that 27% of mutations resulted in the nfvPPA syndrome and 9% the svPPA syndrome (Renton et al., 2011).

Four genome wide association studies (GWAS) have been conducted for FTLD. Van Deerlin and colleagues (2010) identified Transmembrane protein 106B (*TMEM106B*) as a genetic risk factor in 515 FTLD participants with TDP-43 pathology. In a larger study of 2154 participants separated by subtype (bvFTD, semantic dementia, progressive nonfluent aphasia, FTD-MND), Ferrari and colleagues (2014) identified an association with three single nucleotide polymorphisms (SNPs) near the *HLA* (human leucocyte antigen) locus on chromosome 6p21.3. A potential locus was also identified at chromosome 11 encompassing *RAB38* and *cathepsin C* (*CTSC*) for bvFTD participants (Ferrari et al., 2014). A subset of Italian participants (n = 530) from the GWAS study by Ferrari and colleagues (2014) were analysed separately, and highlighted potential loci on a region of chromosome 2p16.3 and 17q25.3 encompassing *CEP131*, *C17ORF89*, and *ENTHD2* (Ferrari et al., 2015). A recent analysis was conducted by Mishra and colleagues (2017) using the multiple regression approach MAGMA (de Leeuw, Mooij, Heskes, & Posthuma, 2015) with GWAS summary data from the study by Ferrari and colleagues (2014). The analysis separated clinical variants, and identified associations with the *TOMM40* and *APOE* genes with bvFTD, and *ARHGAP35* and *SERPINA1* genes with progressive nonfluent aphasia (Mishra et al., 2017).

1.7 Progression of clinical features in PPA and FTD

While international consensus criteria for PPA have been established based on cross-sectional data, longitudinal observations indicate that a single case may present with multiple clinical presentations over the disease course (Harciarek, Sitek, & Kertesz, 2014). As the nfvPPA

syndrome progresses, the initial agrammatism of verbal expression and auditory comprehension are mirrored by qualitatively similar impairments of reading and writing (Graham, Patterson, & Hodges, 2004). Patients may also develop extrapyramidal features consistent with CBS or PSP (Josephs et al., 2005; Santos-Santos et al., 2016), and/or behavioural and cognitive changes similar to bvFTD (Marczinski, Davidson, & Kertesz, 2004).

The pathological overlap between svPPA and bvFTD is often noted in clinicopathological investigations, and svPPA cases often develop behavioural change, including disinhibition, social inappropriateness, and sweet tooth (Kertesz, Jesso, Harciarek, Blair, & McMonagle, 2010; H. J. Rosen et al., 2006). These behavioural changes have been suggested to assist in delineation of both svPPA and nfvPPA from lvPPA (Van Langenhove, Leyton, Piguet, & Hodges, 2016). The semantic based language impairment of svPPA leads to speech which is progressively emptier, and eventually results in mutism (Kertesz et al., 2010).

Progression in lvPPA typically involves the development of impaired episodic memory in addition to phonological encoding and word finding deficits, resulting in a profile more similar to amnesic Alzheimer's disease (Harciarek et al., 2014). Development of motor symptoms are less common than in nfvPPA (Gorno-Tempini et al., 2011; Harciarek et al., 2014).

The development of alternative syndromes is common in bvFTD, and more than half of cases develop signs of nonfluent aphasia or semantic loss, while approximately a quarter develop CBS or PSP symptoms (Kertesz, Blair, McMonagle, & Munoz, 2007). In contrast, a subgroup of people diagnosed with possible bvFTD demonstrate minimal or no progression and are termed phenocopy cases (Devenney, Bartley, et al., 2015).

1.8 Limitations of the ICC classifications for PPA

Multiple studies have highlighted several weaknesses of the PPA diagnostic criteria, with as many as 41% of PPA cases not being classified by the ICC (Botha et al., 2015; Harris et al., 2013; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Sajjadi, Patterson, Arnold, Watson, & Nestor, 2012; Wicklund et al., 2014). Many cases that are not classified have been hypothesised to have been too early in the disease process to identify cognitive impairments on testing (Botha et al., 2015; Wicklund et al., 2014). In contrast, other

unclassifiable cases meet criteria for multiple PPA subtypes simultaneously, either due to a severe global aphasia (Wicklund et al., 2014) or mixed features (Sajjadi et al., 2012). A mixed-PPA presentation, characterised by agrammatism and impaired word comprehension, has been described (Mesulam et al., 2009). Mixed-PPA is associated with inferior frontal and anterior temporal atrophy, and has been demonstrated to be present even in the early stages of the disease (Mesulam et al., 2012). There are also many cases which remain unclassifiable because they present with a profile largely consistent with lvPPA but with preserved repetition (Mesulam et al., 2014; Sajjadi et al., 2012).

Further debate over classification has occurred over the spectrum of PAOS and nfvPPA. The ICC include cases of prominent AOS with aphasia in the nfvPPA sub-classification; however, this has been disputed as these cases do not have aphasia as their presenting feature (Josephs et al., 2013; Wicklund et al., 2014).

1.9 Justification and aims

Evaluation of speech production is necessary for the classification of PPA subtypes in both clinical and research contexts. In the research literature, more accurate characterisation is required to address the issue of unclassifiable cases of PPA (Sajjadi et al., 2012; Wicklund et al., 2014). One of the current difficulties of this process is the broad range of tests and methods that are being implemented by different research groups (for a review see Poole et al., 2017). These limitations have led some to suggest that AOS be removed from the PPA ICC criteria due to lack of quantifiable measures, reliance on expert opinion, and diversity of definitions provided by different research groups (Sajjadi et al., 2012). Attempts to address these limitations have involved detailed evaluation of connected speech changes to establish a quantifiable measure of features such as fluency, rate, phonetic and phonemic errors, and syntax (Ash et al., 2013; Wilson et al., 2010). While these efforts have led to a more detailed and consistent understanding of spontaneous speech changes in PPA and FTD, their application does not extend to clinical practice due to their time intensive nature. Instead, clinical practice currently involves the use of perceptual (listener-based) evaluation of speech features. While perceptual assessment can be readily administered in the clinical setting, evaluations can vary between and within raters, even those with expertise in speech and language disorders (Kent, 1996). In progressive neurological disorders, poor intra-rater

reliability may lead to a lack of accuracy and sensitivity of both the direction and magnitude of change over time.

Currently there is no quantifiable method for evaluating the loss of fluency due to word finding difficulties during connected speech, despite being a core diagnostic feature of lvPPA (Gorno-Tempini et al., 2011). Furthermore there may be application for objective measures that clarify the distinctions between nfvPPA, PAOS and PPAOS, which have been considered to be different stages on a single disease progression by some authors (Gorno-Tempini et al., 2011), and distinct entities by others (Josephs et al., 2013). Currently this distinction is based on expert judgement as to the relative severity of the AOS and agrammatic aphasia, and objective quantifiable correlates of AOS may assist in clarifying and diagnosing these phenotypes. Finally, speech acoustic methods could be applied to identifying the development of motor speech impairments associated with secondary syndromes of PSP, CBS and MND.

Speech acoustic methods offer an opportunity to objectively measure spontaneous speech production, as they do not involve the judgement of an expert rater, nor the time intensive nature of detailed quantitative analysis of connected speech. In order to be effective, acoustic measures are required to be reliable to the construct being measured, sensitive to any real change occurring in the speech signal, and stable in the absence of any neurological change (Vogel, Fletcher, Snyder, Fredrickson, & Maruff, 2011; Vogel & Maruff, 2014).

Acoustic metrics, which could assist in classification and disease monitoring, would be applicable to both clinical and research contexts. In the research context, it would allow for comparable metrics to be used by different researchers/assessors, thereby leading to more consistent clinical evaluations for research of syndrome classification, the neural correlates of speech, and the pathological and genetic associations of specific speech features. In the clinical context, objective metrics may assist with the identification of a neurodegenerative speech disorder by establishing a sensitive baseline, classifying clinical variant, and providing an indication of the rate of progression. As disease-modifying treatments are developed into the future, sensitive speech measures may also assist in the evaluation of medications and speech therapies.

1.10 Conclusion

PPA and FTD can be sub-classified into at least four different syndromes, each of which affect speech production in a different manner. The current classification system provides some prediction for underlying pathology and genetic cause, however there are a proportion of cases of PPA that are not classifiable. Additionally, there are a number of overlapping disorders, including PAOS, MND, PSPS and CBS, which may emerge as a secondary syndrome for patients initially diagnosed with PPA or FTD. Currently, the perceptual approach to assessment presents limitations for accurate characterisation in both research studies and clinical settings. Quantifiable measures which identify the acoustic correlates of speech disturbance in PPA and FTD may provide greater sensitivity and reliability to speech assessments.

A justification of each of the acoustic metrics to be used in the study are presented in Chapter Three – Methodology. The current state of the literature which has aimed to classify the speech phenotypes of PPA and FTD is presented in Chapter Two as the published article 'Motor speech phenotypes of frontotemporal dementia, primary progressive aphasia, and progressive apraxia of speech' (Poole et al., 2017).

JSLHR

Review Article

Motor Speech Phenotypes of Frontotemporal Dementia, Primary Progressive Aphasia, and Progressive Apraxia of Speech

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AQ1 **Purpose:** Our purpose was to create a comprehensive review of speech impairment in frontotemporal dementia (FTD), primary progressive aphasia (PPA), and progressive apraxia of speech in order to identify the most effective measures for diagnosis and monitoring, and to elucidate associations between speech and neuroimaging.
Method: Speech and neuroimaging data described in studies of FTD and PPA were systematically reviewed. A meta-analysis was conducted for speech measures that were used consistently in multiple studies.
Results: The methods and nomenclature used to describe speech in these disorders varied between studies. Our meta-analysis identified 3 speech measures which differentiate variants or healthy control-group participants (e.g., nonfluent and logopenic variants of PPA from all other groups, behavioral-variant FTD from a control group). Deficits within the frontal-lobe speech networks are linked to motor speech profiles of the nonfluent variant of PPA and progressive apraxia of speech. Motor speech impairment is rarely reported in semantic and logopenic variants of PPA. Limited data are available on motor speech impairment in the behavioral variant of FTD.
Conclusions: Our review identified several measures of speech which may assist with diagnosis and classification, and consolidated the brain–behavior associations relating to speech in FTD, PPA, and progressive apraxia of speech.

Frontotemporal dementia (FTD) and primary progressive aphasia (PPA) are clinically and pathologically diverse groups of disorders. There are four distinct variants recognized by international consensus. These are the behavioral variant of FTD (bvFTD) and three PPA syndromes: nonfluent/agrammatic (nfvPPA), semantic (svPPA), and logopenic (lvPPA; Chare et al., 2014; Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Each syndrome has an insidious onset and gradual progression, affecting communication due to impairment of language, motor speech, executive function, or behavior. Progressive apraxia of speech (PAOS) and primary progressive apraxia of speech (PPAOS) are related syndromes which are primarily characterized by the motor programming disorder apraxia of speech (Josephs et al., 2013). Motor speech impairment is most commonly associated with nfvPPA, PAOS, and PPAOS (Gorno-Tempini et al., 2011; Josephs et al., 2013), as well as with movement disorders that have demonstrated clinical and pathological overlap with FTD and PPA (Harciarek, Sitek, & Kertesz, 2014; Josephs & Duffy, 2008; Lillo & Hodges, 2009), namely motor neuron disease, progressive supranuclear palsy syndrome, and corticobasal syndrome (Armstrong et al., 2013; Kiernan et al., 2011; Litvan et al., 1996).

This review examines the literature of motor speech disorders in FTD, PPA, and PAOS with the purposes of clarifying the characteristics and severity of speech impairment, providing an overview of the speech measures which are commonly used in research of these disorders, and summarizing the correlations between speech impairment and neuroimaging measures. In a meta-analysis of behavioral speech data, we aim to identify the measures of speech which are able to differentiate between subtypes of FTD, PPA, and PAOS. Clarification of speech phenotypes and identification of the most salient speech measures may assist with clinical monitoring for identification of onset,

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progression, and transition to related movement disorders. Furthermore, accurate diagnosis allows for greater prediction of the type of pathology underlying these disorders (Grossman, 2010). For example, nfvPPA is most commonly a tauopathy, and svPPA is typically associated with the TDP-43 protein (Hodges et al., 2010; Josephs et al., 2008; Mesulam, 2013; Mesulam et al., 2008).

There is considerable variation in the terminology used to describe the syndromes and their associated speech changes. These terms will be clarified prior to discussing the method of the review.

Speech Disorders

A variety of terms are used to refer to participants' verbal expression in the FTD, PPA, and PAOS literature. Motor speech disorders, broadly, should be distinguished from changes to speech which result from impairment of language (aphasia) or other cognitive deficits. Motor speech disorders of neurologic origin can be conceptually classified as *dysarthria*, *apraxia of speech* (AOS), or *acquired neurogenic stuttering*. Dysarthria describes disordered speech caused by weakness, spasticity, rigidity, incoordination, or involuntary movement of the muscles used in speech production. In contrast, AOS refers to a motor speech disorder caused by a deficit in the programming of the rapid succession of motor movements required for speech, despite intact and functional speech musculature (Kent, 2000). Neurogenic stuttering relates to interruptions of speech fluency that resemble developmental stuttering and have been reported following stroke and neurodegeneration (Theys, De Nil, Thijs, van Wieringen, & Sunaert, 2013).

Each of these disorders may cause articulatory errors which are termed *phonetic speech errors*. These are conceptualized in contrast to *phonemic speech errors*, which are usually considered to be a feature of aphasia. Phonemic errors refer to speech production errors predominated by sound substitutions, additions, and deletions within words (i.e., incorrect selection of speech sounds due to impaired phonological processing) which are related not to motor production, but to language dysfunction (Dell, Juliano, & Govindjee, 1993). Due to the similarities of these errors with those of AOS, articles reporting data on phonemic errors are also included in this review. The term *speech abnormality* has also been used in the literature to describe changes to participants' verbal expression where the distinction between motor speech, aphasia, and cognitive deficits has not been clarified. The terms *disfluent* and *nonfluent* also require clarification due to their reference to different causes of reduced speech fluency. Within the literature on progressive aphasia—and this review article—the term *nonfluent* is used to refer to a form of aphasia characterized by agrammatism which sometimes co-occurs with AOS. The term is used in a similar manner to nonfluent aphasias described in the literature relating to aphasia secondary to stroke (e.g., Broca's aphasia). Several authors also report disfluencies of verbal expression which are described as hesitations, false starts, and extraneous words, commonly due to word-finding difficulties and phonological selection errors. These errors are commonly seen in lvPPA, and should not be confused with nonfluent aphasia.

Clinical and Motor Speech Features

The clinical features of each of these disorders are outlined by diagnostic criteria provided by Neary et al. (1998) and Rascovsky et al. (2007) for bvFTD and by Gorno-Tempini et al. (2011) for the PPAs. Criteria for PAOS and PPAOS have been described by Josephs et al. (2013).

bvFTD

Characteristic of bvFTD is a progressive alteration in personality and social conduct, which may include disinhibition, emotional blunting, loss of insight, and executive dysfunction (Neary et al., 1998). Rascovsky et al. (2011) reported motor speech deficits in 15% of participants in their retrospective study; however, motor speech disorders are not included in the diagnostic criteria for bvFTD. Instead, the diagnostic criteria refer to changes of verbal expression which are related to impairment of pragmatic aspects of communication, such as talking for extended periods without allowing others to speak (press of speech) or apathy toward conversation (Neary et al., 1998). AQ2

nfvPPA

Individuals with nfvPPA (also known as progressive nonfluent aphasia, agrammatic PPA, and nonfluent/agrammatic PPA) present with nonfluent verbal output with agrammatism or effortful speech, as well as an associated impairment of comprehension of syntactically complex sentences (Gorno-Tempini et al., 2011). AOS is one of the two core diagnostic features of nfvPPA in the International Consensus Criteria (ICC; Gorno-Tempini et al., 2011).

svPPA

Also known as semantic-variant FTD or semantic dementia, svPPA is characterized by impairment of word comprehension, object knowledge, and word retrieval (Gorno-Tempini et al., 2011). Diagnostic criteria for svPPA specify the preservation of motor speech in the context of a fluent aphasic presentation (Gorno-Tempini et al., 2011).

lvPPA

The logopenic variant of PPA is characterized by an impairment of phonological processing (Gorno-Tempini et al., 2008, 2011) which presents clinically as a slow speech rate and frequent pauses secondary to word-retrieval difficulty. It is clearly delineated from nfvPPA, because there is no agrammatism of expression (Gorno-Tempini et al., 2011). The syndrome is recognized as a language-onset variant of Alzheimer's disease, and hence is not subsumed in the FTD taxonomy (Mesulam, Weintraub, et al., 2014). Speech production in lvPPA shares some features with nfvPPA due to the fact that both syndromes share a disruption in speech fluency (due primarily to agrammatism and/or

apraxia of speech in nfvPPA, and to word-retrieval difficulty and phonemic speech errors in lvPPA) and a reduced speech rate (Gorno-Tempini et al., 2011). In contrast to nfvPPA, an absence of motor speech impairment may contribute to a diagnosis of lvPPA—spared motor speech is one of four noncore diagnostic features in the ICC, of which three must be present for a diagnosis (Gorno-Tempini et al., 2011).

PAOS and PPAOS

PAOS is a related syndrome involving degenerative apraxia of speech. Agrammatic aphasia may be a secondary feature; however, AOS should be the most salient disturbance (Josephs et al., 2013). This presentation of PAOS and agrammatic aphasia has been subsumed by some authors under the nfvPPA subclassification, with the argument that individuals presenting initially with a progressive form of AOS often develop aphasia (Gorno-Tempini et al., 2011). However, it has also been suggested that people initially presenting with AOS do not have the requisite language disturbance at symptom onset, prohibiting a classification of PPA (Brodtmann, Pemberton, Darby & Vogel, 2016; Josephs et al., 2013; Mesulam, Rogalski, et al., 2014). Josephs et al. (2013) have proposed a distinction whereby syndromes dominated by aphasia are labeled PPA and those dominated by AOS are labeled PAOS. PPAOS has been proposed as a term reserved for cases of degenerative AOS without associated aphasia (Josephs et al., 2012, 2013).

ICC Nomenclature

For consistency, we use the ICC (Gorno-Tempini et al., 2011) terms when referring to the PPA variants: nfvPPA (also subsuming studies referring to agrammatic PPA, progressive nonfluent aphasia, and nonfluent/agrammatic PPA), svPPA (semantic-variant FTD and semantic dementia), and lvPPA (logopenic progressive aphasia). The exception to this will be the inclusion of the terms PPAOS and PAOS (which will also include groups labeled as PPA with dominant AOS), in line with the naming convention proposed by Josephs et al. (2013). There is a potential that some participants who could be labeled with PAOS under this definition (Josephs et al., 2013) may have been labeled with nfvPPA in earlier studies. Terms used in this review article will be consistent with those of the original authors.

Neuroimaging Profiles

Neuroimaging of people with bvFTD reveals atrophy of the frontal, insular, and/or anterior temporal lobes (Rascovsky et al., 2011). Brain-atrophy patterns in PPA syndromes share overlapping features, with some focal differences. There is evidence of predominant involvement of left posterior fronto-insular abnormalities for nfvPPA, left anterior temporal abnormalities for svPPA, and left posterior perisylvian or parietal abnormalities for lvPPA (Gorno-Tempini et al., 2011). There is further overlap of frontal atrophy between PAOS and nfvPPA; however, PAOS and PPAOS have been shown to have more focal atrophy in the superior premotor cortex and supplementary motor area (SMA; Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014; Josephs et al., 2013).

Method

The MEDLINE database was searched for all articles up to February 8, 2016, using the following terms: alzheimer*, (frontotemporal adj2 dementia), (frontal adj2 dementia), "semantic dementia," "progressive aphasi*," (logopenic adj3 aphasi*), (progressive adj2 (AOS or "apraxia of speech")), (frontotemporal adj2 degenerati*). Search results were combined using the Boolean term "AND" with: speech, dysarthri*, anarthri*, apraxi*, dyspraxi*, AOS, voice, vocal, language adj3 (disorder* or impair* or difficult*), communication adj3 (disorder* or impair* or difficult*). We identified 637 abstracts to consider for inclusion against specific criteria. Studies were included if they assessed verbal expression of people with FTD or PPA using objective measures, quantitative analysis, or subjective ratings of speech production using a severity scale. Exclusion criteria were review articles and studies examining disorders of language (except for phonemic errors). AQ3

Of the 637 studies, 47 met inclusion criteria. Studies were reviewed for participant overlap and were excluded if the same participant group was reported using the same assessment (studies were included if there was partial overlap of participants, or if they described different outcomes for the same group). Authors were contacted in cases where it was not clear if there was any overlap of participants. One study was subsequently excluded because it presented equivalent data for a smaller group of participants who were subsumed within another larger study in the review (Josephs et al., 2012). Behavioral data in studies by Grossman et al. (2013) and Whitwell, Duffy, Strand, Machulda, et al. (2013) were excluded, because they were subsequently reported by Ash et al. (2013) and Wicklund et al. (2014), respectively. However, unique neuroimaging data from Grossman et al. (2013) and Whitwell, Duffy, Strand, Machulda, et al. (2013) were retained. Behavioral data were therefore available and reported for 44 studies. The relationship between speech measures and neuroimaging data was reported in nine studies. Six of these studies involved investigations of gray matter (GM), one involved measurements of white matter (WM), and two involved investigations of both GM and WM.

A meta-analysis was conducted on behavioral data when there were two or more studies that reported data using the same form of assessment for the same pathological and control groups, and where means and standard deviations were reported. Studies were not considered when there were participant data reported in another study by the same group for the same metric (i.e., partial participant overlap was accepted into the review but not into the meta-analysis). Where there was partial participant overlap using the same speech metric, the study with the greater number of participants was included in the meta-analysis. Mean or

standardized mean differences were calculated on Review Manager (Version 5.3; the Cochrane Collaboration). Meta-analytic comparisons were not reported in cases where there were only two studies and one of the two had *M* and *SD* = 0. In these cases, a mean difference was not estimable and would involve reporting results of only one study. A total of 12 studies were included in the meta-analysis.

Further analysis was undertaken to account for inclusion of speech measures which were excluded from the meta-analysis due to lack of replication across studies. This analysis identified speech features which were found to be statistically significantly different from those of control groups in more than 80% of studies which provided group comparison with a control group. Studies were excluded from this analysis when there was complete or partial participant overlap. In these cases, the study with the larger number of participants was included. Twelve studies were included in this analysis.

Results

A summary of findings from each study is presented in Supplemental Material 1. A number of assessment tools were reported. Twenty-seven studies were conducted with listener-based severity rating scales (e.g., the Apraxia of Speech Rating Scale; Strand, Duffy, Clark, & Josephs, 2014). Connected speech was quantified in 15 studies by calculating metrics such as words per minute or number of phonetic speech errors. Atypical speech was examined with acoustic analysis in five studies with metrics such as length and variability of pauses, pairwise variability index, and diadochokinetic rate. A summary diagram of speech features which differ significantly from those of control groups is presented in Figure 1. These features were found to be statistically significant from those of a control group in 80% or more of studies which reported on that measure with a between-groups statistical comparison. This figure is an amalgamation of studies which may have defined participant populations differently. For example, some authors may have included participants with PAOS (as defined in this review) with the nfvPPA groups for their analyses.

Clinical Findings

bvFTD

Data for 184 participants diagnosed with bvFTD were reported in seven studies. Proportions reported in two studies indicate that 57%–74% of people with bvFTD present with atypical speech (Diehl & Kurz, 2002; Mendez, Joshi, Tassniyom, Teng, & Shapira, 2013). Dysarthria and AOS were rated on a severity scale in only one study (Wilson et al., 2010), with the authors reporting a mean dysarthria rating of 0.6/7 (n = 10). Six studies attempted to quantify speech errors in connected speech, most commonly by a broad measurement of speech rate (words/min) and number of speech errors, yet found no statistically significant differences (Ash et al., 2009, 2013; Gunawardena et al., 2010; Pakhomov et al., 2010; Wilson et al., 2010). Yunosova et al. (2016) provided more detailed analysis of speech rate and reported significant differences from their control group for the number, percentage, and variability of pauses in a speech sample.

nfvPPA

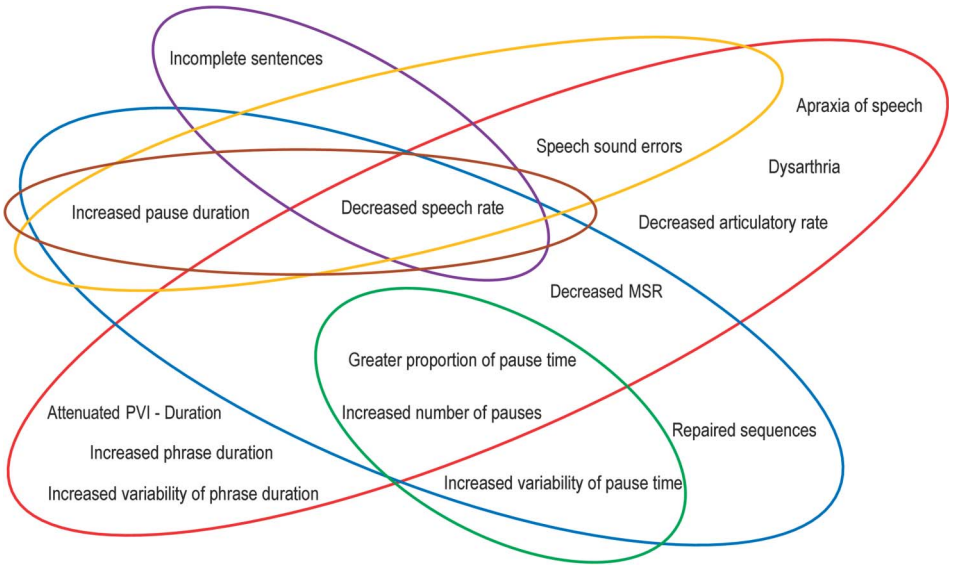
There were 434 participants from 35 studies with a diagnosis of nfvPPA. The majority of participants diagnosed with nfvPPA presented with signs of either AOS or agrammatism (e.g., slowed speech rate, impaired prosody, increased intersegmental duration, and both phonemic and phonetic errors). Those studies which specifically measured AOS with a severity scale identified average AOS ratings which ranged from mild to moderate; however, AOS ratings for individual participants ranged from absent to severe (Botha et al., 2015; Caso et al., 2013, 2014; Croot, Ballard, Leyton, & Hodges, 2012; Gorno-Tempini et al., 2011; Gorno-Tempini, Dronkers, et al., 2004; Gorno-Tempini, Murray, Rankin, Weiner, & Miller, 2004; Josephs et al., 2013; Mandelli et al., 2014; Mendez, Clark, Shapira, & Cummings, 2003; Miller et al., 2013; Ogar, Dronkers, Brambati, Miller, & Gorno-Tempini, 2007; Spinelli et al., 2015; Wicklund et al., 2014; Wilson et al., 2010). It should be noted that it is possible that individual participants in some studies who were labeled as having nfvPPA may have presented with a syndrome dominated by AOS, and whose presentation would therefore have been more consistent with a diagnosis of PAOS as defined in this review article.

Group differences for AOS severity and impaired fluency were found when comparing nfvPPA to other PPA variants (Croot et al., 2012; Gorno-Tempini, Dronkers, et al., 2004; Mandelli et al., 2014). Decreased accuracy of vowel production and nonverbal oral apraxia were also observed (Ackermann, Scharf, Hertrich, & Daum, 1997; Botha et al., 2014).

The prevalence of dysarthria in nfvPPA ranged from 18% (n = 11; Caso et al., 2014) to 60% (n = 18; Ogar et al., 2007) in studies which reported a proportion of cases. A significantly more severe average dysarthria rating for nfvPPA compared with semantic and logopenic PPA variants was reported in three studies (Miller et al., 2013; Rabinovici et al., 2008; Wilson et al., 2010). Spastic features (such as slow rate and strained voice) were the most common characteristics, followed by hypokinetic ones (such as breathy voice, monotone intonation, reduced breath support for speech, and difficulty with initiation of phonation).

Quantification of speech errors during connected speech indicated that, compared with control groups, the nfvPPA group had more speech sound errors (both phonetic and phonemic; Ash et al., 2009, 2010, 2013; Grossman et al., 2013; Knibb, Woollams, Hodges, & Patterson, 2009), longer average pause length (Rohrer, Rossor, & Warren, 2010b), and slower speech rate (Ash et al., 2009, 2010, 2013; Catani et al., 2013; Code, Ball, Tree, & Dawe, 2013; Fraser et al., 2014; Graham, Patterson, & Hodges, 2004; Grossman et al., 2013; Gunawardena et al., 2010; Knibb et al., 2009; Mesulam, Wieneke, Thompson, Rogalski, & Weintraub, 2012; Wilson et al., 2010). The same measures could also

AQ8 **Figure 1.** Speech characteristics of nonfluent-variant primary progressive aphasia (red), logopenic-variant primary progressive aphasia (blue), semantic-variant primary progressive aphasia (purple), behavioral-variant frontotemporal dementia (green), progressive apraxia of speech (yellow), and primary progressive apraxia of speech (brown). Speech characteristics were included where more than 80% of studies which tested that measure found a statistically significant difference from a healthy group.



differentiate nfvPPA from bvFTD and other PPA variants (Ash et al., 2009, 2013; Mesulam et al., 2012; Wilson et al., 2010). Filled pauses (words such as *umm* and *ahh*) were more common in nfvPPA compared with svPPA and bvFTD but not lvPPA (Wilson et al., 2010). Objective measures of speech fluency, such as average pause length, pause-to-word ratio, phrase duration, and proportion of pause within a sample identified the prosodic or agrammatic impairment of nfvPPA and could distinguish nfvPPA from other pathologies and the control group (Ballard et al., 2014; Pakhomov et al., 2010; Rohrer et al., 2010b; Yunusova et al., 2016). One objective measure of lexical stress patterns, the Pairwise Variability Index (PVI), was shown to have high sensitivity and specificity in distinguishing lvPPA and nfvPPA, which is significant because the two syndromes can be difficult to differentiate due to both having reduced speech fluency (Ballard et al., 2014).

svPPA

There were 241 participants in 16 studies diagnosed with svPPA. No AOS or dysarthria were described, with the single exception of a study by Thompson et al. (2012; $n = 6$), who reported a mild impairment of motor speech (rated on a scale inclusive of both dysarthria and AOS) for their participants, with a mean score of 40.83 out of a possible 50 (50 representing typical speech). Objective measurement during connected speech identified features which likely relate to the word-finding difficulties characteristic of svPPA, such as decreased speech rate (Ash et al., 2013; Fraser et al., 2014), increased use of the filler *um* (Fraser et al., 2014), and a higher number of incomplete sentences (Wilson et al., 2010) compared with a healthy control group.

lvPPA

There were 319 participants diagnosed with lvPPA in 20 studies. Motor speech impairments were rare in lvPPA. Although some authors reported impairment on scales of AOS and dysarthria (Brambati et al., 2015; Gorno-Tempini, Dronkers, et al., 2004; Graff-Radford, Duffy, Strand, & Josephs, 2012; Mandelli et al., 2014; Thompson et al., 2012; Wilson et al., 2009), there were no statistically significant differences when compared with controls (Gorno-Tempini, Dronkers, et al., 2004; Mandelli et al., 2014). Only three studies rated the presence of phonemic speech errors (Croot et al., 2012; Josephs, Duffy, Strand, Machulda, Vemuri, et al., 2014; Wicklund et al., 2014). Mean severity ratings in these studies ranged from questionable or mild to moderate, and one study reported a statistically significant increase compared with nfvPPA and PPAOS (Wicklund et al., 2014). In isolation, phonemic errors successfully distinguished between nfvPPA and lvPPA with 86% sensitivity but only 56% specificity (Croot et al., 2012). Quantification of connected speech showed lvPPA to have slower speech rate compared with controls and svPPA (Ash et al., 2013; Silveri et al., 2014; Wilson et al., 2010). Disfluent events (hesitations, false starts, extraneous words; Ash et al., 2013), repaired sequences (sequences of one or more complete word which were made redundant by subsequent amendments or elaborations), and filled pauses (words such as *umm*) were also more frequent in lvPPA (Wilson et al., 2010).

PAOS

One hundred participants with PAOS were included in seven studies. All participants presented with features of AOS which were necessary for their diagnosis. Further exploration of the speech deficits in one study found that participants (n = 37) presented with a form of AOS which affected prosody to a greater degree than articulation when compared with nfvPPA. Severity of AOS was also shown to correlate with increased nonverbal oral apraxia (Botha et al., 2014). Spastic dysarthria was observed in five participants with PAOS, one of whom also demonstrated signs of hypokinetic dysarthria (Josephs et al., 2013).

PPAOS

PPAOS was reported in 58 participants in five studies. Each participant presented with signs of AOS. Spastic dysarthria was shown to emerge later in the disease course for 5/15 participants in longitudinal studies, whereas an additional participant developed hypokinetic dysarthria and five others had equivocal features of dysarthria (Duffy et al., 2015; Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014). Two participants underwent acoustic analysis of speech and were found to have attenuated PVI and decreased temporal measures over the disease course. All 13 PPAOS participants in the larger longitudinal study developed parkinsonian features, with five receiving an updated diagnosis of a progressive-supranuclear-palsy-type syndrome (Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014).

Meta-Analysis of Behavioral Data

Nine studies were included in a meta-analysis of behavioral data. Results of 10 group comparisons are presented in Table 1. **T1** Pooled mean differences indicated that the nfvPPA pathological group is significantly slower than the svPPA, lvPPA, bvFTD, and healthy control groups on the measure of words per minute, and is significantly more severe compared with lvPPA when subjectively rated on the MSE dysarthria and AOS severity rating scales. **AQ9** In turn, the pooled mean difference indicated that the lvPPA group was slower on measures of words per minute compared with the svPPA, bvFTD, and healthy control groups, and had a greater number of phonemic errors compared with control groups. The bvFTD participants had a significantly slower speech rate (words/min) when compared with healthy control groups. Forest plots for each comparison are provided in Supplemental Material 2.

Brain–Behavior Associations

AQ10 Brain–behavior relationships between speech measures and damage to GM or WM were reported in nine studies (see Table 2). **T2**

GM

Measures of GM were correlated with qualitative or quantitative speech measures in seven studies (Ash et al., 2009; Ballard et al., 2014; Grossman et al., 2013; Gunawardena et al., 2010; Rohrer et al., 2010a; Whitwell, Duffy, Strand, Xia, et al., 2013; Wilson et al., 2010). In three of these studies, significant correlations between speech measures and neuroanatomical regions of interest were identified for nfvPPA. Reduced diadochokinetic rate was associated with GM atrophy in the pars opercularis (n = 16; Rohrer et al., 2010a). Speech rate correlated with atrophy in the lateral portion of the left inferior frontal cortex (n = 14; Grossman et al., 2013) and with cortical thickness in the inferior frontal cortex bilaterally and an adjacent region of the left anterior superior temporal cortex (n = 8; Gunawardena et al., 2010).

The relationship between speech measures and brain regions was investigated for mixed pathological groups in three studies. Ash et al. (2009) reported a significant correlation between words per minute and thinning of the inferior frontal and superior temporal cortex in a mixed group of participants with nfvPPA (n = 6), svPPA (n = 7), and bvFTD (n = 9). Wilson et al. (2010) analyzed a group of participants with nfvPPA (n = 14), lvPPA (n = 11), svPPA (n = 25), and bvFTD (n = 10), and found that maximum speech rate was associated with GM atrophy in a range of areas in the left hemisphere, namely the inferior frontal gyrus, ventral precentral gyrus, SMA, posterior superior temporal gyrus, and supramarginal gyrus. The same group of participants also had a correlation between measures of speech fluency (false starts, filled pauses, and repaired sequences) and GM atrophy of the superior temporal gyrus, ventral frontal operculum, angular gyrus, and inferior parietal lobule.

Ballard et al. (2014) investigated speech associations with GM atrophy for a group of participants with nfvPPA (n = 19) and lvPPA (n = 18) and demonstrated that the SMA, precentral gyrus, and inferior frontal gyrus bilaterally were also associated with lexical stress through their analysis of PVI. A model of three variables (PVI duration measures for words with weak–strong lexical stress, variability of silence duration, and proportion of silence time) was shown to correlate significantly with GM atrophy in several areas: the middle frontal gyrus and postcentral gyrus bilaterally, as well as the left SMA and precentral gyrus and right pars opercularis and insular cortex. An additional model created by multivariate discriminant function analysis with two variables (the PVI durational measure for both weak–strong and strong–weak words) was shown to be associated with bilateral atrophy of the SMA, precentral gyrus, and inferior frontal gyrus. An association between scores on the Apraxia of Speech Rating Scale and GM volume of the left premotor cortex was identified for a group of 17 participants with PPAOS (Whitwell, Duffy, Strand, Xia, et al., 2013).

Schematic representations of the correlations identified between speech and GM abnormalities are presented for nfvPPA and PPAOS (see Figure 2), and for all groups **F2** examined together (bvFTD, svPPA, lvPPA, nfvPPA, healthy control; see Figure 3). The review did not identify any **F3** studies presenting correlations between speech and GM abnormalities for PAOS.

Table 1. Pooled mean difference for speech measures and groups included in the meta-analysis.

Group comparison		Measure	Studies	Participants	Pooled mean difference [95% confidence interval]	*Z*	*p*
nfvPPA	svPPA	Words/min	5	139	–46.32 [–71.82, –20.81]	3.56	**.0004**
		Phonemic errors/100 words	2	72	1.27 [0.17, 2.37]	2.26	.02
	lvPPA	Words/min	4	108	–23.79 [–47.23, –0.35]	1.99	**.05**
		MSE AOS rating scale	2	78	1.25[a] [0.35, 2.15]	2.71	**.007**
		MSE dysarthria rating scale	2	78	0.72[a] [0.23, 1.20]	2.91	**.004**
		Phonetic errors/100 words	2	69	5.05 [–5.70, 15.80]	0.92	.36
		Phonemic errors/100 words	2	69	2.28 [–2.28, 6.84]	0.98	.33
	bvFTD	Words/min	3	74	–59.63 [–87.50, –31.77]	4.19	**< .00001**
	Control	Words/min	6	174	–72.80 [–90.27, –55.33]	8.17	**< .00001**
		Phonemic errors/100 words	2	51	3.52 [–2.10, 9.15]	1.23	.22
		Proportion of silence time	2	78	.13 [.06, .20]	3.53	**.0004**
svPPA	lvPPA	Words/min	4	105	30.32 [18.32, 42.32]	4.95	**< .00001**
		Phonemic errors/100 words	2	83	–0.27 [–1.59, 1.05]	0.4	.69
	bvFTD	Words/min	2	70	–15.58 [–35.71, 4.56]	1.52	.13
	Control	Words/min	6	152	–25.73 [–55.23, 3.76]	1.71	.09
		Phonemic errors/100 words	2	65	1.11 [–1.76, 3.98]	0.76	.45
lvPPA	Control	Words/min	4	93	–52.37 [–80.48, –24.27]	3.65	**.0003**
		Phonemic errors/100 words	2	62	0.87 [0.04, 1.69]	2.06	**.04**
	bvFTD	Words/min	2	67	–36.39 [–53.50, –19.28]	4.17	**< .0001**
bvFTD	Control	Words/min	3	90	–26.69 [–42.79, –10.58]	3.25	**.001**

Note. Bold type indicates significant differences between groups. nfvPPA = nonfluent-variant primary progressive aphasia; svPPA = semantic-variant PPA; lvPPA = logopenic-variant PPA; AOS = apraxia of speech; bvFTD = behavior-variant frontotemporal dementia.

[a]Standardized mean difference is provided for the MSE rating scales.

AQ11

WM

Speech measures were compared to measures of WM integrity in four studies (see Table 2). Diffusion tensor imaging in individuals with PPA (nfvPPA [n = 9], svPPA [n = 8], and lvPPA [n = 8]) showed a correlation between speech production scores (a composite measure of the MSE and Western Aphasia Battery fluency ratings) and reductions in fractional anisotropy (FA) in tracts connecting the pre-SMA to BA44, SMA to BA6, BA44 to putamen, and SMA to the caudate (Mandelli et al. 2014). Diffusion tensor imaging data from a heterogeneous group of participants (nfvPPA [n = 14], lvPPA [n = 9], svPPA [n = 8], mixed PPA [n = 2], unclassified or severe PPA [n = 2]) examining the uncinate fasciculus and the frontal aslant tract showed reduced FA and increased radial diffusivity in the frontal aslant tract, which correlated with a reduction in speech rate (Catani et al., 2013). The frontal aslant tract connects the pars opercularis to the anterior cingulate cortex and medial regions of the superior frontal gyrus (including presupplementary motor and anterior cingulate areas).

AQ12

WM volume measured with voxel-based morphometry in 60 participants with PPA and bvFTD was shown to be associated with both maximum speech rate and number of speech distortions in the superior longitudinal fasciculus underlying the left frontal cortex (Wilson et al., 2010). A similar region of the right hemisphere was also associated with speech distortions, but to a lesser degree (Wilson et al., 2010).

Correlation analyses involving only the nfvPPA subtype found that reduced speech rate was associated with FA reductions in several WM tracts, including those connecting the SMA to the pars opercularis and caudate, the superior longitudinal fasciculus II/III (n = 9; Mandelli et al., 2014), and the left anterior corpus callosum (n = 14; Grossman et al., 2013). Total number of speech distortions in nfvPPA participants was also associated with reduced FA between the pre-SMA and pars opercularis, as well as connections between the SMA and caudate and the SMA and the ventral premotor cortex (n = 9; Mandelli et al., 2014).

Discussion

Behavioral data reported in this review article bring together existing knowledge on the characteristics of motor speech impairments in each variant of FTD, PPA, and PAOS. Motor speech disorder is most commonly reported in cases of the nonfluent variant of PPA compared with other PPA subtypes, and is associated with neuroimaging abnormalities in frontal-lobe speech regions. Motor speech impairment is rare in svPPA and lvPPA and requires more accurate documentation in bvFTD. Concomitant dysarthria is a common feature of nfvPPA and PPAOS, particularly later in the disease progression. A number of quantitative speech measures, such as speech rate and articulatory errors, have demonstrated the capacity to differentiate PPA subtypes and may be useful in monitoring disease progression and identifying the emergence of changes to motor speech over time.

Meta-Analysis of Behavioral Data

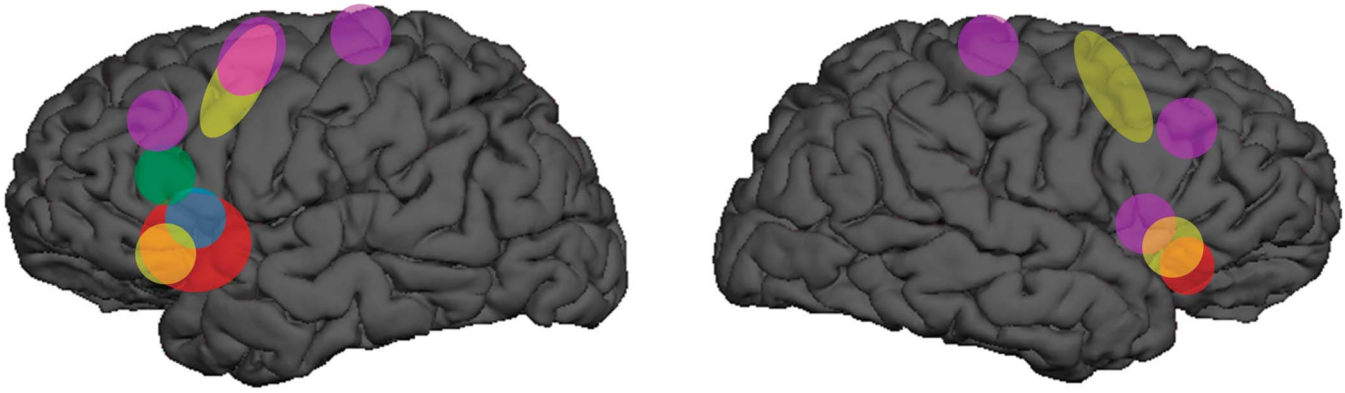
The meta-analysis for atypical speech in these syndromes was limited due to the lack of replication across

Table 2. Neuroimaging data from studies investigating brain–behavior associations.

Study	Participant diagnoses	Imaging method	Findings
Ash et al. (2009)	6 nfvPPA, 7 svPPA, 9 bvFTD, and 10 HC	VBM from 3T MRI for 17 participants and 1.5T for remaining 5 participants	When interpreting results for the entire cohort, words/min correlated with thinning in the left IFG and STG
Ballard et al. (2014)	37 PPA (18 lvPPA, 19 nfvPPA), and 11 HC	VBM from 3T MRI	Model 1 (see Table 1) showed a significant correlation with atrophy in the MFG and PoG bilaterally, the SMA and PrG on the left side, and the pars opercularis and insular cortex on the right side. Model 2 (see Table 1) demonstrated a significant correlation with bilateral atrophy of the SMA, PrG, and IFG
Catani et al. (2013)	35 PPA (9 lvPPA, 14 nfvPPA, 8 svPPA, 2 mixed, 2 unclassified) and 29 HC	FA and RD quantified from 3T MRI with DTI	FA of the frontal aslant tract demonstrated a positive correlation with words/min, whereas RD had an inverse correlation with the same measure. The uncinate fasciculus measures (FA and RD) did not correlate with measures of speech fluency
Grossman et al. (2013)	14 nfvPPA and 28 HC	FA quantified from DWI of 9 participants who underwent 3T MRI	Regression analysis of speech rate demonstrated a relationship with GM atrophy in the lateral portion of the IFG in the left hemisphere. Regression analysis revealed reduced words/min was related to reduced FA in left anterior corpus callosum
Gunawardena et al. (2010)	8 nfvPPA, 7 bvFTD, and 13 HC	Voxelwise cortical-thickness measures from 3T MRI for 6 nfvPPA and 7 bvFTD; 2 nfvPPA underwent 1.5T MRI	Reduced words/min in the nfvPPA group was related to thinner cortex of the IFG (L > R) and left anterior STC **AQ13**
Mandelli et al. (2014)	25 PPA (9 nfvPPA, 8 svPPA, 8 lvPPA) and 21 HC	FA quantified from 3T MRI (T1 weighted and DWI)	Speech production score correlated with left frontal speech tracts (BA44–pre-SMA, ventral PMC–SMA, BA44–putamen, SMA–caudate) in all PPA participants. In the nfvPPA group only, number of speech distortions (counted as per 100 words in WAB picture-description task) correlated with left BA44–pre-SMA, ventral PMC–SMA, and SMA–caudate, but not with SLF or AF. Rate of speech correlated with BA44–pre-SMA, SMA–caudate and SLF II/III in the left hemisphere
Rohrer et al. (2010a)	16 nfvPPA	VBM from 1.5T MRI	Reduced DDK rate correlated with GM atrophy in left pars opercularis
Whitwell, Duffy, Strand, Xia, et al. (2013)	18 AOS with agrammatic aphasia: 17 AOS only and 1 agrammatic aphasia only	Atlas-based parcellation technique used to calculate GM volume and FDG uptake from 3T MRI and FDG-PET	ASRS scores of the entire cohort did not correlate with any measures of GM volume or hypoperfusion at specific regions of interest. When analyzing only those participants with PPAOS, a significant relationship was identified between ASRS and left PMC
Wilson et al. (2010)	14 nfvPPA, 25 svPPA, 11 lvPPA, 10 bvFTD, and 10 HC	VBM from 1.5T (n = 50) or 4T (n = 10) MRI	Speech distortions associated with WM volume loss of SLF underlying frontal cortex (L > R). Reduced maximum speech rate associated with atrophy of left pars opercularis and triangularis, left ventral PrG, left SMA, and WM surrounding these regions (SLF), as well as posteriorly in left posterior STG and adjacent SMG. Increased false starts associated with atrophy of STG and ventral frontal operculum. Posterior regions of the left hemisphere were associated with filled pauses (posterior STG and STS) and repaired sequences (posterior STG, STS, AnG, and IPL)

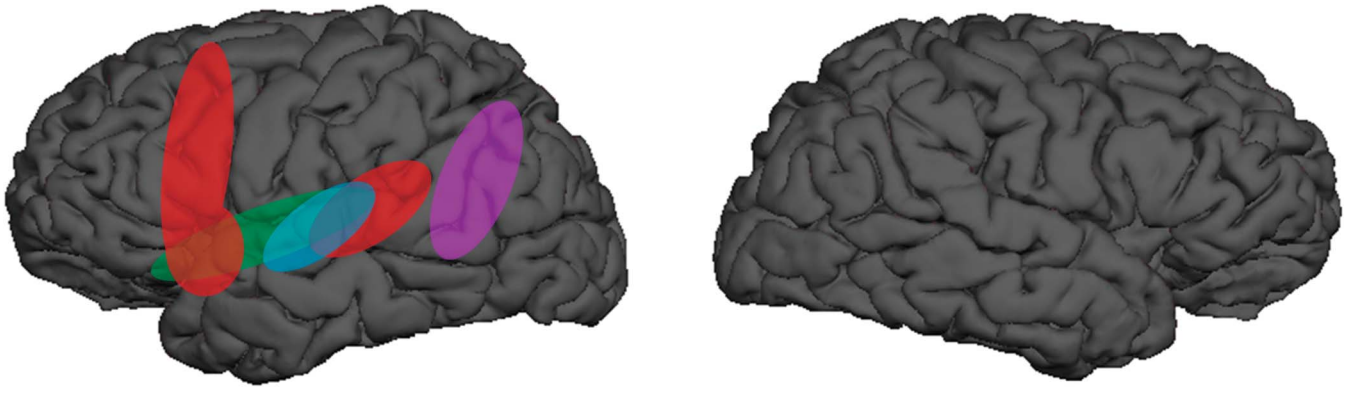
nfvPPA = nonfluent-variant primary progressive aphasia; svPPA = semantic-variant PPA; bvFTD = behavioral-variant frontotemporal dementia; HC = healthy control-group participants; VBM = voxel-based morphometry; MRI = magnetic resonance imaging; IFG = inferior frontal gyrus; STG = superior temporal gyrus; PPA = primary progressive aphasia; lvPPA = logopenic-variant PPA; MFG = middle frontal gyrus; PoG = postcentral gyrus; SMA = supplementary motor area; PrG = precentral gyrus; FA = fractional anisotropy; RD = radial diffusivity; DTI = diffusion tensor imaging; DWI = diffusion weighted imaging; GM = gray matter; BA = Brodmann area; PMC = premotor cortex; WAB = Western Aphasia Battery; SLF = superior longitudinal fasciculus; AF = arcuate fasciculus; DDK = diadochokinesis; AOS = apraxia of speech; FDG = fluorodeoxyglucose; PET = positron emission tomography; ASRS = Apraxis of Speech Rating Scale; PPAOS = primary progressive apraxia of speech; WM = white matter; SMG = supramarginal gyrus; STS = superior temporal sulcus; AnG = angular gyrus; IPL = inferior parietal lobe; CBS = corticobasal syndrome; FTD = frontotemporal dementia; ILF = inferior longitudinal fasciculus; PSP = progressive supranuclear palsy; ROI = region of interest; vPMC = ventral premotor cortex. **AQ14**

Figure 2. Regions of gray-matter atrophy associated with impaired speech production in nonfluent-variant primary progressive aphasia (nfvPPA) and primary progressive apraxia of speech. Shading indicates correlation of neuroimaging abnormalities with speech measures for either nfvPPA or primary progressive apraxia of speech. Red = speech rate (words/min) associated with lateral inferior frontal cortex (L > R) and left anterior superior temporal cortex in nfvPPA (Grossman et al., 2013; Gunawardena et al., 2010); blue = diadochokinetic rate associated with pars opercularis in nfvPPA (Rohrer et al., 2010a); purple = composite measure of Pairwise Variability Index, proportion of silence, and variability of pauses associated with middle frontal gyrus and postcentral gyrus bilaterally, left supplementary motor area and precentral gyrus, and right pars opercularis and insula in nfvPPA (Ballard et al., 2014); yellow = Pairwise Variability Index associated with supplementary motor area, precentral gyrus, and inferior frontal gyrus bilaterally in nfvPPA (Ballard et al., 2014); green = Apraxia of Speech Rating Scale associated with the left lateral premotor cortex in primary progressive apraxia of speech (Whitwell, Duffy, Strand, Xia et al., 2013).



studies for many of the measures used. The meta-analysis is therefore biased toward identifying significant differences for the most common measures, which may or may not be the most successful in differentiating the groups. Despite this, each comparison involved more than 50 participants and gives an indication of the current state of the literature. Speech rate, measured in words per minute, was the most commonly used metric in the meta-analysis. The analysis demonstrated that speech rate is slower in lvPPA and nfvPPA than bvFTD, svPPA, and healthy control groups, and slower in nfvPPA than lvPPA. Reduced speech rate was also shown in bvFTD compared with control groups. In contrast, there was no difference between svPPA and control groups. These distinctions demonstrate that words per minute is a useful measure for identifying speech disturbance; however, it may be affected by impairment to a variety of domains in these syndromes, such as motor speech, language, and cognition (Yunusova et al., 2016). The meta-analysis also identified multiple group comparisons for phonemic errors, albeit from only two studies. We would expect lvPPA to differ from other groups on this measure, given the ICC (Gorno-Tempini

Figure 3. Regions of gray-matter atrophy associated with impaired speech production. Shading indicates correlation of neuroimaging abnormalities with speech measures for behavioral-variant frontotemporal dementia, semantic-variant primary progressive aphasia, logopenic-variant primary progressive aphasia, nonfluent-variant primary progressive aphasia, and healthy control groups. Red = speech rate associated with left inferior frontal gyrus, ventral precentral gyrus, supplementary motor area, and superior temporal cortex (Ash et al., 2009; Wilson et al., 2010); green = false starts associated with left superior temporal gyrus and pars opercularis (Wilson et al., 2010); blue = filled pauses and repaired sequences associated with left posterior superior temporal gyrus and superior temporal sulcus (Wilson et al., 2010); purple = repaired sequences associated with left angular gyrus and inferior parietal lobe (Wilson et al., 2010).



et al., 2011) and evidence found in our review, but the meta-analysis only identified a significant difference for lvPPA compared with control groups. The nonsignificant finding for phonemic errors in lvPPA compared with nfvPPA and svPPA is likely due to the lack of power in the meta-analysis. However, this finding may also be influenced by the difficulty of differentiating phonemic and phonetic errors during listener-based speech assessment. Although only two studies could be included in the analysis, ratings of AOS and dysarthria on a 7-point severity scale were successful in differentiating nfvPPA and lvPPA, which highlights the importance of careful speech characterization for diagnosis of these disorders.

bvFTD

Atypical speech was reported in high proportions of participants with bvFTD; however, detailed descriptions of the severity and characteristics of the speech impairment are not represented in the literature. Detailed investigation of the rate and quality of pauses has been provided by Yunusova et al. (2016), who suggest that these changes are a result of cognitive impairment. Additional research is warranted to better describe the nature, severity, and origin of speech impairment in bvFTD, and to determine whether the atypical speech is related to impairment of motor speech, behavior, or other cognitive deficits. Understanding the prevalence and characteristics of speech impairment in bvFTD is important for identifying individuals who develop bulbar signs of motor neuron disease (Neary et al., 1990; Snowden, Neary, & Mann, 2007). Further exploration of the differences between speech impairment in tau-positive and tau-negative people with bvFTD is also indicated, given the identification of dissimilar speech features in these two groups (Mendez et al., 2013).

nfvPPA

AOS has been well defined in perceptual studies of nfvPPA and includes features of impaired prosody, slow speech rate, and both phonemic and phonetic articulatory errors. Furthermore, features of AOS have been shown to be useful in distinguishing nfvPPA from other PPA variants (Gorno-Tempini, Dronkers, et al., 2004; Mandelli et al., 2014; Wicklund et al., 2014). Dysarthria is a common secondary motor speech feature, identified in up to 60% of people with nfvPPA (Ogar et al., 2007) and most commonly described as spastic or hypokinetic in nature. Apraxic speech errors in nfvPPA were identified with acoustic measures of speech, including attenuation of length difference in long and short vowels (Ackermann et al., 1997), median silence duration, and PVI (Ballard et al., 2014; Pakhomov et al., 2010). The PVI measure has been shown to be a useful diagnostic tool in identifying AOS secondary to stroke (Ballard et al., 2016; Vergis et al., 2014), and further application of the method in PPA is indicated by its success in distinguishing nfvPPA from lvPPA in one study (Ballard et al., 2014).

Measures of atypical speech in participants with nfvPPA correlated with regions typically associated with motor speech planning and execution (Guenther, 2006; Tourville & Guenther, 2011), namely the left middle and inferior frontal gyrus, cingulate, premotor area, and insula (Grossman et al., 2013; Gunawardena et al., 2010; Rohrer et al., 2010a). Several of these areas (SMA, precentral gyrus, and inferior frontal gyrus) were also found to be associated with PVI, an acoustic correlate of AOS (Ballard et al., 2014). The involvement of the pars opercularis, premotor area, postcentral gyrus, and insula is in line with prior evidence of AOS caused by stroke (Graff-Radford, Jones, & Graff-Radford, 2014; Hillis et al., 2004). In addition to these frontal-lobe regions, an adjacent region of the anterior superior temporal lobe was associated with decreased speech rate. There is some evidence from functional MRI studies that the anterior temporal cortex plays a role alongside the inferior frontal cortex in grammatical processing (Gunawardena et al., 2010; Troiani et al., 2008; Xu, Kemeny, Park, Frattali, & Braun, 2005). An alternative hypothesis is that this correlation reflects a common pattern of neuropathological spread in nfvPPA, which occurs alongside further deterioration of the inferior frontal gyrus (Nestor et al., 2003). Atrophy of the postcentral gyrus in both hemispheres was also shown to correlate with a composite measure of lexical stress and syllable segmentation (Ballard et al., 2014). This region is theorized to play a role in somatosensory feedback of speech (Guenther, 2006). The correlation of the postcentral gyrus with characteristics of AOS is suggested to reflect a sensorimotor integration impairment in AOS which results in poor refinement of motor speech movements during speech production (Ballard et al., 2014).

Damaged WM tracts were also associated with speech impairment. The superior longitudinal fasciculus has been shown to have reduced FA in participants with nfvPPA (Galantucci et al., 2011; Whitwell et al., 2010), and damage to it has been hypothesized to be associated with the language deficits typical of nfvPPA (Whitwell et al., 2010). WM connections of the SMA complex to the caudate and inferior frontal gyrus are hypothesized, in regions found to have reduced FA, to be associated with impaired motor speech production in nfvPPA (Mandelli et al., 2014).

svPPA

Motor speech disorder was not identified in any listener-based or acoustic study of the svPPA group, and this is consistent with the diagnostic criteria (Gorno-Tempini et al., 2011). Two studies (Ash et al., 2013; Fraser et al., 2014) reported reductions in speech rate and increased hesitation markers (e.g., *um*). Given the lack of evidence of motor speech impairment in svPPA, these findings are hypothesized to be secondary to linguistic deficits such as anomia. These findings are therefore in accord with a prior review of the literature which suggested that an alternative diagnosis to svPPA should be considered in the presence of motor speech disorder (Duffy, Strand, & Josephs, 2014).

lvPPA

Signs of AOS and dysarthria were identified in some participants with lvPPA; however, severity ratings for these participants were mild, and no statistically significant differences were observed when compared with control groups. Instead, studies which involved severity measures of phonemic errors in lvPPA consistently demonstrated that these were the most common speech error in lvPPA, despite the fact that some participants diagnosed with lvPPA did not present with these errors (Croot et al., 2012). People with lvPPA have been shown to have slower speech rates and greater numbers of false starts, hesitations, and extraneous words when compared with healthy control groups (Ash et al., 2013). It should be noted that the signs of AOS and dysarthria which were described in the perceptual studies may reflect difficulties differentiating motor speech errors and phonemic errors during assessment. With this in mind, the infrequent and mild ratings on dysarthria and AOS rating scales do not contradict the consensus criteria for PPA (Gorno-Tempini et al., 2011), which indicate that spared motor speech is a secondary feature of lvPPA. In fact, a diagnosis of lvPPA can be given in the presence of motor speech impairment, provided that the remaining three secondary criteria are met.

PAOS

AOS was a requisite feature for all cases of PAOS in studies that met criteria for this review article. The characteristics of AOS which were reported in these studies were similar to the speech features reported in cases of nfvPPA (distorted sounds and distorted sound substitutions, impaired prosody, slowed rate, and syllable segmentation). A qualitative difference between AOS features in nfvPPA and PAOS was identified by one study, which found PAOS participants to be more likely to have a form of AOS in which prosodic impairment was more severe than articulatory errors (Josephs et al., 2013).

In addition to AOS, up to half of participants diagnosed with PAOS also present with signs of dysarthria, most commonly features of spastic dysarthria (Botha et al., 2015; Josephs et al., 2013). It should be noted that participants in these two studies of PAOS have an average disease duration of more than 3 years, and dysarthria is likely to be more prevalent later in the disease course, as demonstrated in longitudinal studies of PPAOS (Josephs et al., 2012; Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014).

PPAOS

Prominent AOS is a requisite feature for diagnosis in PPAOS. Although dysarthria presents in few individuals at the time of their diagnosis, a longitudinal study of 13 participants found instances of dysarthria developing as a secondary symptom in almost half of cases (Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014). Spastic dysarthria was the most common form, followed by hypokinetic (Josephs et al., 2012; Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014). Furthermore, parkinsonism commonly emerged in cases of PPAOS when studied longitudinally, and a smaller proportion developed a syndrome with features of progressive supranuclear palsy without early postural or gait instability (Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014). The presence of concomitant spastic dysarthria in PPAOS is likely associated with damage to WM connections below the primary motor cortex (Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014) and GM atrophy in the superior lateral premotor cortex (Josephs et al., 2012, 2013). Degeneration in left premotor cortex was also associated with poorer Apraxia of Speech Rating Scale scores in participants with PPAOS. AQ15

Summary of Speech Measures

Listener-based judgments using some form of severity scale were the most commonly used speech assessments, whereas quantifiable methods were sometimes used as an adjunct to listener-based ratings for diagnosis and monitoring progression. Objective and quantifiable measures present the potential to more sensitively monitor change that occurs with disease progression. Identifying change over time is an important clinical aim for both monitoring deterioration and tracking improvements from therapy and medication. In order to do so, measures must be stable in the absence of change, reliable, and sensitive to change (Vogel, Fletcher, Snyder, Fredrickson, & Maruff, 2011; Vogel & Maruff, 2014). Speech impairment in participants with PPA was objectively characterized in a number of studies by quantifying errors in connected speech. Common features selected for quantification included phonetic speech errors, phonemic errors, disfluencies, and speech rate. Speech rate was commonly observed to be affected by PPA, particularly nfvPPA, and consistently differentiated nfvPPA from healthy control groups (Ash et al., 2010, 2013; Fraser et al., 2014; Grossman et al., 2013; Gunawardena et al., 2010; Rohrer et al., 2010a). Articulatory errors also demonstrated a capacity to differentiate nfvPPA from control groups (Ash et al., 2010, 2013; Grossman et al., 2013), and quantification of disfluencies demonstrated a capacity to differentiate lvPPA from control groups and bvFTD (Ash et al., 2013). Acoustic measures such as pause-to-word ratio, PVI, and average pause time have demonstrated an initial capacity to differentiate nfvPPA from bvFTD and other PPA variants (Ballard et al., 2014; Pakhomov et al., 2010; Yunusova et al., 2016).

Several regions of brain atrophy were associated with measures of speech when statistical analysis incorporated all syndromes (nfvPPA, lvPPA, svPPA, bvFTD) and healthy control groups (see Figure 3). Speech rate was associated with atrophy in the inferior frontal gyrus and anterior temporal lobe, which mirrored atrophy seen in the nfvPPA group alone. This correlation also extended to the precentral gyrus and SMA, regions associated with motor speech production (Tourville & Guenther, 2011). The influence on

speech rate of atrophy in the posterior superior temporal cortex is also established when jointly considering all syndromes. This association may represent a reduction in speech rate caused by impaired phonological retrieval (Binder, 2015; Buchsbaum et al., 2011), as opposed to impaired motor control. In a similar vein, false starts and filled pauses—features associated with impaired phonological processing in lvPPA (Gorno-Tempini et al., 2011)—were found to correlate with overlapping regions of the superior temporal gyrus (Wilson et al., 2010; see also Figure 3). A further posterior language region, involving the angular gyrus and inferior parietal cortex, was associated with reduced fluency (measured as the number of repaired sequences). The association of these regions in the mixed-pathological-group analysis but not in the correlations for the nfvPPA group is likely to be due to the inclusion of lvPPA (Wilson et al., 2010). In addition to associations with GM atrophy, significant correlation of WM tracts with speech rate and articulatory errors (Mandelli et al., 2014; Wilson et al., 2010) suggest that these speech measures can assist in diagnosing and measuring the gradual disease progression in PPA.

Conclusions

There is consistency within the literature that the greatest prevalence of motor speech disorder occurs in nfvPPA, PAOS, and PPAOS, due to the presence of AOS and, less commonly, dysarthria. Speech impairment is rarely documented in svPPA, and impairment of speech production in lvPPA is mostly characterized as phonemic paraphasias. More accurate documentation of motor speech disorder and other atypical speech is required for bvFTD, because this may be clinically beneficial for identifying patients who transition to FTD with motor neuron disease. There was variation in the depth of characterization of speech across the studies included in the review article. Many studies were hampered by heterogeneous groups and very small study numbers. Findings should also be taken with consideration of the ongoing evolution of classification criteria for the progressive aphasias and apraxias. In particular, it is possible that some participants included within the nfvPPA group in some studies may have been labeled as having PAOS or PPAOS in different studies.

Dysarthria is a common feature of PAOS and PPAOS later in the disease process, which is sometimes associated with the development of parkinsonism. The presence of AOS and dysarthria in nfvPPA and PPAOS is associated with the distribution of pathology within the speech motor regions of the frontal cortex. However, neuroimaging correlates of phonemic errors in lvPPA are less well established. Several quantitative measures, such as rate of connected speech, have demonstrated a capacity to assist in diagnosis of disease subtype; however, further studies are required to replicate these findings and investigate whether they can be used to track the progression of the disease. Further use of these quantitative measures will improve the quality of speech characterization in these disorders. We identified few longitudinal studies of speech impairment in these disorders, and further investigation of the progression of atypical speech over time is warranted.

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3 Methodology

3.1 Introduction

Chapter Three describes the methodologies used in the studies presented in Chapters Four to Seven. Perceptual and acoustic methods are described, and the data collection and recruitment processes are outlined.

3.2 Participant recruitment

Participants were consecutively recruited through the Eastern Cognitive Disorders Clinic (ECDC), at Box Hill Hospital, Melbourne, Australia. The ECDC is a diagnostic clinic specifically for patients with focal onset dementias, for those with cognitive syndromes that pose diagnostic difficulties, and for patients with neurological disorders who present with cognitive decline. The clinic has a particular focus on the frontotemporal dementia spectrum of disorders.

3.2.1 Inclusion criteria

The study recruited people who had a probable diagnosis of FTD or PPA. Diagnoses were made by experienced neurologists at the ECDC, following published criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). The clinical diagnosis was used as a starting point, and then the clinical features of each participant were checked against the Rascovsky criteria for bvFTD and International Consensus Criteria (ICC) for PPA. Only patients who fulfilled the Rascovsky criteria for probable (not possible) or definite (confirmed with known genetic mutation) bvFTD were included (Rascovsky et al., 2011). Similarly, only patients who met the ICC for an imaging-supported diagnosis were included as PPA participants (Gorno-Tempini et al., 2011). The diagnostic process is supported by a multidisciplinary team, including neuropsychologists and speech pathologists. Participants were required to be proficient in written and spoken English prior to their dementia diagnosis. Participants were excluded if they were under 18 years of age, had a history of traumatic brain injury, had a developmental intellectual disability, or presented with another neurological condition (e.g., stroke, multiple sclerosis, Parkinson's disease, alcohol related brain damage).

3.3 Data collection

Participants were assessed either within the department of Audiology and Speech Pathology at the University of Melbourne, in their homes, or at the Eastern Cognitive Disorders Clinic, Box Hill Hospital. All assessments were conducted in a quiet room with no background noise or visual distractions. The assessment protocol involved a language assessment and speech audio recording, which was later analysed acoustically and perceptually.

3.3.1 Language assessment

Language assessments were conducted by a qualified speech pathologist with experience in the diagnosis of PPA and FTD. The assessment aimed to address the differential features of the PPA subtype based on international consensus criteria (Gorno-Tempini et al., 2011) and addressed aspects of grammar production, repetition, auditory comprehension, lexical retrieval and semantics. These domains were assessed with the Progressive Aphasia Language Scale (PALS; Leyton et al., 2011). The PALS protocol provides a 4-point rating scale to rate each of the domains presented in Table 3-1. Criteria are provided to guide the ratings which represent: 0 = no deficit, 1 = mild or doubtful deficit, 2 = definite deficit, 3 = severe deficit. An algorithm based on the ratings of the PALS has been used to classify PPA subtypes and demonstrated to have good concordance (94%) with expert clinician judgement (Leyton et al., 2011). Furthermore, the PALS has been shown to have good inter-rater reliability (Spearman's rho = 0.93; Leyton et al., 2011).

Object knowledge, reading and writing were assessed to identify impairments and surface dyslexia/dysgraphia for diagnosis of svPPA. Object knowledge was assessed with the *Semantic Memory* subtest from the Comprehensive Aphasia Test (CAT; Swinburn, Porter, & Howard, 2004). Reading of regular and irregular words, and non-words, was assessed with the *Reading Words* and *Reading Non-words* subtests from the CAT. Writing of regular and irregular words was assessed with subtests from the Boston Diagnostic Aphasia Examination (BDAE; Goodglass et al., 1983).

Table 3-1: Description of tasks used to rate each language domain on the PALS (Leyton et al., 2011)

Language domain	Description of task
Motor speech disorders	Distortions, articulatory groping, labored speech, prosodic abnormalities, and reduced intelligibility rated during a 15 minute informal conversation.
Phonological errors	Substitution, addition or deletion of well-articulated speech sounds rated during a 15 minute informal conversation.
Agrammatism	Omission of closed class words (e.g., prepositions, articles, pronouns), incorrect use or omission of grammatical morphemes, or predominance of simple sentence structures. Each rated during a 15 minute informal conversation.
Naming	Confrontation naming of 10 animals and 10 household objects.
Single word repetition	Repetition of words of increasing length and phonological complexity.
Single word comprehension	Selection of animals from larger group based on features, and definitions of a list of words.
Sentence comprehension	Comprehension of direct two-step commands (e.g., 'touch the pen then the toothbrush') and complex two-step instructions (e.g., 'pass me the pen after touching the toothbrush').
Sentence repetition	Repetition of sentences of increasing length.

3.3.2 Recording equipment

All participants were recorded while completing a standard speech protocol in a quiet room with no background noise. Speech samples were recorded with an AKG C520 cardioid head-mounted condenser microphone (AKG Acoustics Harman ProGmbH, Munich, Germany) with a frequency range of 20-20KHz and sensitivity of -43 dB, onto a Marantz PMD671 solid state recorder (D&M Holdings, Lincoln Park, NJ, USA). The microphone was positioned at a 45^{o} angle 8 cm from the mouth. Recordings were sampled at 44.1 KHz and quantized at 8 bits. Sampling rate and use of solid state recorder with headset microphone were selected in order to maximize the quality of recording and ensure accurate measurement of metrics, particularly perturbation, harmonics to noise ratio, and mean pause length metrics which are affected by the quality of the recording (Vogel & Maruff, 2008; Vogel, Rosen, Morgan, & Reilly, 2015).

3.3.3 Speech protocol

Speech tasks are presented in Table 3-2, alongside the acoustic analysis that was conducted on each speech stimuli. Acoustic methods are described in detail in section 3.3.4.

3.3.4 Acoustic speech analysis

Acoustic analysis involved a range of measures designed to assess changes that occur across different speech subsystems. The metrics were selected based on concepts of sensitivity (the degree to which performance changes in response to actual vocal or neurological changes) and stability (the extent to which measurement is consistent in the absence of any actual change to neurological functioning; Vogel et al., 2011). Vogel and colleagues (2014) have recommended that participants produce speech stimuli twice in order to remove any effects of unfamiliarity with the task. This suggestion follows evaluation of the stability of speech and voice measures over time, which have indicated that performance can change over the first and second productions of a task in the absence of true change in speech functioning. Productions are observed to plateau after the second production, likely due to removal of the effect of factors such as nerves and errors due to unfamiliarity (Vogel et al., 2011; Vogel & Maruff, 2014). Speech stimuli were therefore produced twice to reduce the effect of novelty, with the exception of the extemporaneous monologue task. All metrics were selected based on their brevity of production during the assessment, thereby lending themselves to clinical application.

Table 3-2: Speech stimuli, description of analyses conducted and software required

Speech stimuli	Description of task	Acoustic analysis conducted	Software
Monologue	Participants were asked to talk about something that they enjoyed doing for one minute	Speech timing metrics (mean pause length, proportion of pause time, *SD* of pause time).	Automated scripts conducted using Praat
Reading the Grandfather Passage	Participants read a phonetically balanced passage (Darley et al., 1975)	1) Speech timing metrics (mean pause length, proportion of pause time, *SD* of pause time, speech rate).	1) Automated scripts conducted using Praat
		2) Formant centralisation ratio (FCR) calculated from production of vowels in reading passage	2) Praat
Days of the week task	Participants were asked to say the days of the week starting with Monday	Speech timing metrics (mean pause length, proportion of pause time, *SD* of pause time, speech rate).	Automated scripts conducted using Praat
Speech Diadochokinesis: Alternating motion rates (AMR) and Sequential motion rates (SMR)	Participants were asked to say 'papapa' (AMR) and 'pataka' (SMR) as quickly and clearly as possible	Period, rate, CoV period, perturbation period and CoV peak intensity	Diadochokinetic Rate Analysis conducted with the KayPENTAX Motor Speech Profile
Word repetition	Participants asked to repeat 10 polysyllabic words	Pairwise variability index (PVI)	Praat
Sustained phonation	Participants were asked to produce the /a/ vowel for as long as they could	Voice quality metrics (Mean f0, CoV f0, Harmonics to noise ratio)	Praat

Note. CoV = coefficient of variation; f0 = fundamental frequency; SD = standard deviation.

3.3.4.1 Speech timing

Four metrics were obtained from automated timing scripts on Praat: mean pause length, *SD* of pause length, proportion of pause time, and speech rate. All four metrics were applied to the Grandfather Passage and days of the week tasks. All metrics except for speech rate were applied to the monologue. These metrics were selected as they have been shown to have stability and sensitivity to change over time, and are minimally impacted by biological and technical measurement error (Vogel et al., 2011). The three pause based metrics (mean length, *SD* of length, proportion of pause time) were calculated from the intensity contour of the sample. Pauses were calculated when the intensity fell below a threshold of 85% of the mean scaled intensity of the file for a duration greater than 100 milliseconds (ms; K. Rosen et al., 2010). Mean pause length was calculated by measuring the total time below the set threshold for silences longer than 100 ms, divided by the number of pauses. The standard deviation of pause length was calculated from the same periods of silence as mean pause length. Proportion of pause time was calculated as a percentage of the sample during which the intensity contour was below the threshold for pauses 100 ms or longer. Speech rate was calculated as the number of syllables per second (Vogel et al., 2011). Speech rate was not calculated for the monologue task to remove the influence of high demands of conceptualisation on the speech measure.

The speech timing measures have been shown to be sensitive to changes in motor speech functioning due to fatigue and depression (Mundt, Vogel, Feltner, & Lenderking, 2012; Vogel, Fletcher, & Maruff, 2010). Furthermore, they have identified the acoustic correlates of rate and prosodic change caused by weakness or incoordination of speech production in studies of neurodegenerative dysarthria associated with Parkinson's disease, Friedreich ataxia, spinocerebellar ataxia, and multiple sclerosis (Hammen & Yorkston, 1996; K. Rosen et al., 2010; Schalling, Hammarberg, & Hartelius, 2007).

The application of timing measures (e.g. speech rate, mean pause length) in FTD and PPA raises additional considerations due to the high incidence of cognitive decline and aphasia that may impact on speech timing. In addition to motor speech changes, the timing metrics may be affected by lexical retrieval, dysfluency from phonological assembly errors, or agrammatism (Gorno-Tempini et al., 2011). In prior studies of speech in PPA, broad measures of speech rate have been limited in their ability to differentiate between these different causes of reduced speech rate (Poole et al., 2017). For example, a range of studies

have demonstrated that all PPA and FTD subtypes are significantly slower than controls (Ash et al., 2013; Ash et al., 2010; Ash et al., 2009; Fraser et al., 2014; Gunawardena et al., 2010), however few have identified pathological group differences (Ash et al., 2013; Ash et al., 2009; Gunawardena et al., 2010; Mesulam et al., 2012; Wilson et al., 2010). These previous studies of speech timing are limited by their application to a single task only, usually from recordings of a picture description or story retell task only (Poole et al., 2017). Use of multiple speech stimuli as well as multiple rate and pause metrics may allow for more detailed characterisation of the speech rate deficits in each syndrome. For example, the methods proposed in this study have demonstrated similar decreases in speech rate for lvPPA and nfvPPA, but quantitative differences in the number and length of pauses between nfvPPA and lvPPA (Ballard et al., 2014). These findings led to the suggestion that use of the reading task facilitated more fluent speech in the lvPPA group due the lack of lexical retrieval demands in the task, whereas the nfvPPA group had a longer pause time due to phonetic-motoric impairment (Ballard et al., 2014).

3.3.4.2 Speech diadochokinesis

Diadochokinetic rate (DDK) is often used in the clinical setting in order to obtain a measure of articulation which is free from cognitive and linguistic demands, and to assess motor speech functioning in neurodegenerative disorders (Kent et al., 2000; Kent, Kent, & Rosenbek, 1987; Schmitz-Hübsch et al., 2008). It involves the rapid repeated production of syllables (often the syllables /pə/, /tə/, /kə/) which are counted and timed by the clinician (Kent et al., 1987). When repetitions of the same consonant sound are produced, the DDK task is referred to as an alternating motion rate (AMR), whereas if strings of syllables are placed together in sequence (most commonly /pətəkə/ or "pataka"), the DDK task is called a sequential motion rate (SMR). A person's AMR or SMR production can be compared to normative data based on the amount of syllables produced per second (Kent et al., 1987). DDK has been shown to be sensitive to progressive neurological dysarthrias due to motor neurone disease (MND; Niimi, 2000; Samlan & Weismer, 1995), cerebellar and spinocerebellar ataxias (Kent, Kent, Rosenbek, Vorperian, & Weismer, 1997; Schalling & Hartelius, 2004), and Parkinson's disease (Tjaden & Watling, 2003). In AOS, AMR and SMR tasks are expected to be differentially affected due to the increased phonological and motor programming required for SMR (Ziegler, 2002; Ziegler & Wessel, 1996). Despite this,

no difference between AMR and SMR was observed in a recent study of PPAOS (Duffy et al., 2015).

Acoustic evaluation of the DDK task provides more detailed information regarding DDK production (Wang, Kent, Duffy, & Thomas, 2009). The semi-automated evaluation with the Diadochokinetic Rate Analysis (DRA) protocol on the Motor Speech Profile software (KayPENTAX) produces several DDK metrics. The DRA allows the evaluator to view the intensity of a participant's DDK production over time. The program allows the examiner to set a threshold between the peaks of intensity from phonation and troughs between syllables. Based on this, the program calculates several measures, and those that were selected for the current study are presented in

Table 3-3. Each metric was applied to both the AMR and SMR tasks. DDK rate and period were calculated to investigate group differences in each measure. The coefficient variation of DDK peak intensity metric assessed participants' ability to maintain a constant intensity of syllabic productions. Two measures of DDK production (Coefficient variation of DDK period and perturbation of DDK period) investigated the capacity for constant vocalisation rate. Coefficient variation of DDK period measures the degree of variation of the period across the sample, whereas perturbation calculates the cycle-to-cycle variation. Each measure was calculated to investigate the nature of DDK productions in the PPA and FTD population. We hypothesised that the nfvPPA group would have the greatest difficult with DDK production.

Table 3-3: Metrics derived from Diadochokinetic Rate Analysis

Metric	Unit	Interpretation
Average DDK period	ms	Average period of syllable
Average DDK rate	Syllables/second	Number of syllables per second
Coefficient variation of DDK period	%	Degree of rate variation in the period, indicating capacity for constant vocalisation rate
Perturbation of DDK period	%	Degree of cycle-to-cycle variation in the period
Coefficient variation of DDK peak intensity	%	Degree of intensity variation in the peak of each syllable

3.3.4.3 Voice quality

Three voice quality metrics were calculated from participants' production of the sustained vowel. These were the mean fundamental frequency (f0), coefficient of variation of fundamental frequency (CoV f0) and the harmonics to noise ratio (HNR). Metrics were calculated in Praat using algorithms defined by Boersma and colleagues (1993).

The sustained vowel was selected as the stimuli for these metrics as continuous production of the vowel is considered to be a better identifier of disordered voice than connected speech (Parsa & Jamieson, 2001). The participants' second production was selected as greater stability of measurement occurs following the initial production (Vogel et al., 2011).

Mean fundamental frequency (f0) and the coefficient of variation of f0 (CoV f0) were calculated on Praat (Boersma & Weenink, 2001) using an automated script (Vogel, Maruff, Snyder, & Mundt, 2009). Pitch range settings were set at 70 – 250 Hz for male speakers and 100 – 300 Hz for female speakers, consistent with investigations of the reliability and validity of the automated analysis of frequency (Vogel et al., 2009). Fundamental frequency of the sustained vowel represents the pitch of the speaker's voice. CoV f0 represents the degree of variation from the mean f0 and is calculated as the ratio of the standard deviation from the mean f0 divided by mean f0. CoV f0 has been observed to be affected by fatigue (Whitmore & Fisher, 1996) and to change in concordance with perceptually rated improvements following treatment for spasmodic dysphonia (Cannito, Buder, Chorna, & Dressler, 2012).

The harmonics to noise ratio was first proposed by Yumoto and colleagues (1982) as a measure of the amount of hoarseness within a person's voice. It represents the ratio between the periodic and aperiodic (noise) elements of the waveform to indicate the degree of deviation from perfect periodicity within the signal (Yumoto, Gould, & Baer, 1982). The measure has been applied to the detection of vocal abnormalities in Parkinson's disease (Gamboa et al., 1997; Kent & Kim, 2003; Rusz, Cmejla, Ruzickova, & Ruzicka, 2011; Zwirner, Murry, & Woodson, 1991) and found to be a powerful acoustic metric for identifying differences between Parkinson's disease and control speakers (Tsanas, Little, McSharry, Spielman, & Ramig, 2012).

In statistical comparisons, participants were split by gender for the mean f0 metric, to remove the confounding factor of prominent differences in male and female f0 (Traunmüller &

Eriksson, 1993). The CoV f0 and HNR metrics included both male and female participants in each statistical analysis.

3.3.4.4 Vowel articulation

Accuracy of vowel production was calculated with the formant centralisation ratio (FCR). The FCR was developed to improve the sensitivity of a similar metric, the Vowel Space Area (VSA). VSA is calculated by measuring the first two formants of the corner vowels of English. Formants are the spectral peaks of the sound spectrum, which are formed by the resonant qualities of the vocal tract (Fant, 1971). Variations of tongue position alter the resonant frequency of the tract, which is then perceived by listeners as different vowel sounds. The two formants with the lowest frequency (termed the first [F1] and second [F2] formants), are selected for calculation in both VSA and FCR. As the first two formants are sufficient to distinguish vowel quality, all English vowels can be placed on a two dimensional graph referred to as a formant plot (Ladefoged & Disner, 2012). In doing so, the vowels at the extremes of the formant space, termed the corner vowels, can be used to calculate the size of the space between them. Either a triangular VSA (/i/, /a/, /u/ vowels) or a quadrilateral VSA (/i/, /a/, /u/, /æ/) can be calculated (Roy, Nissen, Dromey, & Sapir, 2009). Dysarthric speech is associated with centralisation of vowels due to insufficient articulatory movements which result in a smaller vowel space area (Kent & Kim, 2003).

The FCR is a modification of the VSA, which was designed to minimise the impact of variability between speakers (Sapir, Ramig, Spielman, & Fox, 2010). These interspeaker differences result from idiosyncratic differences of the vocal tract associated with, for example, anatomy related to gender and age (Hashi, Westbury, & Honda, 1998). The FCR was developed in order to increase sensitivity of differences associated with vowel centralisation, and limit sensitivity to idiosyncrasies of the speaker, largely through constructing the metric as a ratio (Sapir et al., 2010). The FCR has been demonstrated to show much lesser variability due to age and gender than the VSA, allowing for group comparisons regardless of these differences (Sapir et al., 2010). Furthermore the FCR has been demonstrated to be capable of identifying group differences in manual systematic adjustment of vowel space area (Karlsson & Doorn, 2012). FCR has also been shown to have less statistical bias than the vowel articulation index, which was also designed to limit speaker variability in vowel space area (Karlsson & Doorn, 2012).

The vowel formant measures used to calculate the FCR were transformed from Hertz to a Bark scale prior to their inclusion in the FCR calculation (Traunmüller, 1990). Transformation of formant values to a Bark scale is conducted in calculations of VSA in order to reduce the amount of interspeaker variation (Ferguson & Kewley-Port, 2007). When applied to FCR calculations, a Bark transformation has been demonstrated to further reduce sensitivity to interspeaker variation (Fletcher, McAuliffe, Lansford, & Liss, 2017).

FCR calculations were originally constructed with the /i/, /a/, and /u/ vowels of speakers of American English to obtain F1 and F2 measures from three of the most extreme vowels in the vowel space (Sapir et al., 2010). The present study adapted the selection of vowels to suit vowel dispersion in Australian English (Harrington, Cox, & Evans, 1997). The phonetic notation henceforth in this thesis is that of Harrington, Cox and Evan's study of vowel production in Australian English (1997). The vowels selected were the high front vowel [iː] (the vowel in 'heed'), the high back vowel [oː] (the vowel in 'hoard'), and the open vowel [ɐː] (the vowel in 'hard'), consistent with an earlier study of FCR in New Zealand English (Fletcher et al., 2017). The FCR is calculated with the following formula, where *F1* is the first formant, *F2* the second formant (Sapir et al., 2010):

Equation 3-1: Formant centralisation ratio (Sapir et al., 2010) :

$$FCR = \frac{(F2[oː] + F2[ɐː]a + F1[iː] + F1[ɐː])}{(F2[iː] + F1[oː])}$$

These vowels were taken from recordings of participants reading aloud the Grandfather passage. Three tokens of each vowel were averaged for calculation in the FCR. The [iː] vowel was taken from the words 'three' and two productions of 'each'; the [oː] vowel from the words 'organ', 'short' and 'more', and [ɐː] vowel from 'banana' and two productions of 'grandfather'. All calculations were conducted on participants with an Australian English accent. Vowel formants were measured at a 30 ms segment of the temporal midpoint in order to achieve consistent measurement between productions, and to capture the vowel formants at a point temporally furthest from the consonant sounds preceding and following the vowel (Rusz et al., 2014; Rusz et al., 2013; Sapir et al., 2010; Skodda, Grönheit, & Schlegel, 2012; Skodda, Visser, & Schlegel, 2011b). Measurement of vowel formants using this method has been shown to have good intra- and inter-rater reliability (Sapir, Spielman, Ramig, Story, & Fox, 2007). Note that the 'r' in 'organ', 'short' and 'more' is not realised in Australian-English.

The FCR has been shown to differ in speakers with dysarthria from healthy controls (Sapir et al., 2010). Furthermore it has been shown to correlate with listeners perception of dysarthria severity (Lansford & Liss, 2014).

3.3.4.5 Lexical stress – the Pairwise Variability Index

The pairwise variability index (PVI) is a metric developed to investigate lexical stress differences in dialects of English (Ling, Grabe, & Nolan, 2000). The PVI provides a ratio of the level of stress on the first and second vowels of polysyllabic words to establish an acoustic correlate of the perceptual feature of equal and excess stress. PVI was calculated for both duration and intensity, given that equal and excess stress is considered to be a key feature of AOS, and is hypothesized to be caused by the reduced precision of laryngeal and articulatory movements resulting in subtle differences of intensity and duration between syllables (Ballard et al., 2014). Investigations of the speech of people with AOS have identified both prolonged vowel duration, and equalisation of relative peak intensity across syllables (Kent, 1983; Kent & Rosenbek, 1982). Analysis of the acoustic correlates of stressed and unstressed syllables in healthy speakers has identified differences in duration and intensity (Arciuli & Slowiaczek, 2007; Ballard, Djaja, Arciuli, James, & van Doorn, 2012; Choi, Hasegawa-Johnson, & Cole, 2005).

The PVI has since been applied to investigation of ataxic dysarthria and apraxia of speech due to stroke (Stuntebeck, 2002). The measure has been successfully applied to the differentiation of PPAOS and nfvPPA from lvPPA (Ballard et al., 2014; Duffy et al., 2017), and to monitoring progression in PAOS (Duffy et al., 2015).

Four PVI metrics were calculated: two based on repetition of five words with a strong-weak lexical stress pattern over the first two syllables, and two based on repetition of five words with a weak-strong lexical stress pattern. Intensity and duration were analysed separately in each set of words and a PVI value calculated for each. Syllable duration and intensity were calculated manually on Praat. Duration was calculated by measuring the duration of the vowel between the consonants preceding and following it, via visual inspection of the spectrogram on Praat. Intensity was calculated as the mean intensity of the vowel. The words were selected from the Sydney Language Battery word repetition subtest (Savage et al., 2013), following the protocol of Ballard and colleagues (2014). The five words with strong-weak stress were butterfly, bicycle, caterpillar, dinosaur, and stethoscope. The five words with weak-strong stress were banana, computer, pagoda, potato, and thermometer. The first

two vowels in each of these words are produced prior to or following a plosive, fricative, or nasal phoneme, which allows for a clear boundary to be observed in the waveform and spectrogram when visually displayed. The post-vocalic 'r' in 'butterfly', 'caterpillar' and 'thermometer' is not realised in Australian English, which meant that a clear boundary was still observed at the end of the vowel in each of these words. Once the duration and intensity of each of the vowels had been computed, the PVI metrics were then calculated as the absolute value of the following formula, where d = duration in ms or intensity in dBSPL of the first (1) or second (2) vowel:

Equation 3-2: Pairwise variability index (Ling, Grabe, & Nolan, 2000)

$$PVI = 100 \times \frac{d1 - d2}{(\mathrm{d1} + \mathrm{d2})/2}$$

The median PVI value was taken from the five words used in each calculation.

3.3.5 Perceptual speech analysis

Speech was evaluated by two speech pathologists who were blind to the participants' diagnosis, and time point in the case of longitudinal studies (Chapters Six and Seven). Ratings were completed via speech recordings, which were provided a unique identifier (a number between 1 and 100). Allocations of the unique identifier were conducted by a third party who was not involved in the data collection or analysis. The third party retained the link between the unique identifiers for perceptual analysis and participants study ID. The link was provided to the author after the ratings had been completed. The rating scale was based upon a scale used within the Mayo clinic for differential diagnosis of dysarthria (Darley et al., 1969). The rating scale assessed 28 features across eight speech subsystems, as well as DDK production. Speech features are described in Table 3-4 (Duffy, 2013). All features were rated on a five-point scale where 0 = normal production, 1 = sub-clinical, 2 = mild, 3 = moderate and 4 = severe. Speech rate and DDK rate were rated on a 9-point scale ranging from -4 to 4, to account for both abnormally increased and decreased rates. The two raters judged each speech feature independently, and disagreement was resolved by consensus.

Table 3-4: Description of perceptual speech features

Speech subsystem and feature	Description
Pitch	
Monopitch	Voice lacks normal pitch variation
Pitch breaks	Pitch shows sudden and uncontrolled variation
Voice tremor	Voice shows regular shakiness or tremor
Respiration	
Audible inspiration	Audible, breathy inspiration
Loudness	
Monoloudness	Voice lacks normal variation in loudness
Loudness decay	Progressive diminution of loudness within an utterance
Prosody	
Speech rate	Rate of speech is abnormally slow or rapid
Variable rate	Rate varies within or across utterances
Short phrases	Phrases are short (possibly because inspiration occurs more often than normal)
Reduced stress	Speech shows reduction of proper stress or emphasis patterns.
Prolonged intervals	Prolongation of interword or intersyllabic intervals.
Equal and excess stress	Excess stress is placed on usually unstressed syllables (e.g., unstressed syllables of polysyllabic words)
Voice	
Hoarse	Voice is harsh, rough, and raspy
Breathy	Voice is breathy, weak, and thin
Strained-strangled	Voice sounds strained or strangled
Articulation/phonology	
Imprecise consonants	Consonants lack precision (inadequate sharpness, distortions or crispness)
Prolonged phonemes	Phonemes have prolonged duration
Repeated phonemes	Either slow or rapid repetitions of phonemes
Irregular articulatory breakdowns	There are intermittent, non-systematic imprecisions of articulation

Vowel distortions	Vowels are distorted in their phonetic accuracy
Increasing errors with length	Increased errors with increased word length
Groping	Audible groping for articulatory postures in which sounds are distorted
Phonemic errors	Incorrect phonemes are selected during phonological encoding. Errors are clearly articulated insertions, deletions or substitutions of phonemes
Fluency	
False starts	Partial words which were abandoned, usually after one or a few phonemes had been produced*
Resonance	
Hypernasality	Resonance is excessively nasal
Hyponasality	Resonance is denasalised
DDK	
Speed	DDK rate is abnormally slow or fast
Regularity	DDK is irregular in duration, pitch or loudness

Note: Descriptions of speech features based on those from Duffy (2013); * Definition provided by Wilson et al., (2010).

3.3.6 Statistical analysis

All statistical tests were conducted on SPSS (IBM Corp., 2013). Detailed analyses are described in the relevant Methodologies of Chapters Four through Seven. Multiple comparisons were conducted in statistical tests in Chapters 4, 5, 6 and 7. Bonferroni corrections to the statistical significance level were conducted for each test. Trends towards significance were also reported, and these were defined as results that did not reach the Bonferroni corrected level of significance, however had a p value of less than 0.05.

3.4 Ethical approval

The overall study ‘Communication and swallowing as clinical markers for diagnosing and monitoring the progression of dementia’ received ethical approval from the Eastern Health Research and Ethics Committee (E21-1314). Informed consent was obtained from all participants or their legal advocates on their behalf.

4 Subgroup comparisons of speech in FTD and PPA

4.1 Introduction

Classification of PPA subtype according to international consensus criteria requires careful analysis of verbal expression (Gorno-Tempini et al., 2011). Clinical diagnosis typically involves perceptual (listener-based) evaluation of several important speech features such as word finding pauses, effortful speech and speech sound errors (Gorno-Tempini et al., 2011; Rohrer, Knight, et al., 2008). Evaluation of these features in the progressive aphasias has been assisted with the use of tailored rating scales such as the Progressive Aphasia Severity Scale (PASS; Sapolsky, Domoto-Reilly, & Dickerson, 2014) and progressive aphasia language scales (PALS; Leyton et al., 2011). In other cases, clinicians and researchers have applied motor speech rating scales, such as the apraxia of speech rating scale (ASRS; Strand et al., 2014) and motor speech evaluation (MSE; Wertz & Rosenbek, 1991).

In addition to qualitative ratings, attempts to quantify speech changes have been made, such as counting the number of speech and language errors within a sample (Ash et al., 2013; Fraser et al., 2014; Wilson et al., 2010). While these methods provide a more detailed characterisation of speech production, their time intensive nature contraindicates their use in clinical settings. More clinically applicable acoustic measures of speech have been implemented in several studies (Poole et al., 2017).

For example, broad measures of speech rate have demonstrated capacity to differentiate between PPA variants (Ash et al., 2010; Cordella, Dickerson, Quimby, Yunusova, & Green, 2017; Fraser et al., 2014; Wilson et al., 2010). Finer grained analysis, such as maximum speech rate (Wilson et al., 2010) and the pairwise variability index (Ballard et al., 2014) have demonstrated capacity to differentiate nfvPPA from lvPPA.

The use of sensitive and objective acoustic measures of speech may assist clinical classification of PPA variant, as clinician based judgement of speech can vary between and within assessors (Kent, 1996), thereby limiting the capacity to identify gradual change over time. Furthermore, while there have been calls for refinement of the classification criteria set out by the ICC (Wicklund et al., 2014), this process is currently restricted by the broad range of listener based assessments being used, which lack sensitivity and reproducibility between

research groups (Poole et al., 2017). Acoustic measures may address this issue by providing reproducible and comparable metrics which do not depend on the judgement of expert raters.

The importance of differential diagnosis of PPA and FTD subtypes is underlined through the discovery of associations between clinical presentation and pathology (Grossman et al., 2013; Knibb, Xuereb, Patterson, & Hodges, 2006; Mesulam et al., 2008). Classification of subtype will therefore be of considerable importance as people with atypical forms of dementia are screened for medical trials of new treatments. Accurate clinical diagnosis also allows clinicians to inform people with PPA of prognosis and patterns of progression specific to the specific syndrome (Harciarek et al., 2014; Rogalski, Cobia, Harrison, Wieneke, Weintraub, et al., 2011).

In Chapter Four, I investigate the use of the speech acoustic measures described in Chapter Three for differentiation between subtypes of PPA, FTD and the healthy population. Findings will add to the characterisation of speech changes in these disorders and highlight measures which may assist with classification of PPA subtype.

4.2 Methods

4.2.1 Participants

Forty-three participants with FTD or PPA and twenty-four healthy controls were recruited from the Eastern Cognitive Disorders Clinic at Box Hill Hospital, Melbourne, Australia. Participants were diagnosed by experienced neurologists according to established criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Participants' gender, mean age, and estimated disease duration are presented in Table 4-1. Mean PALS ratings for each subgroup are presented in Table 4-2. Due to the heterogenous nature of the PPA participants, the key speech and language features are presented for each participant in Table 4-3. Key speech and language features were selected based on the diagnostic criteria for PPA (Gorno-Tempini et al., 2011). Dysarthria and AOS were judged as present or not based on clinical observations from speech pathologists and neurologists with expertise in PPA and FTD. The presence of surface dyslexia or dysgraphia was judged based on the Writing Regular Phonics and Irregular Forms subtests from the Boston Diagnostic Aphasia Examination (BDAE; Goodglass et al., 1983). Presence of phonologic errors, agrammatism, impaired word retrieval, impaired naming, impaired word and sentence comprehension, impaired object

knowledge, and impaired sentence repetition were judged on ratings from the Progressive Aphasia Language Scales (PALS; Leyton et al., 2011). Participants were excluded if they lacked proficiency in spoken English, or had any other neurological condition that could explain any change to their speech or language, including stroke, acquired brain injury or other neurodegenerative conditions.

Table 4-1: Participant demographics

Diagnosis	No.	Gender	Age		Disease Duration	
		(M/F)	Mean	*SD*	Mean	*SD*
bvFTD	22	(17/5)	63.7	8.9	5.4	4.4
svPPA	8	(4/4)	66.1	7.5	4.5	2.5
nfvPPA	4	(2/2)	61.1	5.6	2.0	0
lvPPA	9	(6/3)	69.8	6.0	4.1	2.2
Healthy controls	24	(10/14)	60.2	9.7	n/a	n/a

4.2.2 Data acquisition

All participants were recorded while completing a standard speech protocol in a quiet room with no background noise. Speech samples were recorded with an AKG C520 cardioid head-mounted condenser microphone (frequency range, 20-20KHz; sensitivity, -43 dB) onto a Marantz PMD671 solid state recorder. The microphone was positioned at a 45^{o} angle 8 cm from the mouth. Recordings were sampled at 44.1 KHz and quantized at 8 bits.

4.2.3 Perceptual analysis

Perceptual rating scales outlined in chapter 3 were used to evaluate the speech recordings. Ratings were conducted by two speech pathologists who were blinded to diagnosis. Disagreement on rating was resolved by consensus.

4.2.4 Acoustic analysis

Acoustic methods outlined in chapter 3 were used to analyse the data.

Table 4-2: Mean PALS ratings for each subgroup

Diagnosis	MSD	Phonemic errors	Agrammatism	Naming	Word comprehension	Word repetition	Sentence repetition	Sentence comprehension
HC	0	0	0	0	0	0	0	0
bvFTD	0.47	0	0	1.2	0.93	0.2	0.53	0.8
svPPA	0	0	0.2	2.6	2.2	0	1	1.6
nfvPPA	2	0.33	1.33	1	1	0.67	1.67	1.33
lvPPA	0	0.83	0.17	2.33	1.67	0.67	2.33	1.67

Note: HC = healthy control; MSD = motor speech disorder

Table 4-3: Speech and language features for each participant with PPA

Participant	AOS	Dysarthria	Phonologic errors	Agrammatism	Impaired word retrieval	Impaired confrontation naming	Impaired word comprehension	Impaired object knowledge	Surface dyslexia/ dysgraphia	Impaired sentence repetition	Impaired sentence comprehension
nfvPPA 1 (WH)	Y	N	N	E	Y	Y	N	N	N	N	N
nfvPPA 2 (JO)	Y	N	N	Y	Y	Y	N	N	N	N	Y
nfvPPA 3	Y	E	E	Y	Y	N	N	N	N	N	Y
nfvPPA 4	Y	E	E	Y	Y	Y	N	N	N	N	Y
svPPA 1	N	N	N	N	Y	Y	Y	N	Y	N	N
svPPA 2	N	N	N	N	Y	Y	Y	N	Y	N	N
svPPA 3	N	N	N	N	Y	Y	Y	Y	Y	Y	Y
svPPA 4	N	N	N	N	Y	Y	Y	Y	Y	Y	Y
svPPA 5	N	N	N	N	Y	Y	Y	Y	N	N	N
svPPA 6	N	N	N	N	Y	Y	Y	Y	Y	N	N
svPPA 7	N	N	N	N	Y	Y	Y	Y	Y	N	Y
svPPA 8	N	N	N	N	Y	Y	Y	Y	N	N	Y
lvPPA 1	N	N	Y	N	Y	Y	N	N	Y	Y	Y
lvPPA 2	N	N	N	N	Y	Y	N	N	N	Y	N
lvPPA 3	N	N	N	N	Y	Y	N	N	N	Y	Y
lvPPA 4	N	N	N	N	Y	Y	N	N	N	Y	N
lvPPA 5	N	N	Y	N	Y	Y	Y	N	N	Y	N
lvPPA 6	N	N	Y	N	Y	Y	Y	N	N	Y	Y
lvPPA 7	N	N	Y	N	Y	Y	N	N	N	Y	N
lvPPA 8	N	N	N	N	Y	Y	N	N	N	Y	Y
lvPPA 9	N	N	N	N	Y	Y	N	N	N	Y	N

Note: Speech and language features based on core diagnostic criteria of PPA diagnostic criteria (Gorno-Tempini et al., 2011). Presence of AOS or dysathria were based on clinical judgements made by speech pathologists and neurologists with expertise in FTD and PPA. Surface dyslexia and dysgraphia assessed with the Boston Diagnostic Aphasia Examination. All other language features were assessed with the progressive aphasia language scales; Y = present; N = not present, E = equivocal; AOS = apraxia of speech; JO = participant reported as JO in Chapter 6; WH = participant reported as WH in Chapter 6

4.2.5 Language assessment

Language production was rated on the domains within the Progressive Aphasia Language Scale (PALS; Leyton et al., 2011). PALS domains included the presence of motor speech disorder, phonemic errors, agrammatism, naming, single word comprehension, sentence comprehension, single word repetition, and sentence repetition. PALS domains were rated on a 4 point scale, where 0 = no deficit, 1 = questionable deficit, 2 = definite deficit, 3 = severe deficit. PALS ratings were conducted in accordance with published criteria (Leyton et al., 2011).

4.2.6 Statistical analysis

All statistical tests were conducted on SPSS (IBM Corp., 2013). Parametric tests were conducted for interval and ratio data obtained from the acoustic metrics. Histograms were inspected for normality, and Shapiro-Wilks tests of normality were conducted for each parametric variable. Normality was violated on several measures: mean pause time, standard deviation of pause, and percentage of pause time for all stimuli (monologue, reading passage, days of the week), the coefficient of variation of fundamental frequency, and on all metrics calculated for the DDK tasks except for average rate, which was normally distributed. A natural log transformation improved the normality of the variables which violated normality. The four pathological groups and controls were compared with a series of analyses of variance (ANOVA)s for each acoustic measure. A Bonferroni correction was conducted to account for multiple comparisons (30 metrics). The adjusted significance level was $p<0.0017$. Tukey's HSD post hoc tests were conducted to identify differences between groups. Group numbers for each comparison differed due to participant's inability to conduct certain speech tasks (e.g., unable to accurately read the Grandfather or Rainbow passage). When there were fewer than three participants, that group was excluded from the ANOVA. The nfvPPA group was not included in the ANOVA for the timing measures (e.g. mean pause length, proportion of pause time) of the monologue and Grandfather Passage and the vowel articulation index.

Receiver operating characteristic (ROC) curves were calculated for parametric metrics which were found to have a statistically significant ($p<0.0017$) mean difference between groups on post-hoc testing. The nfvPPA group was excluded from the ROC analysis as there were fewer

than five participants in that subgroup. Optimal test cut-off values were selected to maximise test accuracy without preference for either sensitivity or specificity.

Non-parametric tests were conducted on the consensus perceptual ratings. Group differences were examined with Kruskal-Wallis analysis of variance, and Mann Whitney post hoc comparisons were conducted for all groups in comparison to each other pathological or control group. A Bonferroni correction was conducted to account for multiple comparisons (28 characteristics). The adjusted significance level was $p<0.0018$. Inter-rater reliability of the perceptual ratings made by each independent rater (prior to consensus) was evaluated by calculating percent agreement for each speech feature.

Correlation analysis was conducted on acoustic measures to investigate relationships with disease duration and language scores. Correlations were conducted on acoustic measures which were observed to have group variance in ANOVA ($p<0.05$). Disease duration was taken as the estimated time in years between the speech assessment and first symptoms (based on report of participant and their next-of-kin). PALS rating scales (motor speech disorder, phonemic errors, agrammatism, naming, word comprehension, word repetition, sentence repetition, sentence comprehension) were correlated with acoustic measures while controlling for disease duration. Pearson's *r* was calculated for disease duration and Spearman's *rho* for the ordinal PALS scores. Analyses were conducted for all pathological groups as a single group, and separately for the bvFTD group. Independent correlations were not investigated in the PPA groups due to the small sample sizes in each PPA group. A Bonferroni correction was conducted to account for multiple comparisons, resulting in an alpha of 0.0026..

4.3 Results

All pathological groups were observed to have perceptual abnormalities for some speech features when compared to controls. Acoustic measures of timing, DDK and PVI differentiated between pathological groups, and indicated statistically significant differences from controls.

4.3.1 Perceptual characteristic of speech in each subgroup

Results of statistical comparisons between groups based on perceptual data are presented in Table 4-4. Details on the proportion of participants with abnormal ratings for each speech feature and number of participants rated as subclinical, mild, moderate or severe are presented in Table 12-1 to Table 12-5 (Appendix A). Percent agreement for ratings conducted prior to consensus for each speech feature are presented in Table 13-1 (Appendix B). Percent agreement ranged from 52-98% (mean = 76.86, *SD* = 12.67). Kruskal-Wallis group comparisons indicated significant variance between groups on features within the speech subsystems of loudness, prosody, articulation, fluency, and DDK production (when corrected for multiple comparisons at $p<0.0018$; Table 4-4). Differences between group ratings of voice, pitch, respiration and resonance did not reach significance. Features of each pathological group in comparison to controls and other pathological groups are detailed below.

4.3.1.1 Perceptual characteristics of healthy controls

Perceptual ratings of the healthy control participants are presented in Table 12-1. The majority of participants were rated as having unremarkable production across each of the speech features. Many healthy controls were rated as having subclinical or mild hypernasality (38%), slow DDK rate (46%), irregular DDK (29%), breathy voice (25%), hoarse voice (26%), and monopitch (38%). Only one control participant was rated as having moderate deviation from normal on any scale, which was rated for hoarse voice quality.

Table 4-4: Kruskal-wallis and Mann-Whitney U comparisons of perceptual features for all groups

Speech subsystem and feature	Mann-Whitney U between group comparisons				Kruskal-wallis
	bvFTD	svPPA	nfvPPA	lvPPA	Chi-square value
Pitch					
Monopitch			β**; a*; d*		11.28*
Pitch breaks					6.44
Voice tremor					3.35
Respiration					
Audible inspiration			β**; a*		17.45***
Loudness					
Monoloudness	β*		β**; a**; d*		13.14**
Loudness decay			β***; a***; b*; d*		48.65***
Prosody					
Speech rate	β**	β*	β***; a*; b**; d*	β**	21.12***
Variable rate	β*			β**	9.65*
Short phrases	β***	β**	β*	β**	14.22**
Reduced stress	β**	β*	β**	β*	12.41*
Prolonged intervals	β***	β***	β*	β**	24.67***
Equal and excess stress	β*		β*; a*		12.41*
Voice					
Hoarse					8.12

Breathy				β*	7.87
Strained-strangled	β**			β**	12.51*
Articulation/phonology					
Imprecise consonants	β**		β**; a*; b**	β**	17.31***
Prolonged phonemes	β*		β***; a**; b**; d*	β*	25.63***
Repeated phonemes				β***; a**; b*	19.64**
Irregular breakdowns			b*	β*; a*	8.68
Vowel distortions			β**; a*		18.67**
Increasing errors with length			β*	β**; a*	10.14*
Groping			β*	β**; a*	17.42***
Phonemic errors	β*			β***; a**; b*	22.96***
Fluency					
False starts		β*		β***; a***; b*; c*	26.36***
Resonance					
Hypernasality					4.72
Hyponasality					2.02
DDK					
Speed	β*	β*	β***; a**; b**; d*	β**	20.42***
Regularity	β*	β**	β*		12.1*

Note: Asterisks denote significantly more severe impairment at * p<0.05, **p<0.01, ***p<0.0018 than [β]healthy controls, [a]bvFTD, [b]svPPA, [c]nfvPPA, [d]lvPPA

4.3.1.2 Perceptual characteristics of bvFTD

Perceptual ratings of bvFTD participants and results of statistical comparisons to healthy controls and PPA subtypes are presented in Table 12-2. Statistically significant differences ($p<0.0018$) were observed between bvFTD participants and controls on ratings of prosody (short phrases and prolonged intervals), while trends toward significance were observed for all other prosodic features and monoloudness. Trends toward significance were also observed for strained vocal quality, DDK speed and regularity, and some articulatory features (imprecise consonants, prolonged phonemes and phonemic errors). The bvFTD group was not statistically significantly more impaired on any rating compared to the PPA subgroups.

4.3.1.3 Perceptual characteristics of svPPA

Perceptual ratings of svPPA participants and comparisons to healthy controls, bvFTD, and other PPA subtypes are presented in Table 12-3. Only one speech feature, prolonged intervals, achieved statistically significant difference from controls at $p<0.0018$. Trends toward significance were observed for other prosodic measures (speech rate, short phrases and reduced stress), as well as false starts and DDK speed and regularity. A large proportion (88%) of participants were rated as abnormal on DDK production measures; however, only 25% of these were rated as mild, with the remainder rated as subclinical. No statistically significant differences (or trends toward significance) were observed between svPPA and other pathological groups.

4.3.1.4 Perceptual characteristics of nfvPPA

Perceptual ratings of nfvPPA participants and comparisons to healthy controls, bvFTD, and other PPA subtypes are presented in Table 12-4. More than half of nfvPPA participants were observed to have abnormalities in at least some features of each speech subsystem, with the exception of false starts. Statistically significant ($p<0.0018$) differences from controls were observed on loudness decay, speech rate, DDK speed and prolonged phonemes. Trends toward significant at $p<0.05$ were observed for all prosodic measures (except for variable rate), monoloudness and monopitch, vowel and consonant distortions, increasing errors with increasing length, and groping. No trends toward significant difference from controls were observed for resonance, voice or fluency measures.

The nfvPPA group was rated more severely than bvFTD on the rating of loudness decay, and additional trends toward significance between bvFTD and nfvPPA were observed for monopitch, monoloudness, audible inspiration, speech rate, equal and excess stress, vowel and consonant distortions, prolonged phonemes and DDK speed. Trends toward more severe ratings for nfvPPA were observed for speech rate, prolonged phonemes, and DDK speed compared to all other pathological groups. A trend was also observed for more severe ratings of monopitch in nfvPPA compared to lvPPA.

4.3.1.5 Perceptual characteristics of lvPPA

Perceptual ratings of lvPPA participants, and comparisons to healthy controls, bvFTD, and other PPA subtypes, are presented in Table 12-5. The articulatory subsystem had the most statistically significant differences from controls for repeated phonemes and phonemic errors, while trends were observed for imprecise consonants, prolonged phonemes, groping and irregular breakdowns. Trends toward significance were observed for all prosodic features except for equal and excess stress. False starts were also significantly different from controls at $p<0.0018$. A majority of participants was observed with subclinical, mild or moderate impairment of vocal quality, with trends toward significance ($p<0.05$ and $p>0.0018$) for breathy and strained voice qualities. All participants were rated as having abnormal DDK speed, and this difference trended toward significant difference from controls.

A statistically significant difference was observed between lvPPA and bvFTD on the rating of false starts, and trends toward significance were also observed for the other PPA subtypes on this measure. Phonemic errors and repeated phonemes also trended toward significant difference (more severe ratings) from bvFTD and svPPA.

4.3.2 Acoustic characteristics of speech by subgroup

Results of the omnibus comparisons and Tukey's HSD post hoc tests are presented in Table 4-5. The number of participants for each subgroup on each task are also presented in the table. Significant differences from controls are described for each pathological subgroup below in section 4.3.2. A description of significant differences between subgroups on post-hoc tests follows each acoustic measure.

Table 4-5: ANOVA and post hoc comparisons of acoustic data

Speech metric	bvFTD		svPPA		nfvPPA		lvPPA		Controls		Omnibus
	$\bar{X}$ (*SD*)	*n*	$\bar{X}$ (*SD*)	*n*	$\bar{X}$ (*SD*)	*n*	$\bar{X}$ (*SD*)	*n*	$\bar{X}$ (*SD*)	*n*	
Timing											
Speech rate											
Days of the week	3.74 (1.24)^{c}	22	3.37 (1.72)	7	1.66 (0.64)**^{a}	4	2.57 (1.46)*	8	4.12 (1.07)	24	***
Grandfather passage	2.92 (0.9)***^{dd}	22	2.74 (0.77)**	6	-	-	1.78 (0.62)***^{aa}	7	3.9 (0.53)	24	***
Mean pause time											
Days of the week	0.1 (0.07)^{c}	22	0.16 (0.15)	7	0.29 (0.22)***^{a}	4	0.14 (0.07)*	8	0.07 (0.04)	24	***
Grandfather passage	0.27 (0.18)**	22	0.21 (0.04)	6	-	-	0.27 (0.16) *	7	0.14 (0.04)	24	**
Monologue	0.36 (0.21)***	21	0.34 (0.25)**	6	-	-	0.23 (0.14)	8	0.15 (0.06)	24	***
SD of pause											
Days of the week	0.06 (0.06)^{c}	22	0.17 (0.24)	7	0.23 (0.15)***^{a}	4	0.12 (0.1)*	8	0.04 (0.04)	24	***
Grandfather passage	0.33 (0.27)*	22	0.26 (0.05)	6	-	-	0.34 (0.21)	7	0.19 (0.07)	24	*
Monologue	0.47 (0.28)***	21	0.52 (0.48) **	6	-	-	0.27 (0.17)	8	0.19 (0.1)	24	***
Proportion of pause time											
Days of the week	12.45 (7.48)	22	24.86 (19.38)	7	25.76 (10.16)	4	21.58 (10.87)	8	12.47 (6.08)	24	**
Grandfather passage	30.97 (11.64)*	22	32.49 (6.14)	6	-	-	33.6 (14.17)	7	22.47 (5.75)	24	*
Monologue	34.96 (12.71)**	21	38.89 (14.45)*	6	-	-	29.95 (15.57)	8	22.39 (7.96)	24	***
DDK											
AMR Period	219 (78)**^{c}	22	234 (29)**	8	419 (354)***^{a,d}	3	206 (31)^{c}	8	162.89 (15.2)	24	***
AMR Rate	4.97 (1.3)***	22	4.34 (0.55)***	8	3.51 (1.99)***	3	4.95 (0.64)**	8	6.19 (0.54)	24	***

CoV AMR Period	18.15 (28.47)	22	17.49 (9.59)	8	21.22 (32.07)	3	22.93 (16.68)	8	9.45 (4.54)	24	ns
Perturbation AMR Period	5.75 (13.17)	22	3.99 (1.91)	8	29.74 (50.47)	3	4.46 (3.17)	8	1.69 (0.95)	24	ns
CoV AMR Peak Intensity	4.07 (2.95)	22	4 (2.34)	8	3.29 (1.29)	3	4.59 (3)	8	2.81 (1.47)	24	ns
SMR Period	287 (202)***	22	224 (61)	8	405 (99)***	3	208 (32)	6	159.42 (20.56)	23	***
SMR Rate	4.52 (1.85)***	22	4.72 (1.12)*	8	2.59 (0.72)***	3	4.94 (0.92)	6	6.38 (0.88)	23	***
CoV SMR Period	35.36 (17.17)	22	42.07 (14.78)	8	35.38 (15.77)	3	36.01 (10.68)	6	28.49 (15.54)	23	ns
Perturbation SMR Period	13.22 (12.27)**	22	13.06 (8.79)*	8	18.47 (7.88)*	3	9.77 (4.3)	6	5.52 (3.14)	23	***
CoV SMR Peak Intensity	4.14 (1.75)[d]	22	5.48 (2.73)	8	8.35 (3.85)	3	8.09 (3.04)[a]	6	6.05 (3.21)	23	*
Formant Centralisation Ratio	1.52 (0.11)	15	1.51 (0.24)	3	-	-	1.46 (0.18)	7	1.54 (0.08)	24	ns
Voice											
Mean f0 (female)	181.78 (23.06)	5	155.59 (13.75)	3	-	-	182.22 (12.63)	3	180.91 (20.82)	14	ns
Mean f0 (male)	127.21 (18.85)	17	117.15 (18.86)	4	-	-	123.09 (14.63)	6	103.26 (16.63)	10	ns
CoV f0	0.07 (0.06)	22	0.1 (0.13)	7	0.14 (0.12)	4	0.09 (0.09)	9	0.07 (0.08)	24	ns
Harmonics to noise ratio	16.53 (6.69)	22	19.93 (4.73)	7	14.27 (11.81)	4	20.52 (4.57)	9	19.93 (8.3)	24	ns
Pairwise Variability Index											
Duration SW	53.25 (18.71)[cc]	16	52.53 (27.79)[c]	4	3.6 (37.03)***[aabdd]	3	58.48 (25.55)[cc]	7	62.33 (18.16)	24	**
Duration WS	-98.7 (29.51)[c]	16	-113.06 (17)[cc]	4	-46.85 (34.15)*[abb]	3	-91.5 (19.13)	7	-95.86 (21.49)	24	*
Intensity SW	5.71 (3.08)	16	4.99 (1.85)	4	5.59 (5.14)	3	6.92 (3.03)	7	5.79 (2.16)	24	ns
Intensity WS	-4.37 (3.65)	16	-4.28 (5.7)	4	-1.96 (9)	3	0.2 (4.41)	7	-2.29 (3.59)	24	ns

Note: AMR = Alternating motion rate (“papapa”); CoV = Coefficient of variation; DDK = diadochokinetic rate; ns = not significant; SMR = sequential motion rate (“pataka”). Asterisks denote significant difference from controls at * p<0.05, **p<0.01, *** p<0.0017, superscript letters denote significant difference to [a]bvFTD, [b]svPPA, [c]nfvPPA, [d]lvPPA.

4.3.2.1 Acoustic characteristics of bvFTD

The bvFTD group was significantly slower than controls on measures of speech timing and DDK production. When adjusting for multiple comparisons ($p<0.0017$) differences were observed for the monologue (increased mean pause time, increased standard deviation of pause) and reading (decreased speech rate) tasks only. No significant differences were identified for the days of the week task. Trends towards significance ($p>0.0017$ and <0.05) were identified for the monologue (increased proportion of pause time) and reading tasks (increased proportion of pause time, increased mean pause time, increased standard deviation of pause time).

Significant differences from controls were also observed for AMR rate, SMR rate and SMR period when corrected for multiple comparisons ($p<0.0017$). Trends towards significance ($p>0.0017$ and <0.05) were observed for AMR period and perturbation of SMR period.

There were no significant differences from controls for measures of vowel articulation index, voice quality, or pairwise variability index.

4.3.2.2 Acoustic characteristics of svPPA

Statistically significant differences corrected for multiple comparisons ($p<0.0017$) were observed for decreased AMR rate only. Trends toward significance ($p>0.0017$ and <0.05) were observed for increased AMR period, decreased SMR rate, increased perturbation of SMR period and impaired speech timing measures for the monologue (increased mean pause time, standard deviation of pause, and proportion of pause time) and reading tasks (decreased speech rate).

No significant differences between svPPA and controls were observed for measures of vowel articulation index, voice quality or pairwise variability index.

4.3.2.3 Acoustic characteristics of nfvPPA

The nfvPPA group differed from controls on measures of timing, DDK production and the pairwise variability index. Timing measures were conducted only for the days of the week task, due to insufficient numbers of participants who could complete the reading and monologue tasks. Mean pause time, and standard deviation of pause were each shown to be statistically significantly increased compared to controls at $p<0.0017$, and a trend towards

significance (p>0.0017 and <0.01) was observed for decreased speech rate. Proportion of pause time demonstrated a non-significant (p>0.05) increase compared to controls. DDK production in the nfvPPA group showed increased period of both AMR and SMR, and decreased rate of both AMR and SMR (p<0.0017). A trend toward significance (p>0.0017 and <0.05) was observed for an increase in perturbation of SMR period. A statistically significant difference (p<0.0017) was observed in the pairwise variability index for the durational measure of multisyllabic words with a strong-weak lexical stress pattern, indicating more equalised stress within multisyllabic words. A trend toward significance was observed for the durational measure of the weak-strong lexical stress pattern. No differences were observed for the PVI intensity measures.

No significant differences were observed between nfvPPA and controls for the voice quality measures. FCR was not compared between nfvPPA and controls due to an insufficient number of nfvPPA participants completing this task.

4.3.2.4 Acoustic characteristics of lvPPA

Differences between lvPPA and controls were identified for the speech timing and DDK production measures. The only statistically significant difference from controls (p<0.0017) was observed for decreased speech rate during the reading task. Despite this, several additional timing measures demonstrated several differences which trended toward significance at p<0.05, namely decreased speech rate (days of the week), increased mean pause time (days of the week and reading) and increased standard deviation of pause time (days of the week). A trend towards significance was also observed for reduction of AMR rate (p<0.01).

No significant differences were observed between lvPPA and controls on the voice quality, vowel articulation, or PVI measures.

4.3.3 Comparison of acoustic measures between pathological groups

4.3.3.1 Timing measures

Pathological group differences were observed between bvFTD and nfvPPA groups on three of four timing measures (speech rate, mean pause time, standard deviation of pause time) for the days of the week task only (p<0.05). Each of these measures indicated more impaired

speech timing for the nfvPPA group, and the bvFTD group did not differ from controls on any of these measures. The same measures could not be analysed for other timing stimuli (monologue and reading) due to insufficient number of participants in the nfvPPA group who completed these tasks.

Additionally, the lvPPA group was observed to have significantly slower speech rate ($p<0.01$) compared to bvFTD during the reading task. No significant differences were observed between svPPA and any other pathological group.

4.3.3.2 Diadochokinetic production

Five of the 10 DDK production measures were observed to have significant variation ($p<0.0017$) between groups on the ANOVA test. These were: AMR period and rate, SMR period and rate, and perturbation of SMR period. CoV SMR peak intensity trended toward significant variation between groups at $p<0.05$. The nfvPPA group had an AMR period more than double that of healthy controls and higher than both the bvFTD and lvPPA subgroups ($p<0.05$). The lvPPA group also had a greater coefficient of variation of SMR peak intensity when compared to bvFTD ($p<0.05$). The svPPA group was not observed to have any significant differences compared to any other pathological group.

4.3.3.3 Formant centralisation ration

No significant differences were observed between groups for the FCR measure. The nfvPPA group was not included in the ANOVA due to insufficient number of participants with nfvPPA who could produce the required stimuli.

4.3.3.4 Voice quality

No statistically significant differences were observed for mean f0 (for either male or female participants), coefficient of variation of f0, or harmonics to noise ratio in the ANOVA or post-hoc comparisons.

4.3.3.5 Pairwise variability index

Durational PVI for strong-weak words identified significant differences between the nfvPPA group and bvFTD, lvPPA ($p<0.01$) and svPPA ($p<0.05$) groups. Similarly, the durational PVI for weak-strong words was found to differ between nfvPPA and bvFTD ($p<0.05$) and lvPPA ($p<0.01$). The nfvPPA group was more impaired than the other groups on each PVI measure.

4.3.4 Sensitivity and specificity of acoustic measures (ROC curves)

ROC curves for variables which were found to be statistically significantly different from controls are shown in Figures 4-1 to 4-3. Area under the curve (AUC) values and cut-off scores for optimal sensitivity and specificity are presented in Table 4-6. High test accuracy was observed for all measures tested (AUC values ranged from 0.794 to 1.0).

4.3.5 Correlation of acoustic measures with disease duration and PALS scores

Results of correlation analysis of acoustic measures with disease duration and PALS ratings for all pathological groups are presented in Table 4-7. Results of correlation analysis of acoustic measures with disease duration and PALS ratings for the bvFTD group are presented in Table 4-8. Average PALS scores for each subtype are presented in Table 4-2. In the analysis of all pathological groups, two statistically significant differences were observed at $p<0.0026$. These were for ratings of phonemic errors, which positively correlated with *SD* of pause during the days of the week task, and motor speech disorder (MSD) which positively correlated with AMR period. Trends toward significance were observed between motor speech disorder ratings and both AMR and monologue timing; word repetition and pause length metrics; sentence repetition and proportion of pause time; and sentence comprehension with speech rate and pause length metrics during the reading task. Disease duration was shown to have trends for speech rate during the days of the week task, AMR rate and PVI duration for words with a weak-strong lexical stress pattern.

The correlation analysis involving only the bvFTD group did not reveal any statistically significant correlations. Trends toward significance were observed between MSD ratings and timing measures for days of the week, reading and monologue tasks. Ratings of sentence comprehension were observed to have a trend toward significant correlation with both mean and *SD* of pause time for the reading and monologue tasks.

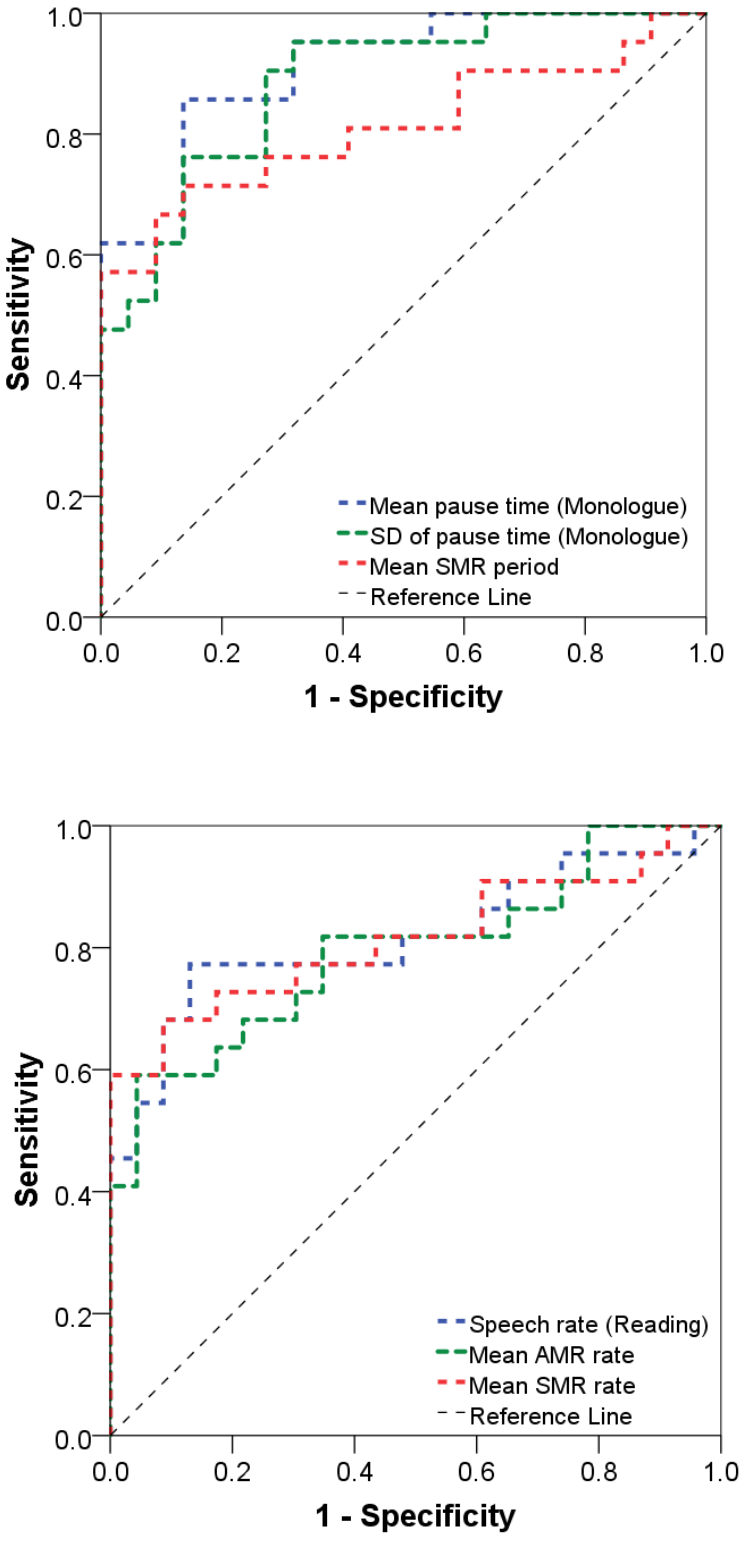

Figure 4-1: ROC curves (bvFTD vs. healthy controls) for variables which were found to be statistically significantly different from controls in ANOVA. Cut-off, sensitivity, specificity and area under the curve presented in Table 4-6

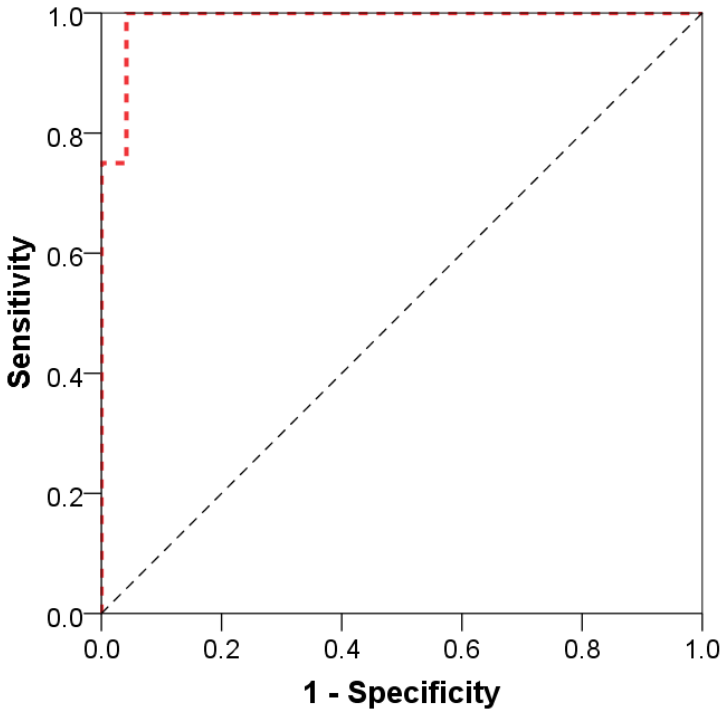

Figure 4-2: ROC curve (svPPA vs. healthy controls) for AMR rate. Cut-off, sensitivity, specificity and area under the curve presented in Table 4-6

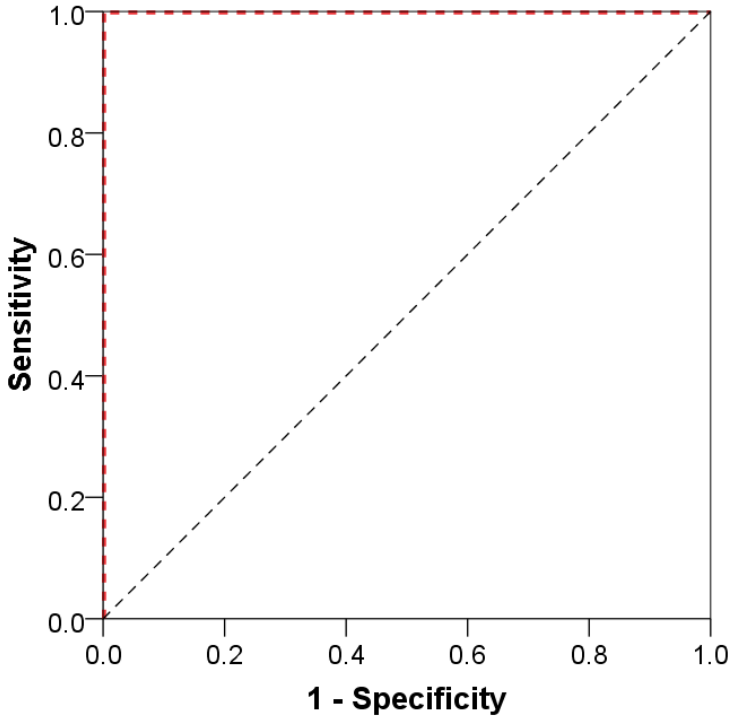

Figure 4-3: ROC curve (lvPPA vs. healthy controls) for speech rate during reading task. Cut-off, sensitivity, specificity and area under the curve presented in Table 4-6

Table 4-6: Sensitivity and specificity of acoustic measures

Group comparison	Metric	AUC	Asymptotic significance	Sensitivity	Specificity	Cut-off value
bvFTD vs HC	Mean pause time (Monologue)	0.911	<0.001	0.857	0.864	0.208
	SD of pause time (Monologue)	0.885	<0.001	0.952	0.682	0.225
	Speech rate (Reading)	0.816	<0.001	0.773	0.87	3.416
	Mean AMR rate	0.794	0.001	0.591	0.913	5.445
	Mean SMR rate	0.814	<0.001	0.682	0.913	5.429
	Mean SMR period	0.812	<0.001	0.714	0.864	176.48
svPPA vs HC	Mean AMR rate	0.99	<0.001	1	0.958	5.265
lvPPA vs HC	Speech rate (Reading)	1	<0.001	1	1	2.814

Note: AMR = alternating motion rate; AUC = area under the curve; bvFTD = behavioural variant frontotemporal dementia; HC = healthy control; lvPPA = logopaenic variant primary progressive aphasia; SMR = sequential motion rate; svPPA = semantic variant primary progressive aphasia

Table 4-7: Correlation analysis of acoustic measures with PALS ratings (Spearman's *rho*; controlled for disease duration) and disease duration (Pearson's r) in all pathological groups

Speech metric	PALS: Spearman's *rho* (p-value)								Disease duration: Pearson's *r* (p-value)
	MSD	Phonemic errors	Agrammatism	Naming	Word comprehension	Word repetition	Sentence repetition	Sentence comprehension	
Timing									
Speech rate									
Days of the week	-0.42 (0.08)	-0.2 (0.39)	-0.22 (0.34)	0.02 (0.95)	0.03 (0.9)	-0.44 (0.05)	-0.28 (0.23)	-0.21 (0.38)	**0.32 (0.04)***
Grandfather passage	-0.22 (0.36)	-0.01 (0.97)	-0.22 (0.36)	-0.27 (0.25)	-0.17 (0.48)	**-0.51 (0.02)***	-0.36 (0.12)	**-0.47 (0.04)***	0.1 (0.56)
Mean pause time									
Days of the week	0.04 (0.87)	**0.62 (0.004)****	0.03 (0.88)	0.22 (0.35)	0.17 (0.47)	0.19 (0.43)	0.32 (0.17)	-0.1 (0.69)	-0.15 (0.35)
Grandfather passage	0.19 (0.43)	-0.26 (0.26)	-0.15 (0.52)	0.17 (0.48)	0.25 (0.29)	**0.45 (0.049)***	0.25 (0.28)	**0.48 (0.03)***	0.17 (0.32)
Monologue	**0.6 (0.005)****	-0.15 (0.54)	-0.11 (0.66)	-0.05 (0.84)	0.003 (0.99)	-0.25 (0.28)	-0.23 (0.32)	0.2 (0.4)	0.02 (0.93)
SD of pause									
Days of the week	-0.09 (0.71)	**0.78 (<0.001)*****	0.03 (0.91)	0.23 (0.32)	0.08 (0.75)	0.27 (0.25)	0.42 (0.06)	-0.15 (0.54)	-0.22 (0.18)
Grandfather passage	0.18 (0.46)	-0.26 (0.27)	-0.22 (0.35)	0.17 (0.48)	0.27 (0.24)	0.36 (0.12)	0.28 (0.24)	**0.63 (0.003)****	0.05 (0.77)
Monologue	**0.45 (0.047)***	-0.17 (0.48)	-0.14 (0.55)	-0.14 (0.57)	0.003 (0.99)	-0.32 (0.17)	-0.2 (0.41)	0.33 (0.15)	-0.03 (0.89)
Proportion of pause time									
Days of the week	-0.18 (0.45)	0.38 (0.1)	0.21 (0.37)	0.24 (0.3)	0.22 (0.36)	**0.55 (0.01)***	**0.63 (0.003)****	0.28 (0.23)	-0.25 (0.12)
Grandfather passage	0.03 (0.89)	-0.35 (0.13)	-0.05 (0.84)	0.15 (0.53)	0.22 (0.34)	**0.54 (0.01)***	0.2 (0.39)	0.43 (0.06)	-0.01 (0.94)

Monologue	0.35 (0.13)	-0.16 (0.51)	-0.07 (0.76)	-0.12 (0.61)	-0.05 (0.85)	-0.15 (0.52)	-0.2 (0.39)	0.18 (0.45)	-0.22 (0.2)
DDK									
AMR Period	**0.65 (0.002)*** **	0.01 (0.98)	0.14 (0.56)	0.08 (0.74)	0.02 (0.93)	0.22 (0.36)	0.05 (0.84)	0.29 (0.22)	-0.25 (0.11)
AMR Rate	**-0.55 (0.012)***	-0.03 (0.89)	-0.14 (0.55)	-0.15 (0.54)	-0.08 (0.74)	-0.25 (0.28)	-0.13 (0.58)	-0.32 (0.17)	**0.36 (0.02)***
SMR Period	0.13 (0.59)	0.12 (0.65)	0.39 (0.09)	-0.07 (0.78)	-0.14 (0.55)	0.04 (0.87)	-0.04 (0.88)	0.12 (0.62)	-0.09 (0.59)
SMR Rate	-0.15 (0.54)	-0.15 (0.54)	-0.32 (0.17)	-0.00 (0.99)	0.01 (0.98)	-0.13 (0.58)	-0.04 (0.89)	-0.15 (0.52)	0.15 (0.35)
Perturbation SMR Period	0.13 (0.6)	0.03 (0.92)	0.3 (0.2)	0.14 (0.55)	0.06 (0.81)	0.02 (0.93)	-0.05 (0.83)	0.07 (0.78)	-0.06 (0.73)
CoV SMR Peak Intensity	-0.15 (0.54)	-0.14 (0.55)	0.29 (0.21)	0.22 (0.34)	0.02 (0.95)	0.32 (0.17)	0.29 (0.21)	0.32 (0.17)	-0.17 (0.29)
Pairwise Variability Index									
Duration SW	-0.2 (0.39)	-0.44 (0.05)	-0.15 (0.54)	0.1 (0.69)	0.01 (0.98)	-0.12 (0.6)	0.09 (0.7)	0.34 (0.14)	-0 (1)
Duration WS	-0.15 (0.54)	0.11 (0.64)	0.15 (0.53)	0 (0.99)	-0.07 (0.76)	0.12 (0.62)	-0.14 (0.56)	-0.4 (0.08)	**-0.39 (0.03)***

Note: Bolded text denotes statistically significantly correlation (2-tailed) at * $p<0.05$, ** $p<0.01$, *** $p<0.0026$ (Bonferroni corrected alpha);

PALS = progressive aphasia language scale

Table 4-8: Correlation analysis of acoustic measures with PALS ratings (Spearman's *rho*; controlled for disease duration) and disease duration (Pearson's r) in bvFTD

Speech metric	PALS: Spearman's *rho* (p-value)								Disease duration: Pearson's *r* (p-value)
	MSD	Phonemic errors	Agrammatism	Naming	Word comprehension	Word repetition	Sentence repetition	Sentence comprehension	
Timing									
Speech rate									
Days of the week	**-0.6 (0.02)***	-0.37 (0.17)	-0.37 (0.17)	0.02 (0.93)	0.01 (0.98)	-0.3 (0.28)	-0.12 (0.68)	-0.41 (0.13)	0.22 (0.34)
Grandfather passage	**-0.65 (0.008)****	-0.06 (0.83)	-0.06 (0.83)	-0.18 (0.51)	-0.24 (0.38)	-0.51 (0.05)	-0.33 (0.23)	-0.48 (0.07)	-0.07 (0.76)
Mean pause time									
Days of the week	0.38 (0.16)	0 (1)	0 (1)	0.4 (0.14)	0.32 (0.25)	0.42 (0.12)	0.32 (0.25)	0.21 (0.46)	0.15 (0.51)
Grandfather passage	**0.69 (0.004)****	0.12 (0.66)	0.12 (0.66)	0.19 (0.5)	0.19 (0.5)	0.46 (0.08)	0.22 (0.43)	0.36 (0.19)	0.16 (0.48)
Monologue	**0.7 (0.005)****	0.31 (0.28)	0.31 (0.28)	0.37 (0.19)	0.2 (0.49)	-0.03 (0.91)	0.23 (0.44)	**0.57 (0.03)***	0.04 (0.86)
SD of pause									
Days of the week	0.27 (0.34)	0.06 (0.83)	0.06 (0.83)	0.36 (0.18)	0.23 (0.4)	0.46 (0.08)	0.25 (0.37)	0.01 (0.97)	-0.03 (0.91)
Grandfather passage	**0.66 (0.007)****	0.12 (0.66)	0.12 (0.66)	0.06 (0.84)	0.12 (0.68)	0.34 (0.22)	0.34 (0.22)	**0.55 (0.03)***	0.01 (0.96)
Monologue	**0.61 (0.02)***	0.24 (0.41)	0.24 (0.41)	0.03 (0.92)	-0.02 (0.94)	-0.31 (0.28)	0.18 (0.54)	**0.64 (0.01)***	-0.04 (0.85)
Proportion of pause time									
Days of the week	0 (0.99)	-0.43 (0.11)	-0.43 (0.11)	0.36 (0.18)	0.4 (0.14)	0.46 (0.08)	0.34 (0.22)	0.39 (0.15)	-0.04 (0.85)
Grandfather passage	0.44 (0.1)	-0.25 (0.37)	-0.25 (0.37)	0.27 (0.33)	0.25 (0.37)	0.46 (0.08)	0.22 (0.42)	0.24 (0.38)	0.03 (0.91)

Monologue	0.44 (0.11)	0.17 (0.56)	0.17 (0.56)	0.11 (0.72)	-0.1 (0.72)	-0.03 (0.91)	0.12 (0.68)	0.45 (0.11)	-0.18 (0.44)
DDK									
AMR Period	**0.54 (0.04)***	0.37 (0.17)	0.37 (0.17)	0.19 (0.51)	0.17 (0.54)	0.51 (0.05)	0.2 (0.47)	0.48 (0.07)	-0.29 (0.19)
AMR Rate	**-0.54 (0.04)***	-0.37 (0.17)	-0.37 (0.17)	-0.19 (0.51)	-0.17 (0.54)	-0.51 (0.05)	-0.2 (0.47)	-0.48 (0.07)	0.34 (0.12)
SMR Period	0.3 (0.28)	-0.19 (0.51)	-0.19 (0.51)	0.31 (0.26)	0.31 (0.26)	0.38 (0.16)	0.35 (0.2)	0.46 (0.09)	-0.07 (0.75)
SMR Rate	-0.3 (0.28)	0.19 (0.51)	0.19 (0.51)	-0.31 (0.26)	-0.31 (0.26)	-0.38 (0.16)	-0.35 (0.2)	-0.46 (0.09)	0.08 (0.72)
Perturbation SMR Period	0.22 (0.42)	0.25 (0.37)	0.25 (0.37)	0.36 (0.18)	0.15 (0.6)	-0.05 (0.86)	0.03 (0.9)	0.19 (0.49)	0.05 (0.84)
CoV SMR Peak Intensity	-0.1 (0.71)	-0.43 (0.11)	-0.43 (0.11)	-0.29 (0.3)	-0.05 (0.86)	0.19 (0.5)	0.01 (0.97)	-0.05 (0.86)	0 (0.99)
Pairwise Variability Index									
Duration SW	**-0.52 (0.05)***	0.06 (0.83)	0.06 (0.83)	-0.27 (0.34)	-0.22 (0.42)	-0.46 (0.08)	0.01 (0.96)	-0.07 (0.81)	-0.29 (0.28)
Duration WS	-0.13 (0.64)	-0.37 (0.17)	-0.37 (0.17)	0.09 (0.74)	0.09 (0.75)	0.41 (0.13)	-0.24 (0.39)	-0.29 (0.29)	-0.4 (0.13)

Note: Bolded text denotes statistically significantly correlation (2-tailed) at * $p<0.05$, ** $p<0.01$, *** $p<0.0026$ (Bonferroni corrected alpha);

PALS = progressive aphasia language scale

4.4 Discussion

Perceptual and acoustic data presented in this chapter add to the characterisation of the speech profile of the FTD and PPA variants. NfvPPA participants had impairments of prosody (speech rate and prolonged phonemes) and articulation which were supported by acoustic correlates of lexical stress, DDK and timing. Similarly, the lvPPA group presented with reduced speech rate and articulatory errors, but without the reduced lexical stress variation of nfvPPA. The bvFTD participants demonstrated subtle motor speech changes and prominent prosodic impairment. In contrast, findings of reduced speech rate for svPPA were largely associated with increased pauses. Accurate diagnosis is important to patient care as it leads to greater understanding for patients and can provide some indication of progression (Harciarek et al., 2014). Comprehensive understanding of the speech phenotype of these syndromes is important for clinicians, as it allows for identification of abnormal features which may indicate transition to a related movement disorder.

4.4.1 Speech profile of bvFTD

Impaired prosody was observed perceptually (short phrases and prolonged intervals) and acoustically (rate and pause length) in the bvFTD group. While perceptual ratings were conducted on a contemporaneous monologue task only, acoustic analysis indicated that timing changes were dependent on the speech task that was measured. Impaired timing was only observed for stimuli with a higher cognitive load, namely the reading and monologue tasks. These task specific findings, with sparing of the more automatic days of the week task, may relate to deficits in executive functioning that are a key feature of bvFTD (Rascovsky et al., 2011). Similarly, while not previously explored in the literature (Poole et al., 2017), DDK production (both AMR and SMR) is shown in the present study to be impaired in the bvFTD group. This finding suggests that a subtle motor speech production impairment may be present in bvFTD in conjunction with the cognitive and behavioural decline which is characteristic of the disorder. Findings of the ROC curve analysis provide further support that both the DDK and timing measures have the potential to differentiate bvFTD and controls, with high sensitivity and specificity ($p<0.001$ – $p=0.001$). These findings support the hypothesis that a proportion of people with bvFTD experience subtle changes to motor function, in line with findings that 27% of people with bvFTD present with subtle signs of motor dysfunction that do not warrant a diagnosis of FTD-MND (Burrell et al., 2011). These

subtle changes are clinically important as they indicate that minor motor speech abnormalities in bvFTD may not be indicative of the development of FTD-MND. These data do not indicate the size or rate of decline which would be expected in the emergence of bulbar FTD-MND. Future longitudinal studies investigating these measures at short time intervals may inform whether acoustic measures could assist with the early identification of transition to FTD-MND.

4.4.2 Speech profile of svPPA

Of all the pathological groups, svPPA presented with perceptual speech ratings which were the most consistent with the healthy control participants, with the exception of significantly prolonged pauses. No more than 2 participants (25%) were rated as more severe than subclinical on any perceptual feature. Features consistent with word finding pauses (prolonged intervals, short phrases, reduced speech rate) were observed, and this is consistent with the known lexical and semantic deficits (word finding pauses) of svPPA (Ash et al., 2013; Fraser et al., 2014). One acoustic measure of DDK production (AMR rate) was observed to differ from controls, but measures of DDK period and SMR production did not. Trends toward impaired DDK production were noted perceptually; however, three-quarters of participants who were rated as abnormal on this feature received only a 'subclinical' rating. Further investigation of DDK production with a larger cohort would clarify whether the acoustic change to AMR rate is accurate. A recent systematic review did not find any investigations of DDK in larger cohorts of svPPA (Poole et al., 2017).

4.4.3 Speech profile of nfvPPA

The nfvPPA group presented with overt motor speech disorder characterised by impaired articulation and prosody (including monoloudness and monopitch), with a milder disturbance of voice quality. Features such as false starts and phonemic errors, which have been documented as key features of lvPPA (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2011), were not observed in this group. These findings are largely consistent with the literature, which documents a high proportion of motor speech disorder in nfvPPA (Gorno-Tempini et al., 2011; Rohrer, Rossor, & Warren, 2010a). Differences between the relative impact of articulation or prosody, as discussed by Josephs and colleagues (2013), were not undertaken due to the small sample size. Acoustic measures of timing and DDK production support the changes identified perceptually, which are likely due to AOS. It should be noted

that people with nfvPPA characterised by agrammatism without AOS are unlikely to have impairments of DDK production. These acoustic findings are consistent with the perceptual finding of more severe ratings of excess and equal stress compared to both healthy controls and bvFTD. It is important to note that the PVI measure is likely to be impacted by AOS only and not agrammatism. While all nfvPPA participants in this study presented with AOS, application of the PVI measure cannot be applied diagnostically to all participants suspected of having nfvPPA due to the possibility of nfvPPA without AOS (Gorno-Tempini et al., 2011; Josephs et al., 2013). PVI should therefore be considered a method of evaluating AOS rather than nfvPPA, and has application to some cases of nfvPPA, and also to PAOS and PPAOS. In addition to PVI, speech timing and DDK metrics are likely to be useful in supporting the characterisation and diagnosis of nfvPPA. A clinically important finding in the perceptual data was that the nfvPPA group was rated more severely on monopitch and monoloudness compared to lvPPA and svPPA. It appears that while changes to fluent speech production are apparent in both lvPPA and nfvPPA, overt reductions in prosodic range may be unique to nfvPPA. Similarly, while the nfvPPA group was impaired across a range of speech subsystems, abnormal resonance was not observed in this group to a greater degree than the healthy population. This is an important clinical consideration, as the emergence of hypernasality could indicate transition to a related disorder such as MND and PSP (Azher & Jankovic, 2008; Frattali & Duffy, 2005; Kertesz et al., 2000; Kühnlein et al., 2008).

4.4.4 Speech profile of lvPPA

Participants with lvPPA presented with speech that was marked with phonemic sound errors and a hesitancy characterised by false starts and repeated speech sounds. Each of these features are consistent with the documented speech errors observed in the connected speech of people with lvPPA (Ash et al., 2013; Wilson et al., 2010). These changes are reflected in the acoustic data by reduced speech rate during the reading task. While the difficulty of differentiating between phonemic speech errors and apraxic speech errors has been discussed previously (Ash et al., 2013), observations of clear phonemic errors in the context of false starts and repeated speech sounds during evaluation of contemporaneous speech suggest a classification of lvPPA rather than the semantic or nonfluent variants.

4.4.5 Correlations between acoustic measures and disease duration

There was no association between disease duration and any of the acoustic measures. This analysis was limited as all pathological groups were included in the same analysis, which added additional variation. Larger participant numbers would allow for further analysis which could investigate associations within each group individually. It is hypothesised that with sufficient statistical power, the metrics that were found to differentiate PPA and FTD groups from controls would become more severely impaired with increased disease duration.

4.4.6 Correlations between acoustic measures and PALS language scores

Correlation analysis with PALS scores was limited due to the small number of participants in the PPA groups. If the study had sufficient statistical power, a correlational analysis could be conducted for each group to identify syndrome specific features. Instead, two correlational analyses were conducted: one involving all pathological groups, and another of the bvFTD group (n = 22). Two correlations were statistically significant when all pathological groups were included in the analysis: phonemic errors with *SD* of pause in the days of the week task; and MSD with AMR period. Similar associations between MSD ratings and timing metrics were observed in the bvFTD group. The finding for phonemic errors likely reflects the link between reduced speech rate and speech sound errors in lvPPA and nfvPPA. A link between perceived severity of motor speech impairment and AMR production is also anticipated and supported by the data due to the motoric nature of DDK production. Trends were observed for the rating of MSD with monologue and DDK tasks, both of which would be expected in a motor speech disorder. An interesting link was observed between the timing measures on the reading passage and sentence comprehension while controlling for disease duration, which suggest that rate of speech in the reading task is also sensitive to impairments of comprehension across modalities.

4.4.7 Acoustic measures that may aid differential diagnosis

Despite the low number of participants in the PPA subgroups, significant differences were observed on several acoustic measures of speech production. These measures may have potential to be used clinically to aid differential diagnosis. Each measure is discussed below.

4.4.7.1 Timing measures

The speech timing changes which were observed across all groups may result from cognitive, linguistic or motor speech based deficits. In nfvPPA these timing changes are likely primarily due to AOS and agrammatism (Croot, Ballard, Leyton, & Hodges, 2012; Gorno-Tempini et al., 2011). In lvPPA, the impairments of speech timing are likely associated with word finding and phonological assembly difficulties which are characteristic of the disorder (Croot et al., 2012; Gorno-Tempini et al., 2008). Disruptions to speech timing in svPPA are unlikely to be associated with any motor speech impairment, and are more likely to be associated with word finding pauses (Duffy, Strand, & Josephs, 2014; Gorno-Tempini et al., 2011; Poole et al., 2017). In bvFTD, the changes to speech timing comparative to healthy controls may be associated with deficits of executive functioning (Rascovsky et al., 2011).

The differential impacts of cognition, language or motor speech on timing measures (e.g. mean pause length, variation of pause length) may be evident in the speech stimuli used for measurement. In this study, speech tasks used in the timing analysis can be considered along a continuum of automaticity, in which the contemporaneous monologue has the highest cognitive-linguistic load, followed by the reading task, and then the highly automatic days of the week task (Vogel, Fletcher, & Maruff, 2014). Data indicate that bvFTD and svPPA groups had changes in only the monologue and reading tasks. Similar studies show a reduction in connected speech rate for svPPA in both picture description and story retell tasks (Ash et al., 2013; Ash et al., 2009; Fraser et al., 2014). Similar investigations for bvFTD have had mixed results, with some studies identifying reduced rate during reading (Yunusova et al., 2016) and story retell (Ash et al., 2009), but no difference from controls on other picture description or story retell tasks (Ash et al., 2013; Gunawardena et al., 2010; Wilson et al., 2010). In contrast to svPPA and bvFTD, the two PPA subtypes with more prominent disruptions to fluency of verbal expression (lvPPA and nfvPPA) presented with changes on the days of the week task. It is reasonable to hypothesise that the nfvPPA group would also have statistically significant reductions in timing measures on all tasks had the number of participants been sufficient for comparison on these measures. Impaired timing across a range of tasks in nfvPPA is expected given the overt AOS and agrammatism reported in this group (Gorno-Tempini et al., 2011; Rohrer, Rossor, et al., 2010a; Wicklund et al., 2014), as well as similar timing impairments that have been observed during story retell (Ash et al., 2010; Ash et al., 2009; Fraser et al., 2014; Gunawardena et al., 2010; Mesulam et al., 2012; Rohrer, Rossor, & Warren, 2010b), reading (Ballard et al., 2014; Yunusova et al., 2016), semi-

structured conversation (Knibb, Woollams, Hodges, & Patterson, 2009) and picture description tasks (Ash et al., 2013; Graham et al., 2004; Wilson et al., 2010).

The nfvPPA group was significantly different from controls for mean pause time, and standard deviation of pause time, while a trend toward significance was observed for speech rate. These findings indicate that reduced rate of speech production was accompanied by increased length and variation of pauses in accordance with perceptual features of prolonged phonemes and short phrases (see Table 12-4). The remaining speech timing metric, proportion of pause time, was not significantly different from controls, which suggests that speech rate is reduced by both longer pauses and more temporally extended syllables for nfvPPA participants. Increased perceptual ratings for prolonged phonemes support this hypothesis.

The data presented in this chapter suggest that there is potential for speech timing measures to be used as a diagnostic tool. There appears to be a capacity for the measures to differentiate nfvPPA from bvFTD; however, the clinical utility of this is limited given the overt behavioural changes of bvFTD which are the first changes to be noticed by patients. The most clinically relevant comparison that can be made from a diagnostic perspective is between the nfvPPA and lvPPA subgroups due to their similar dysfluent presentations. While the current study is likely underpowered to identify all true differences between these subgroups, similar measures (proportion of silence time, duration and variability of silences) have been used in association with the PVI to successfully differentiate nfvPPA and lvPPA (Ballard et al., 2014).

4.4.7.2 DDK production

DDK production was impaired in all subtypes except for lvPPA, which had no statistically significant differences from controls (at $p<0.0017$). AMR rate and/or period was observed to be affected in bvFTD, nfvPPA and svPPA; however, SMR rate was only impacted in bvFTD and nfvPPA. The impairment of the nfvPPA group's DDK production is consistent with Rohrer and colleagues' (2010a) findings for nfvPPA, as well as observations that DDK rate decreases over time in people with PPAOS (Duffy et al., 2015). These changes, particularly greater impairment to SMR relative to AMR, are to be expected given similar changes in DDK production post stroke (Ogar et al., 2006). A trend toward more significantly impaired AMR and SMR rate and period was observed for nfvPPA during post hoc comparison with bvFTD and lvPPA. This difference suggests that these measures may be useful in

distinguishing nfvPPA from other groups, and further investigation with larger participant numbers is therefore warranted.

4.4.7.3 Pairwise variability index

The durational pairwise variability index demonstrated capacity to differentiate the nfvPPA group from all other pathological groups when calculated using measures of duration from the first two syllables of multisyllabic words, but not when calculated based on measures of intensity. Other studies of PVI in the PPA literature have found similar results when based on duration (Ballard et al., 2014; Duffy et al., 2015), likely due to the PVI metric's capacity to identify the excess and equal stress characteristic of AOS. Notably, the PVI metric based on intensity of the first two syllables did not identify any group differences, consistent with other investigations of intensity-based PVI in groups with AOS (Ballard et al., 2014; Vergis et al., 2014). In contrast, the durational measure has been shown to differentiate AOS from aphasia following stroke and in progressive AOS (Ballard et al., 2015; Ballard et al., 2014; Vergis et al., 2014). The discrepancy between the findings of intensity- and duration-based PVI indicates that the perceptually quality of equal and excess stress observed in AOS relates to poor coordination of durational variation across syllables, rather than differences of syllabic intensity. This hypothesis is supported by consistent findings of significant differences for PVI based on duration alongside no differences for PVI based on intensity (Ballard et al., 2014; Vergis et al., 2014). PVI is unlikely to be useful in identifying nfvPPA without AOS, and this is therefore a limitation for diagnosis of nfvPPA based on agrammatism (Gorno-Tempini et al., 2011). The PVI metric was excluded from the ROC curve analysis due to the low number of participants in the nfvPPA group. Further exploration of sensitivity and specificity of PVI in these syndromes would be a worthwhile avenue of future exploration, particularly in the early disease stages.

4.4.7.4 Formant centralisation ratio

Vowel articulation index was not observed to have any variation between groups. A notable limitation to this study is that there was an insufficient number of nfvPPA participants to include this subgroup in the analysis, and it is hypothesised that FCR would be most impaired in cases of AOS or dysarthria. To the authors' knowledge, this measure has not been investigated elsewhere in this population group. Given the noted vowel distortions perceptually in this study and others (Ackermann, Scharf, Hertrich, & Daum, 1997; Ash et

al., 2010), it is hypothesised that the nfvPPA group would show some deterioration on the FCR with sufficient statistical power.

4.4.7.5 Voice quality

Findings of the current study indicate that voice quality measures do not have potential to differentiate between subgroups. While no comparisons were made between the healthy control group of older adults with a group younger adults, it is well documented that changes to vocal quality occur as a result of ageing regardless of progressive pathology (Dehqan, Scherer, Dashti, Ansari-Moghaddam, & Fanaie, 2013; Ferrand, 2002). Similarly, measures of voice may be impacted by a range of lifestyle factors, such as smoking (Coy, 1991) and gastrointestinal reflux (Akyildiz, Ogut, Varis, Kirazli, & Bor, 2012). Findings of this study indicate that vocal changes, when measured acoustically, do not occur in these pathological groups to a greater degree than in the healthy population.

4.5 Conclusion

Further characterisation of each of the FTD and PPA presentations has been provided with the application of acoustic measures which have not previously been documented in these syndromes. Subtle motor speech changes have been observed in the bvFTD group, and this adds to our understanding of the clinical overlap of FTD and MND (Devenney, Vucic, et al., 2015). Acoustic correlates of prosody and articulation were sensitive to change in nfvPPA, and significant differences were observed despite the small sample size of this group.

Evaluation of acoustic measures in this study suggests that they can be used to assist with classification of clinical subtype. In particular, acoustic measures allow for comparable evaluation between different research groups as they do not require the judgement of experienced raters. The measures may therefore play a role in refining the international consensus criteria for PPA. For example, the PVI metric may assist in clarifying the lvPPA, nfvPPA, PAOS and PPAOS syndromes by confirming the presence or absence of apraxia of speech (Josephs et al., 2013). If widely used, such a metric could allow for comparison of AOS severity across case series from different research groups.

In the clinical setting, acoustic metrics may be used to support expert ratings in the identification of speech deterioration in PPA and FTD. Findings suggest that timing, DDK

and PVI measures are the measures which are most likely to be a useful adjunct to listener-based clinical diagnosis.

5 Imaging correlates of speech in PPA and FTD

5.1 Introduction

Speech is a neuromuscular act which draws upon multiple cortical and subcortical regions of the brain to coordinate motor, somatosensory and auditory information (Guenther & Vladusich, 2012). Levelt (1989) described the articulatory process as the final stage of verbal expression following conceptualisation and formation of the message. The neural correlates of this final articulatory stage have been explored via a computational model for speech production known as Directions into Velocities of Articulators (DIVA), which highlights the role of feedback and feedforward systems (Guenther & Vladusich, 2012). The feedforward system incorporates regions of the frontal lobe, including the posterior inferior frontal gyrus (pIFG) and primary motor cortex, to initiate and execute speech motor plans. These regions, alongside the anterior insula, premotor cortex, caudate and left cerebellar hemisphere have been observed to be activated in functional magnetic resonance imaging (fMRI) studies of speech production (Eickhoff, Heim, Zilles, & Amunts, 2009). Within the DIVA model, these motor plans are subsequently modified by comparison of the speech target with auditory feedback at the superior temporal gyrus (STG), and by somatosensory feedback at the supramarginal gyrus (SMG) and its white matter connections (Guenther, 2006). In addition to impairments of speech production, verbal expression may alternatively be impacted by impairments at the formation (i.e., aphasia) and conceptualisation levels (i.e., cognitive communication disorder) of Levelt's model (Levelt, 1989).

Regardless of the level of breakdown in verbal expression, exploration of the neural correlates of speech may allow for prediction of the location of neurodegeneration in PPA and FTD. Researchers have compared speech related brain-behaviour associations in PPA and FTD, and this process has helped to establish speech behaviours which may assist with aetiological diagnosis (Ash et al., 2009; Gunawardena et al., 2010; Whitwell et al., 2013; Wilson et al., 2010).

5.1.1 Neural correlates of speech production in PPA and FTD

Researchers have highlighted several brain regions which are associated with motor speech deficits in PPA. Atrophy of the left pars opercularis has been associated with reduced DDK

rate, and reduced grey matter volume of the left premotor cortex has been correlated with ratings of AOS in nfvPPA and PPAOS (Rohrer, Rossor, et al., 2010a; Whitwell et al., 2013). Pairwise variability index (PVI; Ballard et al., 2015; Ballard et al., 2014; Duffy et al., 2015) has been correlated with atrophy of the supplementary motor area (SMA), precentral gyrus and IFG bilaterally, thereby indicating more severely impaired lexical stress with increased atrophy (Ballard et al., 2014). These findings suggest that prominent features of AOS may only emerge when regions of motor speech control are damaged bilaterally (Ballard et al., 2014; Josephs et al., 2006; Whitwell et al., 2013). Distortion of speech sounds has been associated with reduced white matter volume in the superior longitudinal fasciculus (Wilson et al., 2010), and with reduced fractional anisotropy of white matter tracts connecting the pars opercularis, SMA, premotor cortex, caudate and putamen (Mandelli et al., 2014). The discovery of changes within these networks for participants with nfvPPA but not those with lvPPA or svPPA highlights their role in grammatical and fluent speech production (Mandelli et al., 2014).

At the conceptualisation level of verbal expression (Levelt, 1989), lesions and degeneration of anterior regions of the frontal lobe (dorsolateral, frontal opercula, IFG and anterior cingulate) may result in markedly reduced propositional speech despite intact basic language skills (Bormann, Wallesch, & Blanken, 2008; Warren, Warren, Fox, & Warrington, 2003). Aspontaneity of speech may be associated with abulia or apathy secondary to behavioural change and executive dysfunction, and is commonly observed in bvFTD (Neary et al., 1998). A similar presentation of limited speech output may be associated with a progressive primary language disturbance (dynamic aphasia), whereby basic language skills are preserved despite reduced generation of spontaneous speech (Esmonde, Giles, Xuereb, & Hodges, 1996; Robinson & Robinson, 2013; Robinson, Shallice, & Cipolotti, 2005; Warren et al., 2003). This syndrome is hypothesised to represent a breakdown at the preverbal conceptualisation of the intended message (Bormann et al., 2008; Luria, 1970). In two case studies of patients with progressive dynamic aphasia, bilateral atrophy of the anterior cingulate gyri, dorsolateral cortex, IFG and frontal opercula was demonstrated (Robinson et al., 2005; Warren et al., 2003).

Aphasic presentations of PPA may result from damage to either the frontal lobe or posterior language regions. In the frontal lobe, agrammatism has been correlated with atrophy of the posterior IFG, SMA and related white matter connections (Wilson et al., 2010). In contrast, speech hesitations (repaired sequences and filled pauses) have been correlated with atrophy

of the temporoparietal junction, including the posterior superior temporal gyrus (pSTG), angular gyrus and inferior parietal lobe (Wilson et al., 2010). The temporoparietal junction is the primary location of degeneration in lvPPA (Gorno-Tempini, Dronkers, et al., 2004) and findings of hesitancy correlating with this region are consistent with the dysfluent presentation of this subtype (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2011).

Clinical features of word finding difficulty and reduced speech rate can each be associated with a range of lesions in the brain, in contrast to the more limited regions associated with phonetic or phonemic speech errors (Wilson et al., 2010). In the progressive aphasias, superordinate paraphasias and circumlocution are associated with anterior temporal lobar atrophy (Hodges et al., 1992; Rohrer, Knight, et al., 2008; Wilson et al., 2010). Alternatively, word finding difficulties may be caused by atrophy surrounding the temporoparietal junction, resulting in prolonged pauses or logopaenia in spontaneous speech (Gorno-Tempini, Dronkers, et al., 2004; Rohrer, Knight, et al., 2008). Similarly, reduced speech rate has been correlated with atrophy in a range of cortical regions, including the left IFG, precentral gyrus, STG, and supramarginal gyrus (Ash et al., 2009; Grossman et al., 2013; Wilson et al., 2010). Reduced speech rate has also been observed to correlate with fractional anisotropy of the frontal aslant tract and left anterior corpus callosum (Catani et al., 2013; Grossman et al., 2013), as well as WM volume of the superior longitudinal fasciculus (Wilson et al., 2010).

In Chapter Five, I examine the associations between cortical thickness and subcortical volume with the acoustic and perceptual speech measures discussed in Chapters Three and Four. Regions of neurodegeneration are estimated with measures of cortical thickness and subcortical volume measured from participants' clinical magnetic resonance imaging (MRI) scans.

5.2 Method

Twenty-eight participants were included in the study of brain-behaviour associations. All participants were part of the larger cohort in Chapter Four. Mean age of onset was 65.1 years and mean years since diagnosis was 4.4. Participant demographics for the entire cohort and each subgroup are presented in Table 5-1.

Table 5-1: Participant demographics

Diagnosis	No.	Gender	Age		Disease Duration	
		(M/F)	Mean	SD	Mean	SD
bvFTD	15	12/3	62.6	8.73	5	2.94
svPPA	4	2/2	65.6	7.25	5.3	3.27
nfvPPA	2	1/1	64.4	2.36	2	0
lvPPA	7	5/2	70.3	6.24	3.4	1.59
All participants	28	20/8	65.1	8.29	4.4	2.78

5.2.1 Speech data acquisition and analysis

Speech recordings were collected from all participants using standardised procedure and equipment, as outlined in Chapter Three. Speech stimuli were analysed using the acoustic methods outlined in Chapter 3.3.4.

5.2.2 MRI data acquisition, region of interest choice, and imaging analyses

3D isotropic T1 weighted Magnetization Prepared RApid Gradient Echo (MPRAGE) scans were acquired on a clinical Siemens Aera 1.5 T scanner (Box Hill Hospital, Australia). The following parameters were applied: flip angle = 15 degrees, field of view = 256 x 256, repetition time = 1900ms, echo time = 2.67ms, matrix size = 256x256 pixels, slice thickness = 1 mm, number of slices = 144. Data analyses were conducted using Freesurfer version 5.1.3 using standard defaults (http://surfer.nmr.mgh.harvard.edu). Thickness was measured using a semi-automated approach, with a priori regions of interest (ROIs) identified (Fischl, 2012). ROIs were parcellated according to the method outlined by Fischl and colleagues (2002). Semi-automated calculations of the ROI masks were inspected and manually edited where needed. Global measures of cortical grey and white matter were obtained.

ROIs were chosen based on those identified in prior studies related to speech production in PPA and FTD. ROIs included bilateral insula, pars opercularis, pars triangularis, pars orbitalis, caudal middle frontal gyrus (MFG), precentral gyrus, caudate, temporal poles, STG, inferior parietal lobe (IPL) and SMG. The insula was selected as an ROI because atrophy of the bilateral insula has been associated with motor speech deficits in PPA (Ballard et al., 2014). Furthermore, imaging studies have identified atrophy of the left insula in nfvPPA (Gorno-Tempini, Dronkers, et al., 2004), and bilateral insulae in PAOS (Botha et al., 2015),

as well as left-sided hypometabolism in nfvPPA on fluorodeoxyglucose positron emission tomography (FDG-PET; Nestor et al., 2003b). The IFG (pars opercularis, pars triangularis and pars orbitalis) have been observed to have bilateral atrophy in nfvPPA and PAOS (Botha et al., 2015; Gorno-Tempini, Dronkers, et al., 2004). In addition, atrophy of the left IFG in PPA has been shown to be associated with impaired speech rate, lexical stress, and grammatically accurate sentence production (Ash et al., 2009; Ballard et al., 2014; Grossman et al., 2013; Gunawardena et al., 2010; Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011). The PVI metric has also been associated with atrophy of the bilateral IFG in nfvPPA (Ballard et al., 2014). The caudal MFG was selected as an ROI because atrophy of the left MFG has been observed in nfvPPA (Gorno-Tempini, Dronkers, et al., 2004), and atrophy of the bilateral premotor cortex has been observed in progressive AOS (Botha et al., 2015; Josephs et al., 2006). Furthermore, AOS ratings have correlated with grey matter volume of the left premotor cortex (Whitwell et al., 2013), and with reduced fractional anisotropy of WM tracts connecting the premotor cortex to the SMA (Mandelli et al., 2014). Selection of the precentral gyrus as an ROI was based on observation of left-sided atrophy in nfvPPA (Gorno-Tempini, Dronkers, et al., 2004) and bilateral atrophy in PAOS (Josephs et al., 2006). Atrophy of the precentral gyrus in PPA has also been associated with decreased speech rate (left hemisphere) and impaired lexical stress (bilaterally; Ballard et al., 2014; Wilson et al., 2010). The caudate has been observed to have bilateral atrophy in nfvPPA, svPPA and PAOS (Gorno-Tempini, Dronkers, et al., 2004; Josephs et al., 2006). In addition, quantity of speech distortions and speech rate have been observed to correlate with reduced fractional anisotropy in left WM tracts connecting the caudate to the SMA (Mandelli et al., 2014). The temporal poles were selected due to bilateral (prominently left) atrophy in svPPA (Galton et al., 2001; Gorno-Tempini, Dronkers, et al., 2004; Hodges et al., 1992; Mummery et al., 2000), as well as the association of bilateral atrophy with performance on a word comprehension test in a cohort of PPA participants (Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011). The STG were selected due to bilateral atrophy in svPPA, left posterior temporal lobe atrophy in lvPPA (Gorno-Tempini, Dronkers, et al., 2004), and left-sided atrophy and hypometabolism in nfvPPA (Grossman et al., 1996; Nestor et al., 2003b). Atrophy of the left STG in PPA has also been shown to correlate with speech rate and hesitations (Ash et al., 2009; Wilson et al., 2010), and atrophy of a posterior region of the STG shown to be associated with impaired repetition (Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011). The IFG and SMG were selected as atrophy of both regions has been observed bilaterally in lvPPA (Gorno-Tempini, Dronkers, et al., 2004; Rogalski et al.,

2014), and cortical thinning has been observed in the IPL bilaterally (predominantly in the left hemisphere) in a cohort of mixed PPA subtypes (Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011). Cortical atrophy of the left IPL has also been associated with hesitations in connected speech of PPA (Wilson et al., 2010), and impairments of grammatical speech production (Rogalski, Cobia, Harrison, Wieneke, Thompson, et al., 2011). Atrophy of the SMG has been correlated with speech rate in a cohort of PPA (Wilson et al., 2010).

5.2.3 Statistical analysis

Kruskal Wallis tests were conducted to investigate group differences for cortical thickness or subcortical volume at each of the regions of interest. The nfvPPA group was not included in group comparisons as there were only two participants in the group. Mann-Whitney U post-hoc tests were conducted on variables which were found to have statistically significant variance on the Kruskal-Wallis test. A Bonferroni correction was conducted to account for comparison of the 22 regions of interest. The adjusted significance level was $p<0.0023$.

Correlation analysis was conducted using Spearman's *rho* (one-tailed) between the a priori ROIs and acoustic and perceptual measures of speech production. The non-parametric analysis was undertaken to account for violations of normality, which were determined by visual inspection of histograms. Statistical significance was adjusted to account for multiple comparisons with a Bonferroni correction. The adjusted level of significance was $p<0.0016$.

5.3 Results

The Kruskal-Wallis comparison of groups revealed one group difference that survived the Bonferroni adjusted level of significance ($p<0.0023$). The IPL of the left hemisphere was observed to differ between groups. Trends toward significant group differences were observed for cortical thickness of the SMG and STG of the left hemisphere, and the IPL bilaterally (see Table 5-2). Post-hoc comparisons revealed that the lvPPA group had thinner cortices at each of these regions compared to bvFTD ($p=0.05$-0.0023).

Results of the correlation analysis for all pathological groups (*rho* values) are presented in Table 5-3 and Table 5-4 for acoustic data, and Table 5-5 and Table 5-6 for perceptual data. Two acoustic metrics correlated with cortical thickness at the Bonferroni adjusted

significance level of $p<0.0016$. These metrics were the coefficient of variation of AMR period, which inversely correlated with cortical thickness of the superior temporal gyrus, and speech rate measured during the reading task, which positively correlated with the left IPL. Trends toward significance ($p=0.0016$-0.05) for correlations between imaging and acoustic data are presented in Table 5-3 and Table 5-4. Four perceptual features reached statistical significance ($p<0.0018$) in the correlation analysis with cortical thickness. Severity ratings of hypernasality and regularity of DDK production were each inversely correlated with cortical thickness of the right precentral gyrus.. Perceptual ratings of speech rate and repeated phonemes were each correlated with the right temporal pole. Trends toward significance ($p=0.0018$-0.05) for correlations between imaging and perceptual ratings are presented in Table 5-5 and Table 5-6.

Table 5-2: Kruskal Wallis and Mann Whitney comparisons of regions of interest between pathological groups

Region of interest	Mann-Whitney U comparison			Kruskal Wallis Chi-squared
	bvFTD	svPPA	lvPPA	
Left hemisphere				
cMFG				4.63
IPL			a***	15.36***
Pop				1.76
Por				2.54
PT				2.45
PCG				4.63
STG			a**	9.18*
SMG			a**	9.85*
TP				3.29
Insula				0.91
Caudate				5.04
Right hemisphere				
cMFG				0.82
IPL			a*	8.41*
Pop				0.14
Por				1.99
PT				0.37
PCG				2.71
STG				1.77
SMG				2.91
TP				7.15
Insula				1.52
Caudate				5.24

Note: cMFG = caudal middle frontal gyrus; IPL = inferior parietal lobe; PCG = precentral gyrus; Pop = pars opercularis; Por = pars orbitalis; PT = pars triangularis; SMG = supramarginal gyrus; STG = superior temporal gyrus; TP = temporal pole. Asterisks denote significant difference (lesser thickness or volume) at * $p<0.05$, ** $p<0.01$, *** $p<0.0023$ than [a]bvFTD, [b]svPPA, [c]lvPPA

Table 5-3: Spearman's *rho* values from correlation analysis between acoustic speech and left hemisphere imaging data in all pathological groups

Speech metric	**Left hemisphere ROIs**										
	cMFG	IPL	Pop	Por	PT	PCG	STG	SMG	TP	Ins	Cau
Timing											
Days of the week											
Mean pause	-0.21	-0.26	-0.08	-0.03	-0.11	-0.18	0.01	-0.12	0.31	-0.1	0.09
SD of pause	-0.2	**-0.4***	-0.21	-0.27	-0.27	-0.33*	-0.14	-0.26	0.09	**-0.33***	0.05
Proportion of pause time	-0.19	**-0.51****	0.03	0.04	-0.1	-0.33*	-0.11	**-0.45****	**0.34***	0.11	-0.03
Speech rate	0.29	**0.32***	0.1	0.05	0.17	0.17	-0.02	0.12	-0.16	0.13	-0.12
Reading passage											
Mean pause	-0.09	-0.1	0.04	0.15	0.03	-0.14	-0.08	-0.05	-0.07	-0.13	0
SD of pause	-0.16	-0.09	0	0.1	0.04	-0.16	-0.08	-0.05	-0.06	-0.09	-0.03
Proportion of pause time	-0.07	-0.24	0.15	0.22	0.01	-0.25	-0.09	-0.29	0.16	0.13	-0.08
Speech rate	0.27	**0.61*****	0.08	0.01	0.11	0.31	0.15	**0.36***	-0.24	-0.06	-0.13
Monologue											
Mean pause	-0.14	-0.04	-0.17	-0.27	-0.21	-0.25	0.23	-0.11	-0.2	-0.25	-0.22
SD of pause	-0.11	0.01	-0.23	-0.25	-0.19	-0.15	0.27	-0.08	-0.08	-0.18	-0.2
Proportion of pause time	-0.05	-0.04	0.02	-0.08	-0.06	-0.16	0.26	-0.07	-0.05	-0.07	-0.08
DDK											
AMR Period	-0.17	-0.21	-0.13	0.18	0.09	-0.1	0.2	-0.09	**0.36***	0.14	0.09
AMR Rate	0.17	0.21	0.13	-0.18	-0.09	0.1	-0.2	0.09	**-0.36***	-0.14	-0.1
CoV AMR Period	-0.27	-0.24	-0.32	-0.32	-0.26	-0.24	**-0.59*****	-0.19	**-0.48****	**-0.44****	-0.12

Perturbation AMR Period	-0.27	-0.22	-0.28	-0.18	-0.17	-0.16	**-0.47****	-0.16	-0.24	-0.3	-0.13
CoV AMR Peak Intensity	-0.16	-0.22	-0.17	-0.03	-0.12	-0.14	-0.28	-0.22	-0.11	-0.22	-0.07
SMR Period	-0.05	-0.21	0.1	0.13	0.05	-0.13	0.3	-0.16	0.4*	0.28	0
SMR Rate	0.05	0.21	-0.1	-0.13	-0.05	0.13	-0.3	0.16	-0.4*	-0.28	0
CoV SMR Period	**0.34***	-0.11	0.05	-0.09	0.01	-0.13	-0.14	-0.22	-0.13	-0.23	-0.11
Perturbation SMR Period	0.06	-0.28	-0.05	-0.05	-0.04	-0.27	0.07	-0.3	0.22	-0.08	-0.07
CoV SMR Peak Intensity	-0.14	**-0.43***	-0.18	0.07	-0.16	-0.23	**-0.34***	**-0.35***	0.04	-0.02	0.18
FCR	0.08	0.18	-0.13	-0.26	-0.29	0.19	0.21	0.15	0.06	-0.19	0.05
Voice											
Mean f0 (female)	-0.75	0.12	**-0.75***	-0.64	-0.64	-0.61	-0.04	-0.07	-0.21	-0.43	**-0.75***
Mean f0 (male)	-0.35	0.1	-0.06	0.03	-0.07	-0.01	**-0.4***	0.04	-0.14	-0.19	-0.36
CoV f0	-0.3	-0.25	-0.25	-0.26	-0.13	-0.32	-0.16	-0.22	-0.28	-0.18	0.11
HNR	-0.11	**-0.42***	-0.1	-0.15	-0.1	-0.2	**-0.35***	-0.32	-0.07	-0.16	-0.03
PVI											
Duration SW	-0.16	0.15	**-0.64****	-0.25	**-0.5***	0.03	0.01	-0.08	0.32	-0.27	**-0.4***
Duration WS	-0.09	-0.15	-0.14	-0.12	-0.31	-0.05	-0.2	-0.2	0.04	-0.3	-0.09
Intensity SW	-0.07	-0.19	-0.03	0.36	0.06	0.04	-0.14	-0.04	**0.41***	0.2	0.32
Intensity WS	-0.24	**-0.46***	-0.31	-0.3	-0.37	**-0.55****	-0.26	-0.36	-0.02	-0.15	0.19

Note: AMR = Alternating motion rate ("papapa"); Cau = caudate; cMFG = caudal middle frontal gyrus; CoV = Coefficient of variation; DDK = diadochokinetic rate; f0 = fundamental frequency; FCR = formant centralisation ratio; HNR = harmonics-to-noise ratio; Ins = insula cortex; IPL = inferior parietal lobe; PCG = precentral gyrus; Pop = pars opercularis; Por = pars orbitalis; PT = pars triangularis; PVI = pairwise variability index; ROI = region of interest; SMG = supramarginal gyrus; SMR = sequential motion rate ("pataka"); STG = superior temporal gyrus; SW = strong-weak (lexical stress); TP = temporal pole; WS = weak-strong (lexical stress). Asterisks denote significant correlation at * $p<0.05$, **$p<0.01$, *** $p<0.0017$.

Table 5-4: Spearman's *rho* values from correlation analysis between acoustic speech and right hemisphere imaging data in all pathological groups

Speech metric	**Right hemisphere ROIs**										
	cMFG	IPL	Pop	Por	PT	PCG	STG	SMG	TP	Ins	Cau
Timing											
Days of the week											
Mean pause	0.01	-0.07	0.06	-0.1	-0.32	-0.08	0.16	0.28	**0.4***	0.17	-0.03
SD of pause	-0.06	-0.27	-0.07	-0.2	-0.27	-0.23	0	0.11	0.2	-0.02	-0.06
Proportion of pause time	-0.07	-0.29	0.08	0.04	-0.28	-0.28	0.15	0.19	**0.49****	0.37	-0.06
Speech rate	-0.01	0.11	0.06	0	0.26	0.04	-0.21	-0.28	**-0.38***	-0.16	0.01
Reading passage											
Mean pause	0	0.03	0.02	**0.39***	0.34	**-0.34***	-0.09	0.2	-0.04	-0.09	-0.02
SD of pause	0.01	0.11	0.04	**0.39***	**0.38***	-0.33	0.03	0.27	0.14	0.1	0.07
Proportion of pause time	-0.18	-0.06	0.09	**0.36***	0.2	**-0.45***	-0.02	0.15	0.23	0.29	0.03
Speech rate	0.2	0.3	0.03	-0.07	0.06	**0.4***	0.13	-0.21	**-0.48****	**-0.36***	-0.01
Monologue											
Mean pause	-0.16	0.02	-0.28	0.12	-0.02	**-0.49****	-0.01	0	-0.03	-0.24	-0.12
SD of pause	-0.21	0.03	**-0.4***	0.11	-0.07	**-0.45***	-0.09	-0.07	0.04	-0.3	-0.06
Proportion of pause time	-0.05	0.12	-0.03	0.25	0.07	**-0.41***	0.2	0.21	0.12	0.03	0.05
DDK											
AMR Period	0.03	-0.05	0.15	0.19	-0.11	**-0.35***	-0.07	0.19	**0.37***	0.09	-0.1
AMR Rate	-0.03	0.06	-0.15	-0.19	0.11	**0.36***	0.08	-0.18	**-0.37***	-0.08	0.09

CoV AMR Period	-0.17	-0.29	-0.15	**-0.34***	-0.01	-0.13	**-0.41***	-0.15	-0.31	-0.31	-0.11
Perturbation AMR Period	-0.07	-0.16	-0.06	-0.15	-0.01	-0.12	**-0.33***	0.07	-0.09	-0.21	-0.16
CoV AMR Peak Intensity	-0.18	-0.11	-0.3	-0.09	0.1	-0.15	-0.23	-0.01	-0.17	**-0.4***	-0.01
SMR Period	-0.17	-0.08	-0.08	0.2	-0.32	**-0.35***	0.2	0.18	0.31	0.18	-0.03
SMR Rate	0.17	0.08	0.08	-0.2	0.32	**0.35***	-0.2	-0.18	-0.31	-0.18	0.03
CoV SMR Period	-0.02	-0.15	-0.1	-0.12	0.13	-0.26	-0.15	-0.23	-0.28	-0.16	0.02
Perturbation SMR Period	-0.11	-0.2	-0.18	-0.03	-0.25	**-0.43***	-0.04	-0.01	0.06	-0.1	-0.09
CoV SMR Peak Intensity	-0.25	**-0.38***	0.08	-0.16	0.21	-0.01	-0.21	-0.25	0.24	0.25	0.22
FCR	-0.002	0.15	0.3	0.18	-0.32	0.07	0.22	0.19	-0.1	-0.27	0.01
Voice											
Mean f0 (female)	**-0.79***	-0.18	**-0.79***	**-0.71***	**-0.93****	-0.35	-0.11	0	-0.18	-0.18	**-0.86****
Mean f0 (male)	0.11	0.28	0.08	0.13	0.05	0.18	-0.14	**0.43***	-0.17	0.05	-0.34
CoV f0	-0.02	-0.07	-0.01	-0.08	0.15	-0.26	-0.14	0.07	-0.09	-0.02	0.15
HNR	-0.24	**-0.41***	-0.26	-0.12	-0.01	-0.25	**-0.39***	-0.32	0	-0.25	-0.17
PVI											
Duration SW	-0.2	-0.05	**-0.47***	-0.33	-0.2	0.3	0.02	-0.3	0.26	-0.21	-0.36
Duration WS	0.07	-0.03	0.31	-0.26	-0.26	0.23	0.17	0.29	0.2	0.09	-0.07
Intensity SW	0.08	-0.13	0.3	0.39	0.2	0.11	0.03	0.17	**0.55****	**0.42***	**0.45***
Intensity WS	-0.28	**-0.51***	-0.06	-0.04	0	-0.27	-0.13	-0.23	0.17	0.24	0.12

Note: AMR = Alternating motion rate ("papapa"); Cau = caudate; cMFG = caudal middle frontal gyrus; CoV = Coefficient of variation; DDK = diadochokinetic rate; f0 = fundamental frequency; FCR = formant centralisation ratio; HNR = harmonics-to-noise ratio; Ins = insula cortex; IPL = inferior parietal lobe; PCG = precentral gyrus; Pop = pars opercularis; Por = pars orbitalis; PT = pars triangularis; PVI = pairwise variability index; ROI = region of interest; SMG = supramarginal gyrus; SMR = sequential motion rate ("pataka"); STG = superior temporal gyrus; SW = strong-weak (lexical stress); TP = temporal pole; WS = weak-strong (lexical stress). Asterisks denote significant correlation at * $p<0.05$, ** $p<0.01$, *** $p<0.0017$.

Table 5-5: Spearman's *rho* values from correlation analysis between perceptual evaluation and left hemisphere imaging data in all pathological groups

Speech metric	**Left hemisphere ROIs**										
	cMFG	IPL	Pop	Por	PT	PCG	STG	SMG	TP	Ins	Cau
Pitch											
Monopitch	**-0.34***	**-0.33***	-0.15	0.02	-0.07	-0.32	0.01	-0.23	-0.18	-0.13	0.05
Pitch breaks	**-0.32***	-0.27	**-0.32***	**-0.32***	**-0.32***	**-0.32***	-0.23	-0.27	-0.06	-0.18	-0.2
Voice tremor	-0.12	**0.37***	0.15	0.2	0.04	0.3	0.17	**0.38***	0.02	0.25	-0.22
Respiration											
Audible inspiration	**-0.54****	**-0.43***	**-0.56****	-0.22	**-0.41***	**-0.49****	-0.21	**-0.44****	-0.09	-0.31	-0.14
Loudness											
Monoloudness	-0.26	-0.23	-0.15	-0.01	-0.12	-0.24	0.1	-0.08	-0.12	-0.16	0.17
Loudness decay	-0.16	**-0.33***	-0.24	-0.15	-0.24	-0.21	0.03	-0.22	0.11	-0.16	0.22
Prosody											
Speech rate	0.24	0.31	0.23	0.01	0.13	0.21	-0.3	0.15	**-0.44***	-0.15	-0.27
Variable rate	**-0.34***	-0.22	-0.17	-0.18	-0.24	-0.12	-0.05	-0.18	-0.17	-0.19	-0.2
Short phrases	**-0.47****	**-0.34***	**-0.33***	-0.17	**-0.45****	-0.29	-0.06	**-0.34***	-0.13	-0.31	-0.12
Reduced stress	**-0.48****	**-0.36***	-0.32	-0.12	**-0.41***	-0.37	-0.04	-0.28	-0.22	**-0.36***	0.01
Prolonged intervals	-0.29	-0.1	**-0.33***	-0.21	-0.27	-0.06	0.29	-0.03	0.06	-0.07	-0.12
Equal and excess stress	**-0.47****	**-0.34***	**-0.32***	-0.22	**-0.45****	**-0.37***	0.05	**-0.32***	0.07	-0.12	0.02
Voice											
Hoarse	0.17	0.15	0.12	-0.05	0.05	0.18	0.24	0.22	0.09	-0.05	0.25

Breathy	-0.11	**-0.47****	-0.1	-0.03	-0.07	-0.23	-0.23	**-0.33***	0.28	0.03	0
Strained-strangled	-0.29	0	**-0.43***	-0.14	-0.23	-0.13	-0.2	0.02	-0.02	-0.15	0
Articulation/phonology											
Imprecise consonants	**-0.36***	**-0.35***	-0.31	-0.25	**-0.38***	**-0.43***	0.03	-0.27	0.03	-0.13	0.14
Prolonged phonemes	-0.16	**-0.46****	-0.1	0.01	-0.09	-0.14	-0.04	-0.23	0.18	0.02	0.27
Repeated phonemes	**-0.41***	**-0.54****	**-0.4***	-0.3	**-0.41***	**-0.34***	-0.08	**-0.45****	0.21	-0.03	0
Irregular articulatory breakdowns	**-0.46****	**-0.5****	-0.29	-0.24	**-0.44****	**-0.39***	**-0.43***	**-0.48****	-0.12	-0.28	-0.09
Vowel distortions	-0.22	**-0.36***	-0.18	-0.17	-0.31	**-0.41***	0.08	-0.32	0.03	-0.08	-0.02
Increasing errors with increasing length	**-0.39***	**-0.52****	-0.31	**-0.32***	**-0.41***	**-0.37***	-0.04	**-0.4***	0.12	-0.06	-0.06
Groping	**-0.44***	**-0.46****	-0.28	-0.17	**-0.38***	**-0.37***	-0.02	**-0.41***	0.11	-0.11	0.05
Phonemic errors	**-0.36***	-0.3	-0.3	-0.2	-0.28	**-0.39***	**-0.36***	-0.27	-0.26	-0.31	0.02
Fluency											
False starts	**-0.38***	**-0.54****	**-0.32***	-0.19	**-0.33***	-0.28	-0.21	**-0.53****	0.29	0.1	-0.24
Resonance											
Hypernasality	-0.05	-0.3	0	-0.06	0.06	**-0.39***	0.19	-0.19	-0.07	0.06	0.25
Hyponasality	0.13	0.16	0	-0.05	0.01	0.26	0.19	0.23	0.14	0.07	0.25
DDK											
Speed	0.2	0.31	0.14	0.04	0.08	0.25	-0.17	0.23	**-0.39***	-0.19	0.01
Regularity	-0.16	-0.18	-0.19	-0.16	-0.15	-0.31	0.04	-0.24	-0.05	-0.03	-0.17

Note: Cau = caudate; cMFG = caudal middle frontal gyrus; Ins = insula cortex; IPL = inferior parietal lobe; PCG = precentral gyrus; Pop = pars opercularis; Por = pars orbitalis; PT = pars triangularis; ROI = region of interest; SMG = supramarginal gyrus; SMR = sequential motion rate ("pataka"); STG = superior temporal gyrus; TP = temporal pole. Asterisks denote significant correlation at * $p<0.05$, **$p<0.01$, *** $p<0.0018$.

Table 5-6: Spearman's *rho* values from correlation analysis between perceptual evaluation and right hemisphere imaging data in all pathological groups

Speech metric	**Right hemisphere ROIs**										
	cMFG	IPL	Pop	Por	PT	PCG	STG	SMG	TP	Ins	Cau
Pitch											
Monopitch	-0.32	-0.23	-0.12	-0.11	-0.01	**-0.5****	-0.16	-0.17	0.05	-0.11	0
Pitch breaks	-0.27	-0.13	-0.23	-0.27	-0.18	-0.3	-0.13	0.01	0.15	0.08	-0.11
Voice tremor	-0.12	0.24	-0.13	0	-0.21	0.27	0.18	0.09	-0.12	0	-0.34
Respiration											
Audible inspiration	**-0.46****	**-0.46****	**-0.49****	**-0.47****	**-0.36***	**-0.47****	-0.23	-0.27	-0.01	-0.31	-0.12
Loudness											
Monoloudness	-0.28	-0.12	-0.18	-0.17	-0.13	-0.31	-0.03	0.05	0.11	-0.08	0.15
Loudness decay	-0.09	-0.18	-0.1	-0.19	-0.19	-0.16	0.07	0.06	0.25	-0.01	0.27
Prosody											
Speech rate	0.09	0.08	0.07	-0.09	0.32	0.21	-0.09	-0.26	**-0.57*****	-0.28	-0.19
Variable rate	-0.1	0.07	-0.12	0.01	0.04	-0.16	0.1	0.3	0.14	-0.01	-0.13
Short phrases	**-0.33***	-0.16	-0.26	-0.2	-0.24	-0.32	0.13	0.15	0.15	-0.15	-0.08
Reduced stress	**-0.52****	-0.28	**-0.41***	-0.25	-0.27	**-0.46****	-0.14	-0.13	-0.01	-0.26	-0.02
Prolonged intervals	-0.23	0.02	-0.3	0.06	-0.15	-0.28	0.13	0.17	0.25	-0.13	-0.12
Equal and excess stress	**-0.44****	-0.22	-0.22	-0.17	**-0.34***	**-0.44****	-0.02	0.03	0.19	-0.04	-0.09
Voice											
Hoarse	**0.35***	**0.36***	0.27	**0.34***	**0.33***	0.18	**0.48****	**0.49****	0.26	0.23	**0.32***

Breathy	-0.03	**-0.32***	0.04	-0.05	0.02	-0.17	-0.08	0.04	**0.34***	0.23	-0.02
Strained-strangled	-0.15	-0.08	-0.06	-0.16	0.05	0.01	-0.19	-0.05	-0.02	0.06	-0.09
Articulation/phonology											
Imprecise consonants	**-0.49****	-0.29	**-0.33***	-0.12	-0.2	**-0.34***	-0.11	-0.14	0.17	-0.02	0.13
Prolonged phonemes	0.02	**-0.37***	-0.04	-0.01	-0.29	-0.13	-0.05	0	0.29	-0.05	0.08
Repeated phonemes	-0.18	**-0.33***	-0.16	-0.14	-0.15	-0.01	0.19	0.05	**0.58*****	0.29	-0.03
Irregular articulatory breakdowns	**-0.33***	-0.28	-0.22	-0.18	-0.16	-0.21	-0.11	0.02	0.17	0.03	-0.01
Vowel distortions	**-0.4***	**-0.51****	**-0.33***	-0.11	**-0.33***	**-0.32***	-0.05	**-0.36***	0.01	-0.19	-0.15
Increasing errors with increasing length	-0.29	**-0.35***	-0.27	-0.18	-0.24	-0.17	0.12	0.07	**0.36***	0.15	-0.18
Groping	-0.29	-0.22	-0.15	-0.18	-0.27	-0.24	0.09	0.06	**0.39***	0.18	0.03
Phonemic errors	-0.22	-0.21	-0.16	-0.22	0	-0.16	-0.1	-0.08	-0.02	0.07	0.06
Fluency											
False starts	-0.19	**-0.35***	-0.09	-0.11	-0.16	-0.09	0.04	-0.04	**0.33****	**0.36***	-0.29
Resonance											
Hypernasality	-0.25	**-0.39***	-0.17	0.11	0.01	**-0.62*****	-0.17	**-0.34***	-0.12	-0.17	0.08
Hyponasality	0.26	0.22	0.29	-0.08	-0.05	**0.44****	0.24	0.29	0.09	0.22	0.24
DDK											
Speed	0.12	0.16	0.03	-0.2	0.2	**0.38***	-0.02	-0.18	**-0.39***	-0.2	0.06
Regularity	**-0.41***	-0.27	-0.29	0	-0.02	**-0.58*****	-0.14	**-0.37***	0.04	-0.13	-0.16

Note: Cau = caudate; cMFG = caudal middle frontal gyrus; Ins = insula cortex; IPL = inferior parietal lobe; PCG = precentral gyrus; Pop = pars opercularis; Por = pars orbitalis; PT = pars triangularis; ROI = region of interest; SMG = supramarginal gyrus; SMR = sequential motion rate ("pataka"); STG = superior temporal gyrus; TP = temporal pole. Asterisks denote significant correlation at * $p<0.05$, ** $p<0.01$, *** $p<0.0018$.

5.4 Discussion

Motor speech disorders in PPA are associated with atrophy of the frontal lobe in nfvPPA and PAOS (Botha et al., 2015; Gorno-Tempini, Dronkers, et al., 2004; Grossman et al., 1996; Josephs et al., 2006). In particular, atrophy of the premotor cortex, SMA and IFG has been reported in progressive AOS (Ballard et al., 2014; Josephs et al., 2012; Whitwell et al., 2013). Cortical thickness of the equivalent regions in the current study (the caudal MFG, pars opercularis, pars triangularis and pars orbitalis) were not correlated with speech metrics in either hemisphere. In contrast, a correlation was observed between cortical thickness of the right precentral gyrus and perceptual ratings of both hypernasality and regularity of DDK production. Hypernasality is not considered a feature of AOS, and is more commonly associated with dysarthria (Darley et al., 1969; Duffy & Josephs, 2012; Duffy et al., 2014; Josephs et al., 2012; Strand et al., 2014). In nfvPPA and PPAOS, features of dysarthria, most commonly spastic or hypokinetic, are described alongside AOS in up to 60% of cases (Botha et al., 2015; Caso et al., 2014; Graff-Radford, Duffy, Strand, & Josephs, 2012; Josephs et al., 2013; Ogar et al., 2007), and become more common with disease progression in PPAOS (Josephs, Duffy, Strand, Machulda, Senjem, et al., 2014). Researchers specifically investigating resonance as part of dysarthria characterisation identified hypernasality in 5/18 participants with nfvPPA (Ogar et al., 2007), and 2/4 of our current nfvPPA cohort presented with hypernasality (Chapter Four). Dysarthria has not been comprehensively characterised in bvFTD (Poole et al., 2017); however, 9/22 participants (39%) in our cohort presented with some level of hypernasality (see Appendix A, Table 12-2).

The ventral precentral gyri contain the cortical origins of the corticobulbar tracts (Penfield & Roberts, 2014), and are consistently found to be activated bilaterally in fMRI studies of overt speech production (Turkeltaub, Eden, Jones, & Zeffiro, 2002). Unilateral lesions affecting the precentral gyrus typically have a minimal impact on speech; however, bilateral damage causes spastic dysarthria characterised by strained voice, slowed rate and hypernasality (Darley et al., 1969; Strand, 2013). Right hemisphere cortical atrophy of this region has been previously documented in nfvPPA, alongside the right SMA and IFG, and homologous regions of the left hemisphere (Mandelli et al., 2016). In bvFTD, motor system dysfunction has been suggested to be the result of the spread of atrophy to the precentral gyrus (Burrell et al., 2011), and bilateral atrophy of the precentral gyrus is observed in FTD-MND (Chang et al., 2005). The correlation between perceptual ratings of hypernasality and regularity of DDK

production with the right precentral gyrus in the current study may therefore be indicative of the spread of atrophy in the nfvPPA and bvFTD subtypes into the right precentral gyrus (Burrell et al., 2011; Gorno-Tempini, Murray, Rankin, Weiner, & Miller, 2004), thereby resulting in a more severe motor speech disorder. The right hemisphere relationship with impaired motor speech in this study is consistent with previous findings in nfvPPA cohorts, suggesting that more prominent features of AOS emerge when regions of motor speech control are atrophied bilaterally (Ballard et al., 2014; Josephs et al., 2006; Whitwell et al., 2013).

A significant correlation was observed for cortical thickness of the right temporal pole and perceptual ratings of both speech rate and repeated phonemes. Both left and right temporal poles have been demonstrated to be activated during semantic processing in functional imaging studies (Patterson, Nestor, & Rogers, 2007). In bvFTD, thickness of the bilateral temporal poles has been associated with DDK production, indicating that the poles may play a role in fluent speech production due to impaired higher level cognitive and attentional processes (Vogel et al., 2017). Alternatively, anterior temporal lobe thinning may not cause impaired DDK production, but rather an association may exist due to the significant atrophy that occurs at the temporal pole in bvFTD and svPPA (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

The cortical thickness of the left inferior parietal lobe was observed to be correlated with speech rate, measured acoustically during the reading task. This region of the left hemisphere is a primary locus of degeneration for lvPPA, which presents with hesitancy as a key feature of the syndrome (Gorno-Tempini et al., 2011). The IPL is hypothesised to play a role in phonological processing for fluent speech production, and causes logopaenia when atrophied (Gorno-Tempini, Dronkers, et al., 2004; Rohrer, Warren, et al., 2008). This finding is supportive of earlier documentation of an association between the atrophy of the IPL in PPA and increased repaired sequences and reduced speech rate (Wilson et al., 2010).

Cortical thickness of the STG was correlated with CoV of AMR period, which reflects participants' ability to maintain a constant rate of vocalisations during DDK. Given that this region is most commonly atrophied in the logopaenic variant (Gorno-Tempini et al., 2011), this correlation is consistent with data in Chapter Four indicating that the lvPPA group had more difficulty with consistent production of DDK than all other groups. Researchers have suggested that the posterior portion of the STG (pSTG) plays a role in sensory-motor

integration for speech production, which allows for both phonological coding and processing of auditory feedback to correct motor speech movements (Buchsbaum et al., 2011; Guenther, 2016; Hickok, Okada, & Serences, 2009; Hickok & Poeppel, 2004).

In the DIVA model, the temporoparietal region supports speech production by processing tactile, proprioceptive and auditory feedback for correction of articulatory positions during speech production (Guenther, 2006). The pSTG is suggested to be involved in this process by receiving the auditory target projections from the ventral premotor cortex, which are compared to auditory feedback via the primary auditory cortex (Guenther, 2006, 2016). This hypothesis is supported by findings of increased activation at the STG during speech when auditory feedback is altered (pitch shifted) so that it does not match the speakers' expected target in studies utilising blood-oxygen-level dependent (BOLD) fMRI (Tourville, Reilly, & Guenther, 2008) and magnetoencephalography (MEG; Heinks-Maldonado, Nagarajan, & Houde, 2006). In addition to processing auditory feedback, there is evidence to suggest that the pSTG may play a role in phonological encoding prior to auditory feedback. This has been indicated by activation of the pSTG in BOLD fMRI studies in which subjects named images with overt articulation but without phonation (Hickok et al., 2000), or by masking auditory feedback with white noise during a syllable repetition task (Paus, Perry, Zatorre, Worsley, & Evans, 1996). Activation of the pSTG has been suggested to be related to the process of phonological encoding rather than motor execution, following observations of greater activation (measured with BOLD fMRI) during speech tasks compared to non-speech oral movements (Basilakos, Smith, Fillmore, Fridriksson, & Fedorenko, 2017). Furthermore temporal investigations of cortical activity during picture naming in an MEG study have documented activation of the pSTG at a time hypothesised to be the phonological encoding stage of speech production (Levelt et al., 1998). In a repetition task involving non-sense syllables, which was comparable to the DDK task in the current study, researchers found that cerebral blood flow to the pSTG (measured via positron emission tomography) increased with rate of production in healthy participants (Paus et al., 1996), thereby indicating that activity in the region may increase with phonological load (Hickok & Poeppel, 2000). In PPA and FTD, previous authors have noted an association between temporoparietal atrophy and reduced speech fluency (Wilson et al., 2010). Considered together, these findings indicate that lesser cortical thickness of the pSTG is associated with reduced fluency of DDK production, likely due to the role that the region plays in phonological encoding and the integration of auditory feedback with motor speech.

5.4.1 Limitations

The study was limited by the use of clinical 1.5 Tesla MRI scans and volumetric measurements rather than functional investigations of speech production. The findings are further limited by the unequal number of participants in each subgroup. As a result of this, regions involved in the bvFTD disease process, and to some extent lvPPA, were more likely to be identified as correlates of the speech metrics, which may have led to increased involvement of the right frontal lobe, and left temporoparietal junction. This limitation may have therefore downplayed the influence of frontal lobe motor speech regions in DDK production, by instead highlighting the role of the STG in phonological assembly and auditory feedback due to the low numbers of nfvPPA participants in comparison to lvPPA.

5.5 Conclusions

Investigations of the imaging correlates of speech impairments in PPA and FTD, irrespective of subtype, have suggested that speech measures may assist with aetiological diagnosis of PPA and FTD (Ash et al., 2009; Catani et al., 2013; Mandelli et al., 2014; Wilson et al., 2010). Despite the aforementioned limitations of the present study, this exploratory investigation provides an indication of the use of acoustic measures to assist with localisation of degeneration. Findings suggest that DDK metrics are sensitive to cortical thickness of the superior temporal lobe, and that the task may be affected by damage to this region. Despite this, larger studies which better reflect the range of PPA syndromes are required to elucidate the associations between speech metrics and neuroimaging abnormalities.

6 Monitoring speech decline in two cases of nonfluent/agrammatic variant primary progressive aphasia

6.1 Introduction

One of the primary aims of quantifying speech in progressive aphasia is to establish speech metrics that can track disease progression. The clinical reasons for this are threefold: to improve clinicians' capacity to identify the existence of a progressive speech or language disorder; to provide patients with information regarding the rate of their progression once a neurodegenerative disease has been established; and to identify the emergence of motor symptoms which may indicate a diagnostic transition to motor neurone disease (MND) or Parkinson's plus syndromes. Chapter Four sought to establish speech metrics which were quantifiably different between PPA, FTD and controls, while Chapter Five linked the acoustic correlates of change with their neurological basis. In order to investigate whether these metrics can monitor progression, they will be applied to longitudinal case series in Chapters Six and Seven. In this chapter, the metrics will be applied to two cases of nfvPPA who were assessed longitudinally over a period of one year.

The disease progression of nfvPPA is typically slow, and has an average survival time of 8-10 years (Harciarek et al., 2014; Kertesz, Davidson, & Munoz, 1999; Spinelli et al., 2017). The initial symptoms are commonly reported to be word retrieval deficits (Blair, Marczinski, Davis-Faroque, & Kertesz, 2007; Knibb et al., 2009), however AOS has also been reported as the first presenting sign (Gorno-Tempini, Dronkers, et al., 2004). Over time, syntax and grammar constructions become progressively basic and the incidence of paragrammatisms increases (Ash et al., 2009; Blair et al., 2007; Mesulam et al., 2009). The rate of progression in nfvPPA is not uniform, and differences in the rate of disease progression have been noted due to different pathologies (Caso et al., 2014; Spinelli et al., 2017).

Later in the disease course, a large proportion of nfvPPA cases have been noted to develop behavioural features, while others develop extrapyramidal signs of corticobasal syndrome or progressive supranuclear palsy associated with an accelerated course (Kertesz et al., 1999). The remainder continue to have a predominantly aphasic presentation for many years after diagnosis (Kertesz et al., 1999).

A systematic review of the literature (Chapter Two; Poole et al., 2017) identified only one longitudinal study of nfvPPA that documented speech changes in any detail, either quantitatively or on a severity rating scale. Gorno-Tempini and colleagues (2004) described a case report of a woman who developed a syndrome consistent with nfvPPA with onset at age 51, which began with the development of slow speech with reduced pitch variation in connected speech. At age 55, she had developed nonfluent aphasia and mild AOS, which became significant over the following year. She also developed compulsive and impulsive behaviours. Ten years into the course of the disease she developed hyperkinetic dysarthria and signs of corticobasal syndrome (including alien limb and dystonia). Measurement of her speech disorder showed clear progression based on the 7-point-scale of the Motor Speech Evaluation (MSE). Over a one year period, her MSE AOS rating increased from 2 to 6, and dysarthria rating from 0 to 2. While these MSE ratings give a broad indication of motor speech decline, further descriptions of the patient's speech were qualitative (Gorno-Tempini, Murray, et al., 2004).

A detailed evaluation of speech decline has been described in two cases of PPAOS (Duffy et al., 2015). Speech was measured twice perceptually over a 2-2.5 year period using the Apraxia of Speech Rating Scale (ASRS), and supported by acoustic measures: the pairwise variability index (PVI) on the single word 'catastrophe'; AMR and SMR rates; and duration and rate of words of increasing length. The PPAOS participants were found to have longer sentence and word durations and fewer syllables per second, which deteriorated over the course of the study. The authors noted an effect of word length, whereby the PPAOS cases were more impaired on longer words (i.e., catastrophe) compared to short words (cat), consistent with the similar pattern seen in AOS due to stroke (Haley & Overton, 2001).

In this chapter, I aim to provide two more examples of speech decline in nfvPPA using a comprehensive speech evaluation at three time points over a year. Analysis will involve perceptual and acoustic methods.

I hypothesised that those acoustic measures which were observed to be significantly different between nfvPPA and controls in Chapter Four would also demonstrate deterioration over time. These measures were: PVI calculated for duration; SMR rate, period and perturbation of period; and three metrics of speech timing taken from the days of the week task (speech rate, mean pause time and *SD* of pause time). It was anticipated that changes on the days of the week task would indicate progression of AOS rather than agrammatism in these

participants, due to the automatic nature of the task and lack of grammatical and syntactic complexity (Vogel et al., 2014). Similarly, PVI was anticipated to be affected by the progression of AOS only, as opposed to cognitive or linguistic effects, due to evidence of its unique association with AOS (Ballard et al., 2014). The SMR task was anticipated to be produced in a more slow and segmented manner, resulting in increased period and perturbation, and decreased rate. These changes would be consistent with the expected effects of AOS due to the high motor programming demands of this articulatory sequencing task (Strand et al., 2014).

The following measures were analysed in an exploratory manner: the proportion of pause time, CoV for SMR period and peak intensity, PVI based on intensity, and the voice quality metrics (mean f0, CoV f0, HNR). Although these metrics were not observed to differentiate nfvPPA from controls in Chapter Four, they were examined in order to establish whether they could identify within-individual change secondary to increased severity of speech disturbance.

For the perceptual data, we hypothesised that the two participants with nfvPPA would deteriorate on ratings of articulation, DDK production and prosody, as these are suggested to be prominent features of progressive and post-stroke AOS (Josephs et al., 2012), and were observed to have group differences for nfvPPA in Chapter Four. It was also anticipated that the monopitch and monoloudness ratings would deteriorate due to their perceptual similarity with dysprosody.

6.2 Methods

6.2.1 Participants

Two participants with a diagnosis of nfvPPA were recruited from the Eastern Cognitive Disorders Clinic, Victoria, Australia. Participants were diagnosed with nfvPPA by an experienced neurologist, based on the international consensus criteria (Gorno-Tempini et al., 2011). Clinical diagnoses were supported by 3D isotropic T1 weighted MPRAGE scans from a Siemens Aera 1.5 T MRI scanner and FDG-PET imaging patterns. Both participants were female. The two participants will be referred to by the pseudonyms WH and JO (not the patients' actual initials). WH and JO were each recorded at three time points at six-month intervals over a one-year period.

Acoustic speech metrics were compared to a group of 14 female healthy controls which were taken at a single time point (mean age = 59, *SD* = 9.53). Healthy controls were recruited through word of mouth and advertisement at community centres and universities around Melbourne. Family members of participants with PPA and FTD were invited to participate as control participants.

6.2.1.1 WH

WH completed her first speech assessment at the time of her clinical diagnosis. At this time, she was 66 years old and had been referred to a tertiary assessment clinic for evaluation of a speech disturbance. WH estimated the speech disturbance to be of approximately 16 months' duration. WH reported that her speech had become slurred, laboured, and that she was having difficulty expressing herself, despite knowing the content of what she intended to express. WH did not report any other concerns regarding her cognition, and felt that she was able to complete her clerical work, drive and complete all of her ADLs. There was no self-reported evidence of memory concern, disorientation, or confusion.

WH left school at the age of 17 and conducted clerical work for her entire working life. She ceased smoking at age 62 and consumed two units of alcohol each week. WH's mother and two maternal aunts were diagnosed with Alzheimer's disease in their 70s.

At her initial assessment, WH scored 30/30 on the Mini Mental State Examination (MMSE) and 89/100 on the Addenbrookes Cognitive Examination – Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006). Cognitive testing revealed a subtle attenuation of planning, with intact memory, intellectual ability and social comportment. Confrontation naming was noted to be mildly reduced. WH's comprehension was found to be intact on testing and adequate for conversation during assessments. Her repetition of words and sentences was preserved, and there were no signs of semantic loss (no deficits of word comprehension or object knowledge). WH did not produce paragrammatisms, nor were there signs of loss of grammatical markers. A speech pathologist who had evaluated her external to our service noted that WH relied on simple grammatical and syntactical constructions. WH therefore met clinical criteria for nfvPPA with effortful speech, equivocal agrammatism, and preserved single word comprehension and object knowledge. Results of formal language assessment at time point 1 and 3 are presented in Table 6-1. WH's cranial nerves were examined at the first time point and no abnormalities were noted. There were no signs of movement disorder. Extraocular and saccadic movements were observed to be normal. There

was no limb apraxia or ideomotor apraxia. An MRI scan revealed some minor white matter changes and minor atrophy in the left operculum.

Table 6-1: Participant demographics and results of language assessments at time points 1 and 3, and the degree of change observed between time points.

Demographics and language assessment	WH			JO		
	T1	T3	Overall change (T1 to T3)	T1	T3	Overall change (T1 to T3)
Age (years)	66	67	1	63	64	1
Disease duration (estimated in months)	16	28	12	18	30	12
PALS*:						
Motor speech disorder	2	3	1	2	3	1
Phonemic errors	0	1	1	0	1	1
Agrammatism	1	2	1	2	2	0
Naming	1	1	0	1	3	2
Single word comprehension	0	0	0	1	1	0
Sentence comprehension	0	0	0	2	2	0
Single word repetition	0	0	0	0	- [β]	-
Sentence repetition	0	1	1	3	- [β]	-
CAT:						
Semantic memory (/10)	10	9	-1	9	4	-5
Comprehension spoken words (/30)	28	27	-1	26	28	2
Comprehension spoken sentences (/32)	32	28	-4	23	26	3
Reading words (/48)	47	47	0	0	0	0
Reading non-words (/10)	8	6	-2	0	0	0
BDAE:						
Writing regular phonics to dictation (/5)	5	5	0	5	0	-5
Writing common irregular forms to dictation (/5)	5	5	0	3	0	-3

Note: [β] Unable to be tested due to severity of motor speech impairment; * PALS subtests rated with a 4 point scale (0=no deficit, 1=questionable deficit, 2=definite deficit, 3=severe deficit); BDAE = Boston diagnostic aphasia examination; CAT = comprehensive aphasia test; PALS = progressive aphasia language scale; T1 = time point 1; T3 = time point 3.

6.2.1.2 JO

At the initial time point, JO was a 63-year-old woman with an estimated 18-month history of speech and language impairment. Her initial sign of speech disturbance was reported to be word finding difficulty and inaccurate articulation. Conversations reportedly became shorter and difficult to understand. Over the six months prior to her initial assessment, JO's family reported that she had begun to experience behavioural change, becoming more withdrawn and apathetic.

JO left school at the age of 14, and worked in several secretarial positions throughout her life. She retired eight years prior to the first time point. She had never smoked and consumed approximately one unit of alcohol per day. JO's mother and maternal aunt were both diagnosed with Alzheimer's disease. In neurological assessment, there was no evidence of MND and or Parkinsonism.

JO met clinical criteria for nfvPPA with effortful and agrammatic speech, impaired comprehension of grammatically complex sentences, and preserved semantic knowledge and single word comprehension.

An MRI revealed left anterior temporal, orbito-frontal, perisylvian, and anterior frontal atrophy. She had minimal white matter change and her hippocampi were slightly atrophic bilaterally. A PET scan revealed marked bilateral hypometabolism in the frontal lobes, consistent with nfvPPA.

6.2.2 Data acquisition

Speech recordings were collected from all participants using standardised procedure and equipment, as outlined in Chapter Three.

6.2.3 Language assessment

Language assessments were conducted at time points 1 and 3. Speech and language production were rated with the Progressive Aphasia Language Scale (PALS; Leyton et al., 2011). PALS domains included the presence of motor speech disorder, phonemic errors, agrammatism, naming, single word comprehension, sentence comprehension, single word repetition, and sentence repetition. PALS domains were rated on a 4 point scale, where 0 = no deficit, 1 = questionable deficit, 2 = definite deficit, 3 = severe deficit. PALS ratings were

conducted in accordance with published criteria (Leyton et al., 2011). Further information on comprehension was obtained with the *Comprehension of Spoken Words* and *Comprehension of Spoken Sentences* subtests from the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004). Object knowledge was assessed with the *Semantic Memory* subtest from the CAT. Reading of regular and irregular words, and non-words, were assessed with the *Reading Words* and *Reading Non-words* subtests from the CAT. Writing of regular and irregular words was assessed with subtests from the Boston Diagnostic Aphasia Examination (BDAE; Goodglass et al., 1983).

6.2.4 Perceptual analysis

Perceptual rating scales outlined in Chapter Three were used to evaluate the speech recordings. Speech recordings were rated by two speech pathologists who were blinded to participant and time point. Ratings were conducted during evaluation of the larger cohort presented in Chapter Four, thereby ensuring raters were blind to diagnosis. Disagreement was resolved by consensus.

6.2.5 Acoustic analysis

Acoustic methods outlined in Chapter Three were used to analyse the data. Analysis included measures of speech timing derived from the days of the week task (mean pause time, proportion of pause time, standard deviation of pause time, speech rate), SMR production (mean period, mean rate, CoV of period, perturbation of period, CoV of peak intensity), pairwise variability index (duration and intensity for strong-weak and weak-strong stress patterns), and voice quality (mean fundamental frequency, CoV of fundamental frequency, harmonics-to-noise ratio). Speech timing data are not presented for JO on the reading and monologue tasks due to her inability to provide a sufficient sample for analysis at the second and third time points. The PVI and voice quality metrics could not be calculated for JO at the third time point, as JO could not produce the required stimuli due to her motor speech disorder.

6.3 Results

6.3.1 Clinical progression

Over the one year duration of the study, WH's speech and language declined. She reported that her speech was more effortful, and her intelligibility had decreased. She had also noted that reading was more difficult and slower. WH retired three months after her initial assessment, citing her speech disturbance to be the primary reason for her early retirement. She remained independent in her activities of daily living throughout the course of the study.

JO's speech and language continued to decline over the year following her initial assessment. She became more impulsive, lethargic and apathetic, affecting her ability to complete activities of daily living with her usual degree of proficiency. A second MRI taken one year after the initial time point indicated profound orbitofrontal, frontal polar and lateral pre-frontal cortical atrophy, consistent with her frontal network dysfunction, and bilateral anterior temporal lobe atrophy.

6.3.2 Progression on language assessments

Language assessment results for time points one and three are presented in Table 6-2. PALS ratings for WH increased in severity for motor speech disorders and agrammatism. She developed equivocal phonemic errors in her speech and difficulty repeating sentences due to her motor speech impairment. Semantic memory, Comprehension of spoken words, Comprehension of spoken sentences and Reading non-words all declined, yet were still within normal limits on the CAT.

JO was rated more severely on the motor speech disorder and naming subtests of the PALS, and equivocal phonemic errors were observed. Semantic memory had declined on the CAT, while comprehension of spoken words and sentences remained relatively stable. JO was no longer able to write to dictation at the final time point.

6.3.3 Acoustic analysis of speech

6.3.3.1 Speech timing

Speech timing measures for the days of the week task are presented in Figure 6-1. JO was observed to deteriorate over time on all speech timing measures. JO was outside of the control group range (based on two standard deviations from the control group mean) for each of the measures at the initial time point. Over the period of the year, analysis revealed a 56% increase of mean pause time (1% decrease followed by 58% increase at each six-month period), 157% increase of *SD* of pause time (65% increase followed by 55% increase), 96% increase of proportion of pause time (43% increase followed by 37% increase), and a 40% reduction of speech rate (8% and 36% reductions at each six-month period). WH was observed to have smaller changes over time, and was within the healthy control group range on all measures at all time points. Change was observed at each six-month period of -12% and 24% for mean pause time (total increase of 9% over one year), 11% and 61% for *SD* of pause time (total change of 81%) and reductions of 5% and 11% for speech rate (-16% over one year). A decrease in the proportion of pause was observed for WH, with a reduction of 8% over the year.

6.3.3.2 Diadochokinetic production

DDK metrics are presented in Figure 6-2. SMR period and rate for both nfvPPA participants were outside of the control group range at all time points. WH's average SMR period increased by 34% over one year (31% and 3% over each six-month interval), and JO's by 69% over six months. SMR rate was observed to decrease by 26% for WH (24% and 3% at each six-month interval) and 67% for JO. Perturbation of SMR period also deteriorated significantly for JO (363% over six months), whereas WH was observed to more gradually decline by 62% over the full year (32% and 23% at each six-month interval). The nfvPPA participants' production measured with CoV of peak intensity was within the control group range at all time points. Minimal change was observed for JO (0.4% increase), whereas variation over time was seen in WH's production (decrease of 76% followed by an increase of 44%). Similarly, WH's CoV SMR period was within the control group range at all time points, while JO's initial production was within the control group range before increasing by 75% over six months.

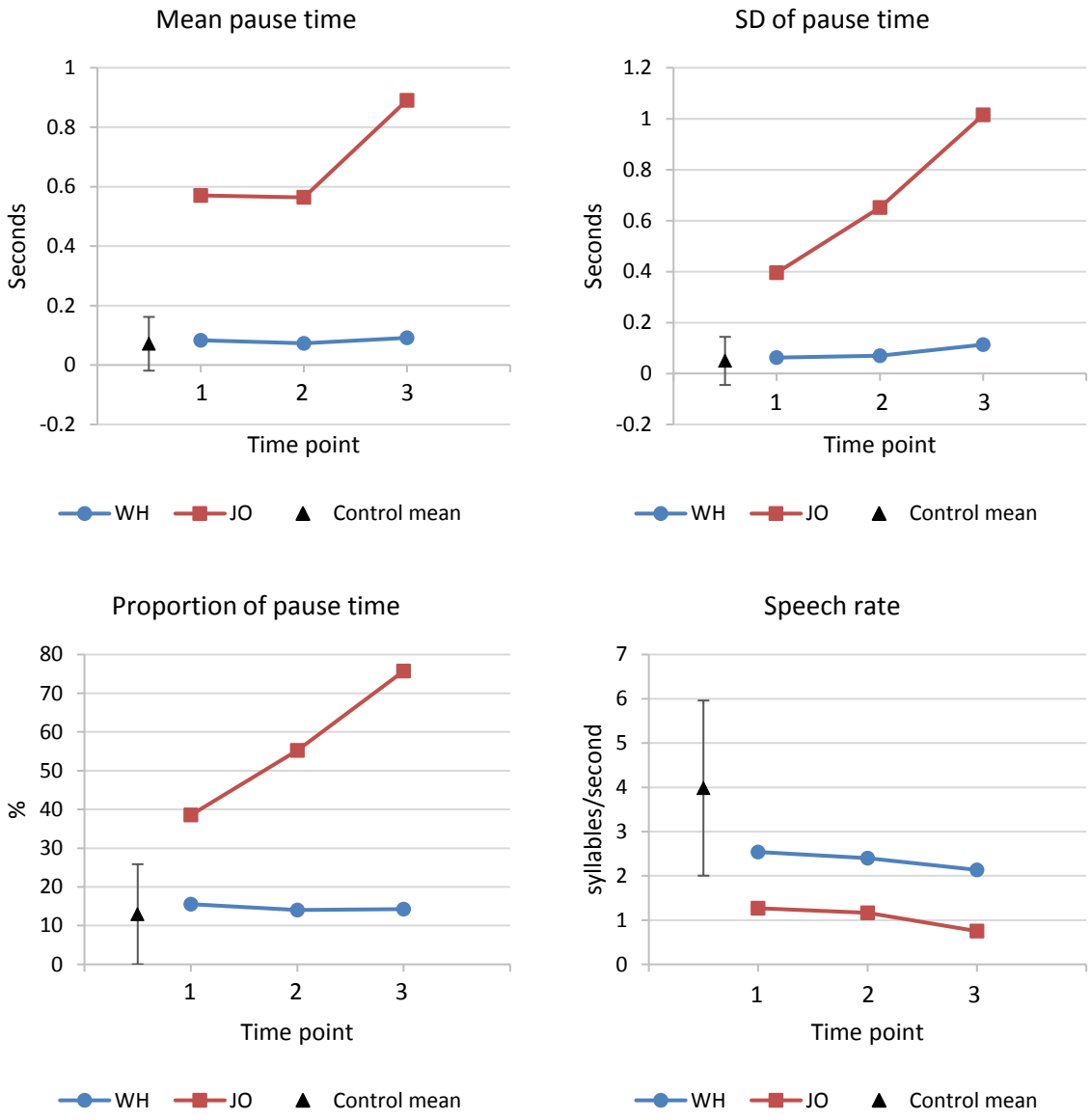

Figure 6-1: Speech timing metrics for the days of the week task for WH and JO at the three time points, and control mean at a single time point (n=14). Note. Error bars indicate two *SD* from the control group mean.

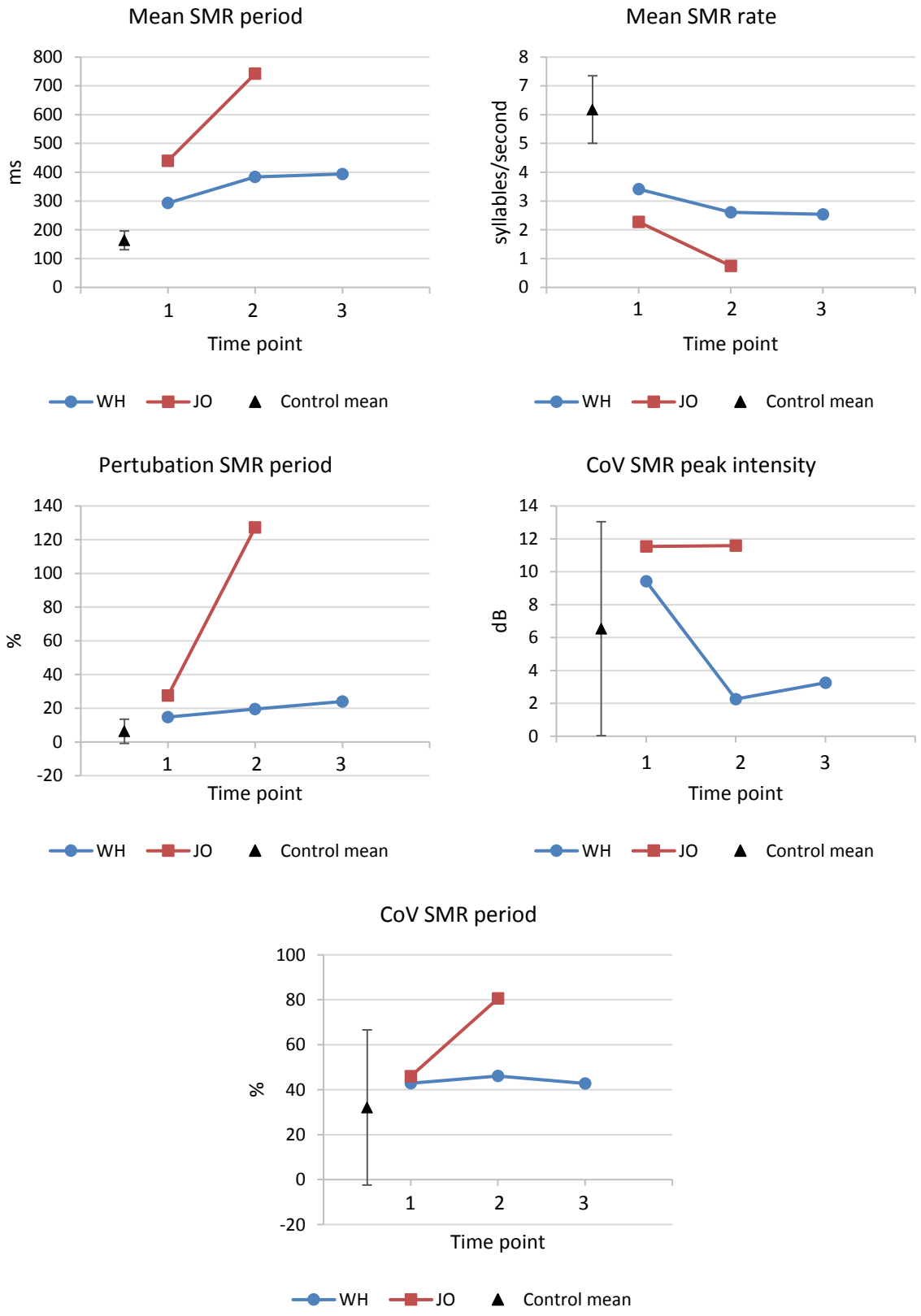

Figure 6-2: Sequential motion rate (SMR) metrics for WH (three time points) and JO (first two time points), and control mean at a single time point (n=14). Note. Error bars indicate two *SD* from the control group mean.

6.3.3.3 Vocal quality

Voice quality metrics are presented in (Figure 6-3). JO's mean fundamental frequency (f0) was within the control group range at both time points, however a 22% reduction over six months was observed. WH's mean f0 was initially below the control range, but increased by 9% over six months to be within the control range at the remaining two time points (decreasing by 2% between time points 2 and 3). All measures of CoV f0 were within the control group range, and variability over time was observed for WH (decrease of 64% followed by an increase of 203%), while a decrease of 58% over six months was observed for JO. Similar variability was observed on the harmonics to noise metric for WH (increase of 73% followed by a decrease of 14%), while JO was observed to have a 95% reduction over six months.

6.3.3.4 Pairwise variability index

PVI metrics are presented in Figure 6-4. PVI duration measures for WH showed a gradual deterioration from the control group (29% for strong-weak stress, and 28% for weak-strong stress over one year). For the strong-weak stress pattern, WH was outside of the control group range at all time points, and was within the control group range for the initial two assessments for the weak-strong stressed words. JO was outside the control range at all time points on the same measures, but demonstrated a change back toward normal stress at the second time point. PVI intensity measures did not show any abnormality or consistent change over time. Both nfvPPA participants were within the control range for the intensity measure of strong-weak multisyllabic words, and were calculated to have more varied stress than controls on the weak-strong stressed words when calculated with relative levels of intensity.

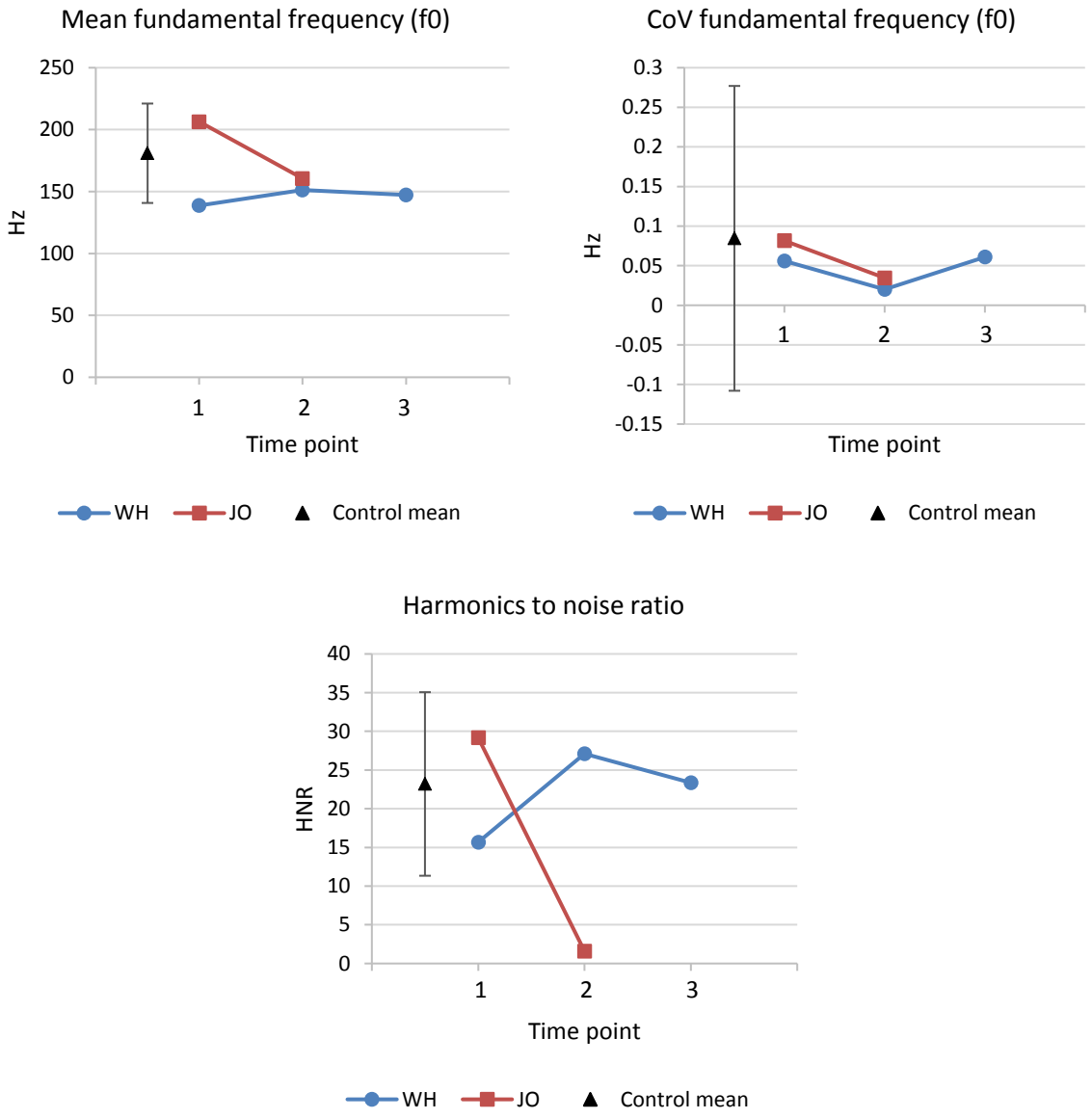

Figure 6-3: Voice quality metrics for WH (three time points) and JO (first two time points), and control mean at a single time point (n=14). Note. Error bars indicate two *SD* from the control group mean.

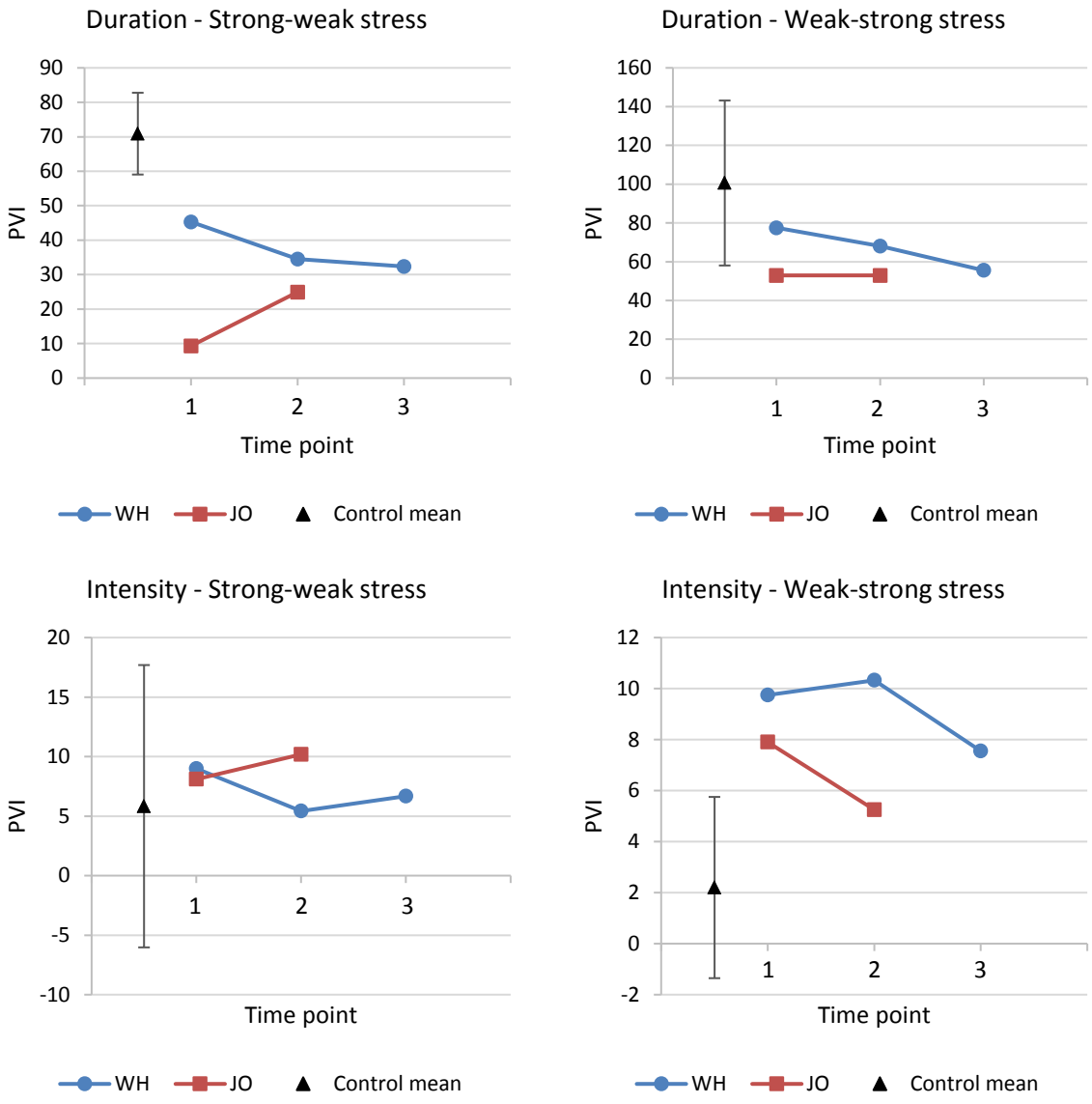

Figure 6-4: Pairwise variability index (PVI) metrics for WH (three time points) and JO (first two time points), and control mean and *SD* at a single time point (n=14). Note. Error bars indicate two *SD* from the control group mean.

6.3.4 Perceptual evaluation of speech

Consensus ratings from perceptual evaluation of speech are presented in Table 6-2 for each time point. Deterioration over time was seen for both participants on several speech features, and changes are outlined below. Both participants were found to have AOS at their initial assessment. Judgements were made by an experienced speech pathologist and neurologist based on key distinguishing features in a sample of connected speech (distorted sound substitutions and additions, increasing distortions with increasing utterance length and rate,

inaccurate speech AMRs and reduced words per breath relative to maximum vowel; Strand et al., 2014).

6.3.4.1 Articulation

JO was observed to progress from a moderate to a severe rating on both consonant and vowel accuracy, as well as audible indications of groping. Irregular breakdowns, prolonged phonemes and increasing errors with increasing length were observed initially, but were later rated as unimpaired. WH was observed to have consistent deterioration of prolonged phonemes and increasing errors with increasing length. In contrast, ratings were not consistent with disease progression for irregular articulatory breakdowns, distorted vowels, groping, and phonemic errors. Imprecise consonants were not observed in WH's speech at any assessment. Neither participant was rated as having an abnormal frequency of repeated phonemes at any time point.

6.3.4.2 Prosody

All prosodic features were impaired for WH and JO except for variable rate. Impaired speech rate was observed to be consistent over time for both participants (WH rated as mild and JO as severe). Variable rate was not observed as each participant maintained a consistent rate throughout the speech sample at each time point. Deterioration of WH's speech was observed in ratings of short phrases, reduced stress, and equal and excess stress. For JO, deterioration was identified in ratings of reduced stress and prolonged intervals.

6.3.4.3 DDK production

JO's DDK rate and regularity deteriorated from moderate to severe. WH's DDK rate was observed to be consistently mildly slow, while regularity was rated as mildly impaired at time point 2, and normal at the remaining time points.

6.3.4.4 Pitch, loudness and respiration

Both participants were rated as impaired on the monopitch and monoloudness scales. Monopitch ratings for each participant demonstrated progression of speech impairment between time points 2 and 3, as did monoloudness for JO. Pitch breaks, voice tremor and audible inspiration were not seen in either participant at any time point.

Table 6-2: Perceptual ratings at time points 1, 2 and 3, and degree of change between T1 and T3. Note. All speech features were rated by consensus on a 5 point scale, except for speech and DDK rate which were rated on a 9 point scale with reductions represented by negative numbers and increases by positive numbers (0 = normal, 1 = sub-clinical, 2 = mild, 3 = moderate, 4 = severe); T1 = time 1; T2 = time 2; T3 = time 3; * Positive numbers indicate increased severity; [β] Stimulus could not be produced due to severity of speech impairment.

	WH				JO			
Speech feature	T1	T2	T3	Change* (T1 to T3)	T1	T2	T3	Change* (T1 to T3)
Pitch								
Monopitch	2	2	3	1	3	3	4	1
Pitch breaks	0	0	0	0	0	0	0	0
Voice tremor	0	0	0	0	0	0	0	0
Respiration								
Audible inspiration	0	0	0	0	0	0	0	0
Loudness								
Monoloudness	2	3	2	0	3	3	4	1
Loudness decay	1	0	0	-1	0	2	0	0
Prosody								
Rate	-2	-2	-2	0	-4	-4	-4	0
Variable rate	0	0	0	0	0	0	0	0
Short phrases	0	1	2	2	4	4	4	0
Reduced stress	1	2	2	1	3	3	4	1
Prolonged intervals	0	1	0	0	3	4	4	1
Equal and excess stress	0	2	2	2	3	3	- [β]	-
Voice								
Rough	2	2	1	-1	0	2	2	2
Breathy	1	1	0	-1	0	0	0	0
Strained	0	1	0	0	1	2	1	0
Articulation								
Imprecise consonants	0	0	0	0	3	4	4	1
Prolonged phonemes	1	2	2	1	3	2	0	-3
Repeated phonemes	0	0	0	0	0	0	0	0
Irregular breakdowns	0	1	0	0	3	0	0	-3
Distorted vowels	0	2	0	0	3	4	4	1
Increasing errors with length	0	1	2	2	3	0	- [β]	-
Groping	0	2	0	0	3	4	4	1
Phonemic errors	0	1	0	0	3	4	3	0
False starts	0	1	0	0	0	0	0	0
Resonance								
Hypernasality	0	1	0	0	0	2	1	1
Hyponasality	1	0	0	-1	0	0	0	0
DDK								
Rate	-2	-2	-2	0	-3	-3	-4	1
Regularity	0	2	0	0	3	4	4	1

6.3.4.5 Voice

Ratings of vocal roughness decreased for WH and increased for JO. Similarly, ratings indicated that breathiness reduced over time for WH and were constant for JO. Ratings of strain fluctuated over time for both participants.

6.3.4.6 Resonance

WH was rated as having a sub-clinical level of hyponasality at time point 1, and hypernasality at time point 2. At time point 3, WH was rated as having normal resonance. JO was agreed to have mild hypernasality at time point 2, which was later rated as subclinical at time point 3.

6.4 Discussion

Speech was observed to deteriorate on some measures over time, most prominently for articulation, prosody and DDK production. These changes confirmed our hypothesis that acoustic changes would be observed on speech timing, PVI and DDK metrics. One participant, JO, was observed to have a more rapid rate of progression than the other.

Currently, the literature presents few studies of the progression of PPA (Poole et al., 2017), and the use of detailed quantitative measures of speech is rare (Duffy et al., 2015). Results demonstrate the capacity of acoustic measures to represent diverse rates of disease progression.

6.4.1 Progression of speech decline in nfvPPA – Case WH

Over the course of the one year study, WH complained of deteriorating verbal expression and difficulty writing. Language assessments at the beginning of the study and one year later indicate the emergence of more frank AOS and agrammatism, and difficulty comprehending grammatically complex sentences. Mild confrontation naming deficits were constant over the course of the study.

WH's speech disturbance primarily affected prosody. While it was unexpected that her speech decline was not reflected in ratings of speech rate, we identified deterioration of prosody in ratings of monopitch, short phrases, equal and excess stress, and prolonged

phonemes. Considered together, articulatory ratings did not reflect progression of the speech disturbance for WH, in contrast to JO. There is potential that this was due to the fact that perceptually identifying and classifying types of speech errors is a difficult process (Ash et al., 2013), and this may partly explain the identification of vowel distortions at the second time point but not the third. A further notable aspect of WH's articulation was the lack of consonant imprecision. Her speech disturbances therefore reflect an AOS profile dominated by prosodic, rather than articulatory, disturbance. Differing presentations of AOS have been described along an articulation/prosody dichotomy, with the suggestion that a more prosodic presentation is found in PAOS, as opposed to progressive agrammatic aphasia (Josephs et al., 2013).

Period and rate of WH's sequential motion rates (SMR) deteriorated with progression of AOS. This finding was in contrast to perceptual ratings which were constant for rate and variable for regularity. Speech timing metrics (decreased speech rate, increased pause time) demonstrated gradual decline and were consistent with perceptual findings of prolonged phonemes and short phrases. PVI metrics of duration (but not intensity) were observed to decline with progression, indicating increasing severity of the lexical stress impairment of AOS.

6.4.2 Progression of speech decline in nfvPPA – Case JO

Progression during the course of the study for JO involved the emergence of signs of frontal network involvement, including impulsivity and apathy. Language assessments indicated agrammatism at initial assessment, which remained relatively stable over the course of the study. An impairment of confrontation naming emerged and was judged to be moderate at the final time point. Comprehension of sentences was consistently impaired throughout the study. Repetition could not be adequately assessed at time point 3 due to the severity of her motor speech impairment. No extrapyramidal or lower motor neuron signs were identified on clinical neurological examination at any time point.

At the final time point, JO was rated as moderate to severe on many speech features. Progression was implied with more severe ratings for aspects of prosody (monopitch, monoloudness, reduced stress, prolonged intervals) and articulation (imprecise consonants, distorted vowels, groping, DDK rate and regularity). Mild hypernasality was identified on the second rating, but was reduced to a sub-clinical rating at the third and final time point. The

absence of clear impairments of resonance or respiration with prominent impairments of prosody and articulation are consistent with former characterisations of progressive AOS (Josephs et al., 2012).

The perceptual findings of impaired prosody (monopitch, monoloudness, reduced stress, prolonged intervals) were supported by clear deterioration on all speech timing metrics. Similarly, a deterioration of SMR rate and period was observed over a six-month period. Voice metrics decreased over time, however were mostly within the control group range. The findings from the PVI calculations were unexpected given that they were either stable or improving over the course of six months. It was noted at the second recording that JO had significant difficulty producing the multisyllabic words (i.e., significant vowel distortions, deletion of some final syllables of the trisyllabic words), and it may be the case that the PVI metric does not demonstrate a linear decline in the later stages of the course of progressive AOS, but instead plateaus after reaching a certain level of severity. At the time of writing, the pattern of decline of PVI in the late disease stages has not yet been explored longitudinally in a sufficient number of participants to give insight into this hypothesis.

6.4.3 Heterogeneous rates of decline

The two cases presented here reflect the diversity of courses that speech and language deficits can take in nfvPPA. The cases differ in terms of severity at initial presentation, rate of progression and, to some extent, the qualitative aspects of their speech and language. It was evident that the acoustic measures were sensitive to different rates of change.

The initial presentation of WH and JO was notably different. Although both participants have an estimated disease duration of 16-18 months (based on self-report and that of next of kin), JO was more impaired on perceptual speech and formal language testing at the initial assessment. Furthermore, WH's impairment was largely confined throughout the study to apraxia of speech with agrammatism and mild receptive impairments. While JO experienced similar disturbances initially, these impairments were followed by clear behavioural and mild semantic impairments. MRI imaging revealed that JO has atrophy of a wider frontal and temporal region of the brain when compared to WH.

The rate of progression of each participants' verbal expression was also noticeably different, as JO has a more rapid progression of her speech decline. The absence of any significant

difference of age, education or disease duration raises the question as to whether the nonfluent aphasic presentations of the two participants were caused by different underlying pathologies. Tau pathology is the most common cause of nfvPPA (Josephs et al., 2006; Spinelli et al., 2017); however, cases of TDP-43 have been observed to have more rapidly progressing AOS (Caso et al., 2014). More diffuse grey matter atrophy alongside associated behavioural change, similar to the case of JO, have also been reported in cases of nfvPPA caused by PiD pathology (Rohrer et al., 2011; Spinelli et al., 2017). Furthermore, atypical forms of PSP pathology with progressive AOS, aphasia and behavioural change but without typical signs of PSP have also been reported (Boeve, Dickson, et al., 2003). Lack of pathological confirmation in the cases presented in the current study precludes a sufficient answer to these hypotheses; however, future studies of larger cohorts may clarify the impact of specific pathology on nfvPPA progression.

6.4.4 Acoustic measures for tracking progression

Changes were identified by many of the measures which were hypothesised to indicate deterioration over time. Speech timing, DDK production and PVI duration measures all indicated clear deterioration for one participant and minimal change for another. These findings support similar longitudinal case series and suggest that these acoustic measures of speech can be used to support disease monitoring in nfvPPA and PPAOS (Duffy et al., 2015).

6.4.4.1 Speech timing

Changes were observed for speech rate, mean pause time and SD of pause time, but were inconsistent for proportion of pause time. This supports the findings of Chapter Four which identified post-hoc group differences for these metrics. For each of the measures, JO demonstrated greater change at each time point, highlighting the rapid progression for this participant. Proportion of pause time for WH remained constant at approximately the level of the control group mean, which may seem counterintuitive to increases in mean pause time. However, it is thought that her increased pause length was associated with a similar increase of phoneme length, thereby retaining a constant ratio of pauses and phonation. WH's perceptual ratings of increased phoneme length over time support this explanation.

Similar speech timing metrics have been investigated at a single time point and shown to be more sensitive than a perceptual rating scale for differentiating the three PPA variants

(Cordella et al., 2017). The authors found that while nfvPPA differed significantly from controls, there were few statistically significant differences from svPPA and lvPPA, which were also impaired. These findings therefore suggest that the measures are affected by higher level stages of the speech production process, such as lexical retrieval deficits in addition to motor speech impairment (Cordella et al., 2017). However, it is important to consider speech stimuli when comparing studies that have utilised speech timing metrics. Speech rate in the current study is anticipated to reflect motor impairments due to the low linguistic and cognitive demands of the task selected (days of the week). This approach is in contrast to Cordella and colleagues (2017), who calculated speech rate based on a picture description task, which draws on linguistic and cognitive processes such as planning content, generating syntactic structure, and lexical retrieval (Mortensen, Meyer, & Humphreys, 2006). While limited by the task selected, the authors were able to identify an acoustic correlate of motor speech decline in nfvPPA by calculating 'articulation rate' (Cordella et al., 2017). This metric is calculated by identifying a segment of speech with minimal pausing, which was hypothesised to identify reductions in speech rate due to motor speech impairment (Cordella et al., 2017; Wilson et al., 2010). The use of speech timing metrics to differentiate PPAOS and nfvPPA supports the suggestion that the metrics can identify motor speech impairments in the context of concomitant cognitive and linguistic change (Duffy et al., 2017).

It should be noted that while the expected downward trajectory was observed for WH on the metrics of speech rate, mean pause time and SD of pause time, all of her values were within the control group range. It is expected that all nfvPPA patients will decline from a point within the normal range. Further longitudinal studies of nfvPPA participants early in the disease course would clarify this hypothesis, and the inclusion of longitudinal control data would elucidate the degree of change that occurs in the healthy population due to normal ageing.

6.4.4.2 DDK production

We hypothesised that three DDK metrics would reflect change, based on post hoc differences from controls in Chapter Four (SMR rate, SMR period, SMR period perturbation). Each of these metrics demonstrated a gradual decline away from control group production for WH, while JO's production rapidly deteriorated between time points 1 and 2. Increased perturbation of period indicates that temporal regularity of production decreased in accordance with slowness of production (rate and period), all of which are consistent with

degenerative AOS (Josephs et al., 2012). The progression indicated by these measures contrasts with findings of the blind perceptual ratings, which did not identify any change of DDK production for WH, and failed to identify decreased rate between time 1 and time 2 for JO. This is not surprising given the poor intra- and inter-rater reliability of DDK production that has been reported, even amongst expert raters (Gadesmann & Miller, 2008). The acoustic findings are consistent with longitudinal investigations of DDK production in PPAOS, and while the influence of aphasia and dysarthria cannot be ruled out without direct comparison to those conditions, it is hypothesised that the deterioration in these cases is due to AOS (Duffy et al., 2015).

6.4.4.3 Voice quality

Voice quality was analysed in an exploratory manner (despite finding no group differences in Chapter Four) in order to investigate the possibility of within-individual change. Voice quality measures for WH were variable, did not indicate deviations from the control group range, and did not reflect the gradual progression of the disorder. JO demonstrated decline over the first two time points, but it is not clear if this represents a true change given the variability of WH's voice. Therefore, the metrics do not appear to be suitable for monitoring progression of AOS in nfvPPA. Despite this, voice quality metrics have been successfully used to track progression and identify improvements following treatment in Parkinson's disease (Hoffman-Ruddy, Schulz, Vitek, & Evatt, 2001; Skodda, Grönheit, Mancinelli, & Schlegel, 2013). Given the measures' ability to detect change in progressive hypokinetic dysarthria due to Parkinson's disease, the HNR and f0 changes could be considered in future investigations of PPA and FTD for monitoring the development of dysarthria associated with PSP and CBS (Hartelius, Gustavsson, Astrand, & Holmberg, 2006; Kluin et al., 1993; Müller et al., 2001; Rinne, Lee, Thompson, & Marsden, 1994).

6.4.4.4 Pairwise Variability Index

PVI deteriorated at a gradual rate for WH when calculated by duration but not intensity. The intensity based metric did not identify group differences in Chapter Four, nor in previous studies of lexical stress in PPA and stroke induced AOS (Ballard et al., 2014; Vergis et al., 2014). PVI was not calculated using intensity in two recent investigations of PPAOS (Duffy et al., 2017; Duffy et al., 2015). Based on the findings of this study and others, it is likely that the changes to lexical stress in progressive AOS, which are identified perceptually as equal

and excess stress, are predominantly due to equalisation of duration rather than intensity (Ballard et al., 2014). It is suggested that the change observed in the durational PVI measures is unique to AOS rather than aphasia or dysarthria (Ballard et al., 2014; Duffy et al., 2015). In contrast to WH, JO's PVI for duration was either stable or improving, which was unexpected. Her improvement on this lexical stress metric may be due to the severity of her speech disorder, as discussed in section 6.4.2. It may be the case that the PVI metric is not applicable to severely distorted speech, or that lexical stress impairments lack stability as a person reaches a particular severity of dysfluency.

6.4.4.5 Limitations and future directions

Interpretation of the findings in this study is limited by the fact that JO's speech was too severe for many measures at the final time point. Furthermore, without confirmation of pathology we are limited in our discussion of the potential cause of the diverse disease progressions presented here. In a larger cohort, we may be able to establish the expected rate of decline in nfvPPA, and whether deviations from this course might suggest development of MND, PSP, CBS or a different underlying pathology. Such investigations would be supported by confirmation of pathology.

The use of different stimuli for speech timing analysis could be further investigated, particularly if change over time were observed to decline with a task specific effect. Cordella and colleagues (2017) found minimal group differences on these metrics using a picture description task, but did not investigate the metrics on other stimuli. For example, the degree of decline in the days of the week task could be compared to the degree of decline in a picture description task. It is anticipated that the degree of change would be more consistent across tasks in PPAOS and nfvPPA groups due to motor speech impairment. In contrast, an inconsistency between tasks may be observed in lvPPA and svPPA due to the high lexical retrieval demands of the picture description task in comparison to a highly learned phrase such as the days of the week.

An additional avenue of investigation is the way in which the above acoustic measures change in people with progressive dysarthria, particularly if there are key differences to AOS progression. For example, voice quality and vowel production metrics may demonstrate greater decline in people with progressive dysarthria, whereas PVI would be expected to remain relatively stable. Similarly, decline of SMR production with stable AMR would be anticipated in progressive AOS, in contrast to consistent decline of AMR and SMR in

dysarthria (Josephs et al., 2012). While this effect was not observed by Duffy and colleagues in their longitudinal study (2015) it warrants further investigation. Differences between the acoustic correlates of dysarthria and AOS may be clinically useful for identifying development of PSP, CBD and MND in people presenting with PPA and FTD.

6.5 Conclusion

Acoustic correlates of speech decline were observed, and were shown to be more sensitive to change than perceptual evaluations on a severity scale. Consistent with our hypothesis, the metrics which demonstrated change were those based on speech timing, PVI and DDK production. Overall, the measures indicated a consistently more rapid rate of progression in one nfvPPA participant over another. The measures were therefore sensitive enough to identify different rates of disease progression, despite the current study being limited to two participants. Furthermore, it became apparent that change (and possibly rate of change) can be indicated over a short time period. In this case a six-month period was sufficient to identify change, and this is suggested as an ideal time period for clinical follow up in PPA (Harciarek et al., 2014). The ability to identify change over a relatively short period is a clear advantage that acoustic methods have over perceptual evaluation by expert raters. Considering both the findings in this study and those presented for PPAOS (Duffy et al., 2015), the key acoustic measures that should be used to track progression in nfvPPA with AOS are PVI measured by duration, SMR rate and regularity, and speech rate and pauses based on a simple speech task.

7 Objective monitoring of dysarthria in FTD-MND

7.1 Introduction

Chapter Six provided a longitudinal case series of two cases of nfvPPA, which provided a preliminary investigation as to whether acoustic metrics can be used to monitor the rate of change of a neurodegenerative speech disorder. While Chapter Six examined progression of one syndrome, this chapter will investigate the changes that occur as a participant transitions from one diagnosis to another. Acoustic methodology will be applied to a case of FTD-MND in comparison to three cases of bvFTD in order to evaluate whether the metrics can identify the acoustic correlations of bulbar decline in the context of bvFTD-related cognitive change.

Motor neurone disease (MND) is a neurodegenerative disorder characterised by progressive paralysis due to impaired functioning of upper and lower motor neurons (Kiernan et al., 2011). Limb or bulbar onsets are recognised, the latter affecting the muscles responsible for speech and swallowing (Kiernan et al., 2011). The resulting speech disorder of MND is commonly one of mixed spastic and flaccid dysarthria, owing to the involvement of both the upper and lower motor neurons (Tomik & Guiloff, 2010). Features of dysarthria in MND may include decreased speech rate, distortions of consonants and vowels, increased nasal resonance, reduced respiratory capacity and a hoarse, strained voice quality (Tomik & Guiloff, 2010).

While initially considered as distinct disorders, MND and FTD are now conceptualised as clinical syndromes within a clinicopathological spectrum, with the pure motor involvement of MND at one end and the frontal lobe cognitive deficits of FTD at the other (Devenney, Vucic, et al., 2015). The TDP-43 protein has been identified as the underlying pathological cause in a majority of familial and sporadic MND cases and a large subgroup of FTD cases (Neumann et al., 2006). Furthermore, there are several genes that have been associated with the FTD-MND spectrum of disorders. The commonest is the *C9orf72* intronic repeat mutation which has been identified in up to one third of FTD cases, half of MND cases and the majority (70-80%) of FTD-MND cases (DeJesus-Hernandez et al., 2011; Devenney, Vucic, et al., 2015; Renton et al., 2011; Rohrer et al., 2015).

A continuum of clinical features has also been reported in addition to the genetic and pathological overlap of FTD and MND. Within the FTD subtypes, bvFTD has the strongest

link to MND, as opposed to the language onset forms of FTD (progressive nonfluent aphasia and semantic dementia), due to the strong association between *C9orf72* and the bvFTD and FTD-MND syndromes (Devenney, Vucic, et al., 2015; Rohrer et al., 2015). People with MND may present with clinical evidence of cognitive decline which does not meet criteria for FTD, or can present with a bvFTD phenotype, a syndrome which is commonly termed FTD-MND (Giordana et al., 2011). As many as 25% of MND patients meet criteria for bvFTD, while a greater proportion (up to 45%) experience some cognitive and/or behavioural changes consistent with FTD (Lillo et al., 2012; Phukan et al., 2012). These include deficits in social cognition, apathy, disinhibition, stereotypy and aggression (Abrahams, 2011; Lillo et al., 2012; Phukan et al., 2012). Similarly, motor dysfunction which is sufficient to meet criteria for MND has been identified in 10-15% of people with FTD, while up to 36% show some signs of motor dysfunction such as wasting, fasciculations or weakness (Burrell et al., 2011).

Assessment of bulbar involvement in MND is traditionally performed by neurological examination or listener-based speech assessment. This is despite evidence to suggest that bulbar dysfunction occurs prior to observable changes in speech intelligibility (Green et al., 2013). Objective and quantifiable measures have been evaluated to identify the onset of bulbar involvement in MND and for monitoring disease progression. Acoustic correlates of bulbar involvement in the MND population relate to measures of voice instability (Ramig, Scherer, Klasner, Titze, & Horii, 1990), temporal measures such as utterance duration and segment duration (Weismer, Jeng, Laures, Kent, & Kent, 2000), and measures of articulation such as vowel space area and formant trajectories (Weismer et al., 2000; Weismer, Martin, Kent, & Kent, 1992). Rong, Yunusova, Wang, and Green (2015) investigated independent quantitative measures of respiration (speech pausing and subglottal pressure), phonation (harmonics to noise ratio, jitter, and shimmer), articulation (motion capture of lip and jaw movements) and resonance (nasometric measurement of oral and nasal acoustic signals) in 66 patients with MND over an average time period of 15 months. Changes in articulation, in particular velocities of lip and jaw movement, and phonation (fundamental frequency at participant's highest possible pitch on a sustained vowel) were reported to identify change prior to a discernible change in speech and intelligibility. These measures are hypothesised to correlate with decreased strength of lip and jaw musculature and vocal fold weakness (Rong et al., 2015). Speech rate has been shown to be impaired in both MND and bvFTD groups; however, decreases in articulatory rate (a measure of syllables per minute with pauses

between words removed) were solely impaired in MND patients with a primary bulbar or mixed bulbar/respiratory impairment (Yunusova et al., 2016).

Accurate and early identification of disease parameters that can lead to changes in diagnosis have significant clinical and empirical value for informing disease trajectory. Data may also act as a surrogate marker for treatment response in future clinical trials. Here we present a unique longitudinal case series comparing objective speech outcomes in MND and bvFTD. One participant with FTD-MND is compared over a two-year period to three participants with bvFTD but without bulbar signs on clinical examination.

We hypothesised that voice quality and vowel articulation index would decline in FTD-MND in comparison to a relatively stable voice quality and vowel production in bvFTD, due to established acoustic correlates of dysarthria in MND (Ramig et al., 1990; Weismer et al., 2000; Weismer et al., 1992). It was also anticipated that speech timing measures would be affected by dysarthria in FTD-MND to a greater degree than the cognitive change of bvFTD (Weismer et al., 2000; Yunusova et al., 2016). On perceptual ratings, it was hypothesised that the FTD-MND case would demonstrate greater change over time across the respiratory, articulatory, prosodic, resonatory, and phonatory speech subsystems, consistent with the characteristics that can be present in dysarthria due to MND (Tomik & Guiloff, 2010).

7.2 Method

7.2.1 Participants

Four participants with a diagnosis of bvFTD were recruited from the Eastern Cognitive Disorders Clinic (see Table 7-1 for demographic information). All participants were diagnosed according to the diagnostic criteria (Rascovsky et al., 2011). One of these cases, VP, presented with concomitant dysarthria associated with MND. All participants were assessed at two time points, two years apart. All participants gave informed consent prior to participating in the study. Ethical approval was obtained from Eastern Health and The University of Melbourne.

Table 7-1: Participant demographics

	VP	bvFTD 1	bvFTD 2	bvFTD 3
Gender	M	M	M	M
Age at first assessment	71	59	70	76
Age at second assessment	73	61	72	78
Time between assessments (months)	25	23	26	22
Age at onset (years, approx.)	67	54	60	61
Age at diagnosis	69	55	65	69
Education (years)	13	13	11	18

7.2.1.1 VP

At his initial assessment, VP was a 71-year-old man, who had been referred to a tertiary assessment clinic for investigation of his suspected frontotemporal dementia and dysarthria. His onset was at 67 years. VP had no significant past medical or psychiatric history. His family medical history included late onset memory loss in his mother. VP had never smoked and drank alcohol only socially. His wife described changes to his behaviour (disinhibition, social inappropriateness, compulsive eating with sweet food preference, hyperorality, stereotypic behaviours, loss of empathy) of four years' duration and signs of dysarthria in the 12 months prior to the first assessment. His wife also described gait and balance changes at the first assessment.

On initial assessment by a neurologist with expertise in behavioural neurology, VP had an Addenbrooke's Cognitive Examination – Revised score of 74/100 (ACE-R; Mioshi et al., 2006) and a Mini-Mental State Examination score of 26/30 (MMSE; Folstein, Folstein, & McHugh, 1975). Neuropsychological testing confirmed executive, retrieval and higher attentional deficits. VP's brain magnetic resonance imaging (MRI) scan showed marked symmetrical frontal lobe atrophy (including medial and orbital regions), atrophy of the anterior and body of the corpus callosum, and bilateral atrophy of the opercula. A single-photon emission computerised tomography (SPECT) scan showed left greater than right hypoperfusion in the frontal lobes, as well as medially in the anterior cingulate regions. An FDG-PET scan showed frontal hypometabolism (left greater than right; see Figure 7-1). VP satisfied criteria for probable bvFTD. The presence of dysarthria suggested potential MND.

VP demonstrated progressive decline of his dysarthria and speech intelligibility. By the time of his second speech assessment, 25 months following his initial assessment, he had also developed signs of dysphagia. His presentation was of predominantly upper motor neuron-bulbar involvement, with no evidence of lower motor neuron signs, such as muscle wasting or fasciculations.

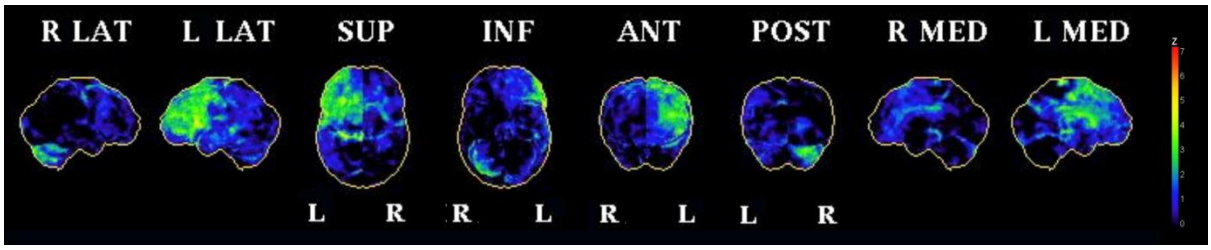

Figure 7-1: FDG-PET scan of VP at first time point showing significant hypometabolism (> 2 SD below normal) asymmetrically in L dorsolateral, medial and lateral orbital frontal regions including anterior cingulate cortex. Images are created from NeuroStat analysis with raw images subtracted from average of 25 healthy subjects' scans, and coloured based on standard deviation values (scale on R). Legend: L = left, R = right, LAT = lateral, SUP = superior, INF = inferior, ANT = anterior, POST = posterior, MED = medial.

7.2.1.2 bvFTD Case 1

bvFTD case 1 is a male participant who underwent his first speech assessment at age 59. His age at onset was estimated to be 54. He had a history of personality and behavioural change, including social inappropriateness and lack of interest in his usual routines, and a motor stereotypy. He had no family history of dementia. Neuropsychological assessment revealed deficits in planning, organisational, problem solving and word retrieval skills. Language and visuospatial function were intact. His executive dysfunction was causing significant memory retrieval difficulties. It was noted that he lacked insight into these cognitive impairments. An MRI revealed bilateral anterior temporal lobe atrophy (but images were degraded due to movement artefact). An FDG-PET scan revealed prominent frontal hypometabolism.

7.2.1.3 bvFTD Case 2

bvFTD case 2 is a male participant who underwent his first speech assessment at age 70. He had received a diagnosis of behavioural variant frontotemporal dementia at age 65, following a 4 – 6-year history of behavioural and personality change. At the first time point he was noted to have fatuous behaviour and word finding difficulties, and his wife reported personality changes including inappropriate comments and rudeness. His speech was fluent and grammatical, but hesitant due to word finding difficulties. Neuropsychological testing

revealed deficits of attention and behavioural features of executive function. Repeat neuropsychological examinations at ages 66 and 68 demonstrated a decline in executive function and semantics. An MRI conducted at age 65 revealed generalised atrophy of the cerebral hemispheres bilaterally, most pronounced in the temporal lobes, with no features of underlying ischaemic change. A second MRI scan conducted at age 69 revealed profound bilateral anterior temporal lobe atrophy (right greater than left).

7.2.1.4 bvFTD Case 3

bvFTD case 3 underwent his first speech assessment aged 76 years, with a 15-year history of slowly progressing bvFTD with behavioural features of increased fatuousness, irritability and impulsiveness. His age at onset was 61 years. A neuropsychological assessment conducted at age 76 revealed impairments of executive functioning (concreteness, difficulty shifting attention), naming, word comprehension, semantic knowledge, and memory retrieval. He had surface dyslexia. Visuospatial function was intact. His MRI revealed bilateral (right greater than left) anterior temporal lobe atrophy.

7.2.2 Speech sample recording and stimuli

Participants provided four speech samples: (i) a one minute monologue about something that they enjoyed; (ii) saying the days of the week; (iii) producing a sustained /a/ vowel on one breath (maximum phonation time); (iv) repetition of multisyllabic words; (v) diadochokinetic rate (DDK; saying "pataka" repeatedly as quickly and clearly as possible). All tasks were produced twice, with the exception of the monologue, and the second iteration was used in all analyses in order to mitigate the effect of unfamiliarity on the novel tasks (Vogel & Maruff, 2014). The tasks have been shown to have reliability, stability over time, and sensitivity to impairment for measures of speech timing (Vogel et al., 2011; Vogel & Maruff, 2014). The speech samples were recorded using a Marantz PMD671 solid state recorder with an AKG C520 condenser cardioid head mounted microphone positioned 8 cm from the participants' mouth at a 45° angle. Recordings were sampled at 44.1 KHz and quantized at 8 bits.

7.2.3 Speech Analysis

Speech was quantified objectively using acoustic analysis and subjectively via listener based evaluations at both first and second time points. Details of these methods and the stimuli utilised are outlined below.

7.2.3.1 Acoustic analysis of speech

Measures of speech timing and voice (harmonics to noise ratio) were conducted. Speech timing measures (syllables per second, mean pause length, and proportion of pause time) were calculated for the days of the week stimulus using automated scripts derived from the methodology of Vogel et al. (2010) in Praat (Boersma & Weenink, 2001). The days of the week stimulus was selected for timing measurement as it was hypothesised to be less influenced by cognitive and behavioural impairment compared to the monologue due to its automaticity.

The harmonics to noise ratio (HNR) quantifies the amount of additive noise in the voice signal relative to the harmonic component (Yumoto et al., 1982) to provide an objective evaluation of the degree of hoarseness in a person's voice.

7.2.3.2 Listener-based speech assessment

The participants' speech was rated by two speech pathologists (MLP & APV) based on the monologue, sustained vowel and DDK tasks at each time point. The raters were blinded to participant, diagnosis and time point. Speech samples were rated independently by each rater and disagreement was resolved by consensus. Samples were assessed on a range of speech domains with a five-point severity rating scale (0 = no impairment, 1 = sub-clinical, 2 = mild, 3 = moderate, 4 = severe impairment). Twenty-five speech features were assessed for severity within the domains of pitch, respiration, loudness, prosody, voice, articulation, resonance and DDK production.

7.3 Results

7.3.1 Acoustic analysis of speech

7.3.1.1 Speech timing

The degree of change in participants' mean pause length between assessments is presented in Figure 7-2. Mean pause length for the bvFTD participants ranged from 25 to 48 milliseconds (ms) at the first time point, and increased for all participants by the second time point (values ranging 49 to 77 ms). VP presented with a mean pause length of 58 and 323 ms at the first and second time points respectively.

Figure 7-2 shows the proportion of silence in each speech sample at each time point and the degree of change between each recording. Proportion of silence at the initial time point ranged between 6.12% and 13.97% for the bvFTD group. At the second time point, the proportion of silence reduced for two bvFTD participants and increased for the other. VP's proportion of silence increased from 27.26 at the initial time point to 33.13 at the second time point.

Speech rate is presented in Figure 7-2. Speech rate ranged between 2.72 and 4.33 syllables/sec for the bvFTD group at the first time point. VP's speech rate was also within this range at 3.08 syllables/sec. Speech rate decreased for two bvFTD participants over the course of the study, and increased for the third. VP's speech rate also declined during this time, with a decrease of 1.16 syllables/sec.

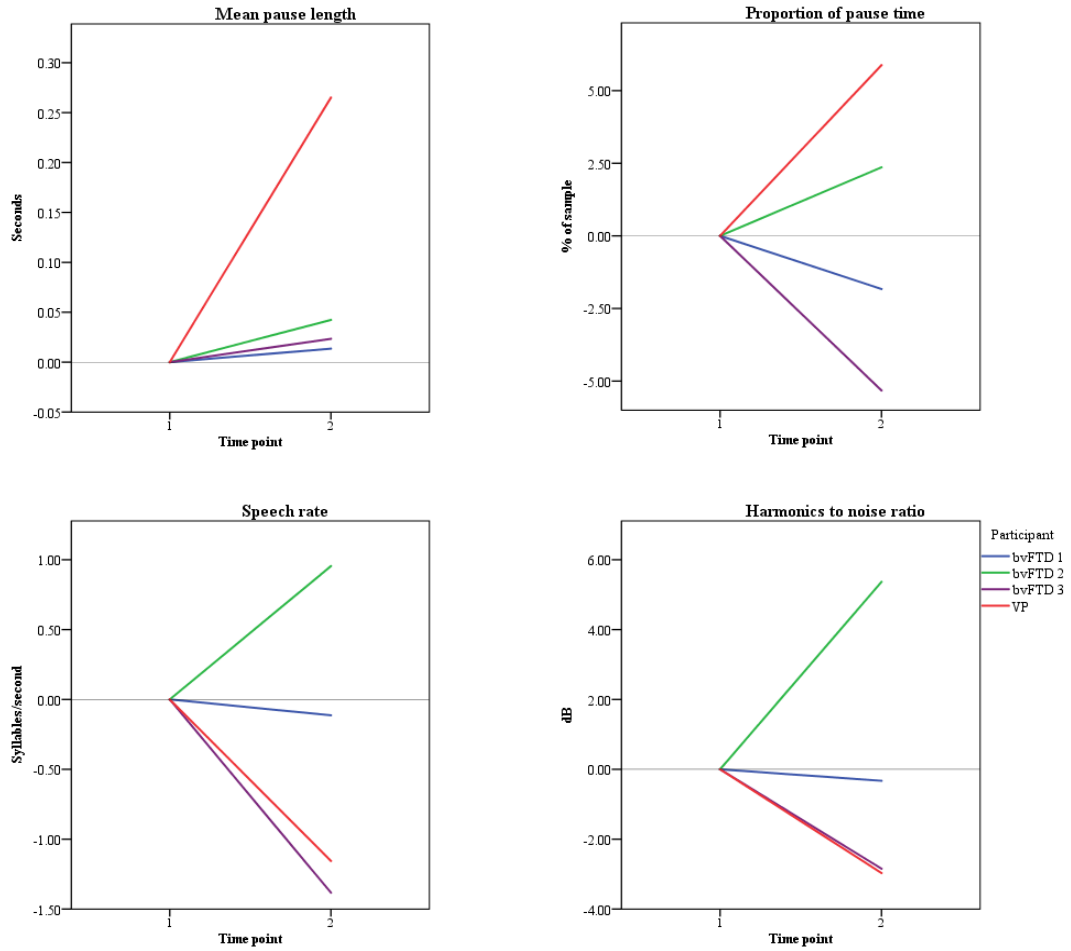

Figure 7-2: Degree of change between time points for each participant on measures of mean pause length, proportion of pause time, speech rate and harmonics to noise ratio. Blue = bvFTD 1; green = bvFTD 2; purple = bvFTD 3; red = VP; dB = decibels.

7.3.1.2 Harmonics to noise ratio

Participants' harmonics to noise ratios are presented in Figure 7-2. The bvFTD group demonstrated a large range of change (increase of 24% for bvFTD 2, and decrease of 12% for bvFTD 3). VP did not obviously differ in his rate of change (decrease of 14%).

7.3.2 Listener-based speech assessment

Listener-based consensus ratings are presented in Table 7-2. At time point 1, VP demonstrated speech impairments in all domains except for respiration and voice. At the second time point, VP was rated more severely on measures of prosody, articulation, and the monopitch scale.

Table 7-2: Listener-based consensus ratings at time points 1 and 2.

	VP		bvFTD 1		bvFTD 2		bvFTD 3	
Time point	1	2	1	2	1	2	1	2
Pitch								
Monopitch	2	3	1	2	2	2	1	1
Pitch breaks	0	0	0	0	0	0	0	1
voice tremor	1	0	0	0	0	0	1	2
Respiration								
Audible inspiration	0	0	0	0	0	0	0	1
Loudness								
Monoloudness	2	2	0	1	1	1	0	1
Loudness decay	1	0	0	0	0	0	0	0
Prosody								
Rate	-3	-3	0	-1	0	0	0	0
Variable rate	2	2	0	1	1	0	0	0
Short phrases	3	3	0	0	0	1	0	0
Reduced stress	2	3	1	1	1	2	0	1
Prolonged intervals	3	4	0	1	0	1	0	0
Equal and excess stress	1	2	0	0	2	1	0	1
Voice								
Rough	1	1	1	2	1	1	2	2
Breathy	0	1	0	0	0	0	1	2
Strained	0	0	1	1	0	1	0	0
Articulation								
Imprecise consonants	3	3	0	0	0	0	1	0
Prolonged phonemes	2	3	0	0	0	0	0	0
Repeated phonemes	1	2	0	0	0	0	2	1
Distorted vowels	2	3	0	0	0	0	0	0
Resonance								
Hypernasality	1	1	0	3	2	1	1	0
Hyponasality	0	0	2	0	0	0	0	0
DDK								
Rate	-3	-3	-1	1	-2	-1	-2	-2
Regularity	3	2	0	1	1	1	1	1
Phonemic errors	1	1	0	1	1	0	1	1
Groping	2	0	0	0	0	0	1	1

* Rated on a 5-point scale with the exception of speech rate and DDK rate which were rated on a 9-point scale with reductions in rate represented by negative numbers and increases represented by positive numbers (0 = normal, 1 = sub-clinical, 2 = mild, 3 = moderate, 4 = severe).

7.4 Discussion

Acoustic measures allowed for detection of the greater motor speech disorder change associated with the MND diagnosis, as opposed to the cognitive-linguistic and behavioural impairments of bvFTD. Consensus ratings from two speech pathologists blinded to participant and time point confirmed a perceptual change to VP's speech across multiple speech sub-systems, predominantly those of pitch, articulation and prosody. Deterioration of speech quality was also observed in the bvFTD participants; however, these were restricted to changes in voice quality and prosody. These features will be discussed in relation to the acoustic correlates of timing, vowel articulation and voice quality.

7.4.1 Speech Timing

Change between the two time points was observed for both VP and the bvFTD participants on measures of speech rate and proportion of silence time, suggesting that these measures may also be sensitive to cognitive or behavioural change. Of particular note is the fact that each of the three bvFTD participants presented with word finding difficulties and bilateral atrophy of the anterior temporal lobes. The anterior temporal lobes are involved in semantic processing, and impairment of semantic processing are likely to affect the speech timing metrics due to increased word finding difficulty (Patterson et al., 2007). Mean pause duration was identified as the most effective timing method for identifying changes of speech secondary to motor dysfunction, as demonstrated by the large increase in VP's mean pause length relative to the bvFTD participants.

These quantifiable acoustic measures directly relate to the listener-based perceptions of prolonged intervals and equal and excess stress, which were rated as being more prominent at the second time point for VP. Investigation of these timing measures in MND and FTD at a single time point has shown that the proportion of pause time measure differentiates MND patients with predominantly respiratory symptoms (Yunusova et al., 2016) from bulbar onset MND, bvFTD and progressive nonfluent aphasia, and may act as a measure of respiratory function deterioration (Rong et al., 2015). Speech rate measured as syllables per second has been shown to be effective in differentiating bvFTD from bulbar MND at the group level; however, the mean pause length did not differentiate either bvFTD or MND from controls in the same study (Yunusova et al., 2016). Despite this, the significant increase in VP's mean pause length in this study may indicate that this measure has utility in measuring within-

individual change. Larger longitudinal studies will further clarify which speech timing measures (e.g. proportion of pause time, variation of pause length) can be used as a surrogate marker for motor speech change in these groups.

7.4.2 Voice Quality

There was variation in harmonics to noise ratio (HNR) for both VP and the bvFTD participants, with bvFTD participants experiencing both increases and decreases in HNR. Deterioration of HNR is expected in healthy ageing (Ferrand, 2002), and this is consistent with known changes to vocal fold physiology in older adults (Pontes, Brasolotto, & Behlau, 2005). In this case series, HNR was shown to decline in VP's phonation, which is consistent with more severe ratings of breathiness at the second time point. HNR also highlighted a decline in the voice quality of bvFTD case 3, which was associated with a perceptual rating of increased breathiness over time. The magnitude of change of HNR for bvFTD cases 1 and 2 were less consistent with their perceptual ratings. Therefore, in this case series, the HNR was not useful in identifying change that was specific to motor dysfunction as opposed to changes associated with ageing.

7.5 Conclusion

Several quantitative speech measures have demonstrated capacity to monitor change in both MND and bvFTD. Measures of mean pause rate and vowel articulation index were shown to be sensitive to the greater magnitude of change experienced by our MND-FTD patient with frank motor speech dysfunction, in comparison to the more general behavioural and cognitive changes related to FTD. These quantitative measures were largely consistent with listener-based ratings of speech changes, and therefore have potential for objective monitoring which could be utilised as an adjunct to listener-based ratings in clinical settings. In particular, while these findings are based on a small group of individuals, such measures may have potential to assist in the early identification of bulbar onset MND in the FTD population. Future longitudinal studies involving larger numbers of participants could allow for the sensitivity and specificity of these measures to be established. A focus on assessing speech changes over shorter time periods of months rather than years would further clarify their potential as clinical measures.

8 Summary, Limitations, and Future Directions

8.1 Summary of research justification

Our understanding of the classification of PPA and FTD subtypes has developed over the past 35 years, from Mesulam's initial description of PPA (1982) through to the introduction of the logopaenic subtype (Gorno-Tempini, Dronkers, et al., 2004), and the development of the International Consensus Criteria (ICC; Gorno-Tempini et al., 2011). Despite these advancements, there is still progress to be made in classifying subtypes which do not fit into the ICC (Sajjadi et al., 2012; Wicklund et al., 2014). These debates range from the defining features of lvPPA to the existence of seemingly mixed variants involving both agrammatism and semantic impairment (Mesulam et al., 2009; Sajjadi et al., 2012). The conceptualisation of PAOS and PPAOS requires elaboration as clinicians and researchers define the terminology of these syndromes and establish consistent guidelines for classification of patients presenting with both agrammatism and AOS early in the disease course (Gorno-Tempini et al., 2011; Josephs et al., 2013; Josephs et al., 2012). While the identification of speech abnormalities in bvFTD does not hold the diagnostic importance that it does in PPA due to the early behavioural disturbance, the current state of the literature indicates that there is a high incidence of speech disturbance in bvFTD which is poorly characterised (Poole et al., 2017). Characterisation of the expected speech disturbance in bvFTD is important so that the development of signs of bulbar MND and parkinsonian syndromes can be monitored for and identified in clinical settings (Harciarek et al., 2014; Kertesz et al., 2007; Santos-Santos et al., 2016).

A key advantage of objective speech measures is that different research groups can apply them to their diverse study samples in a manner that is both consistent and quantitative, thereby allowing for comparison between research groups and capacity for larger meta-analyses. Currently, the range of measures used during classification is highly variable (Poole et al., 2017), and the ICC do not specify measures or assessment tools which should be used to identify the diagnostic features of PPA (Gorno-Tempini et al., 2011). Furthermore, descriptions of some features such as AOS are not consistently defined among researchers (Sajjadi et al., 2012). Increasingly widespread use of objective measures may therefore clarify the distinguishing features of PPA by providing consistency to the variety of research groups investigating speech phenotypes, brain-behaviour associations, and therapies. Ideally,

metrics for classification would be highly reliable and stable, without reliance on expert rater judgement (Vogel & Maruff, 2014). Over the past four years, there has been a growing interest in objectively quantifying the speech abnormalities of FTD and PPA with speech acoustics (Ballard et al., 2014; Cordella et al., 2017; Duffy et al., 2017; Duffy et al., 2015; Yunusova et al., 2016). The pairwise variability index (PVI) and measures of speech timing have been shown to differentiate progressive AOS from agrammatic and logopaenic aphasia (Ballard et al., 2014; Cordella et al., 2017; Duffy et al., 2017). Furthermore, timing, diadochokinesis (DDK) and PVI metrics have identified progression in two cases of PPAOS (Duffy et al., 2015). These examples from three different research groups demonstrate the capacity of objective measures to provide consistency to the field. In future, these could be applied as outcome measures for speech therapies and clinical trials, thereby reducing researcher bias. In the clinical setting, these objective measures of speech may support clinicians' ability to distinguish between clinical syndromes and monitor disease progression.

8.2 Summary and clinical implications of the research

8.2.1 Speech profiles of FTD and PPA

Perceptual and acoustic evaluation in Chapter Four characterised the impairments of verbal expression within the cohort. bvFTD was characterised by impaired prosody and DDK production on both acoustic and perceptual assessment. These findings indicate that subtle motor speech changes may occur in bvFTD and do not necessarily indicate the development of an FTD-MND syndrome. Non-speech motor abnormalities observed in earlier studies have led authors to suggest that motor changes may be secondary to degeneration of the primary motor cortex and lower motor neurons in the brainstem and spinal cord (Burrell et al., 2011). The progression of these speech abnormalities was reported in Chapter Seven, with comparison to one case of FTD-MND. This longitudinal investigation suggested that pause time in the days of the week task, may track the emergence of prominent bulbar MND changes which occur in addition to changes associated with bvFTD. While the findings are promising for clinical application, larger studies are required to evaluate the sensitivity and specificity of this measure for tracking motor impairment in the context of cognitive decline.

AOS was present in all cases of nfvPPA, primarily affecting perceptual features of articulation and prosody. Impaired pitch variation was a key perceptual feature that

distinguished nfvPPA from the dysfluent presentation of lvPPA. Acoustic changes of nfvPPA included impaired PVI and DDK production, which demonstrated potential for differentiation from lvPPA, and supported the perceptual findings. Notably, while AOS in nfvPPA affected multiple speech subsystems, abnormalities of resonance were not observed to be significantly different from other groups following perceptual evaluation. If replicated in larger studies, the preservation of velopharyngeal coordination in nfvPPA may be helpful for identifying the development of parkinsonian speech disturbance in this group, which is most commonly characterised as spastic dysarthria (Kluin et al., 1993). Progression of speech decline in nfvPPA was explored in Chapter Six. Measures of PVI, DDK and speech timing were observed to be sensitive to progression in nfvPPA and identified two distinct rates of clinical progression. The more rapid rate of decline in the second participant was consistently present across each of these measures. Importantly for clinical speech evaluation, acoustic changes were observed for both participants in the relatively short six-month period between the first two assessments, whereas perceptual ratings only identified deterioration over the full year of the study. We hypothesise that the PVI and DDK metrics are identifying the acoustic correlates of AOS, and are therefore likely to be applicable to PAOS, but not to nfvPPA characterised by agrammatism without AOS.

The lvPPA group differed from nfvPPA by increased frequency of false starts and phonemic errors, and these findings are consistent with previous studies of connected speech in lvPPA (Ash et al., 2013; Wilson et al., 2010). In contrast to the nonfluent speech of nfvPPA, the lvPPA group did not differ from controls on perceptual ratings of prosodic impairment including monopitch, monoloudness, and equal and excess stress. Instead, the lvPPA group differed from controls on features that were suggestive of poor phonological encoding such as repeated phonemes, phonemic errors and false starts, consistent with earlier studies (Wilson et al., 2010).

Speech in svPPA was characterised by increased pauses and silences, likely due to word finding difficulty. These pauses affected speech rate and phrase length, and were consistent with features of anomia (Ash et al., 2013; Fraser et al., 2014). Motor speech impairments were not a feature of svPPA in this cohort, and this is consistent with earlier studies that have suggested the presence of motor speech impairment to be indicative of an alternative diagnosis (Ash et al., 2013; Gorno-Tempini et al., 2011; Wilson et al., 2010).

8.2.2 Use of acoustic measures for classification and monitoring progression

The speech timing metrics were impaired compared to controls for all subtypes, likely due to different cognitive and motor sources of reduced rate, such as AOS, anomia and abulia (Levelt, 1989; Rohrer, Knight, et al., 2008). Larger studies of these tasks may be able to determine whether different PPA variants have characteristic differences when the tasks are considered together; for example, we hypothesise that rate in nfvPPA would be affected relatively equally on each task in contrast to svPPA participants who would have greater difficulty with tasks requiring lexical access such as the monologue. In the present study, speech timing metrics differentiated bvFTD from nfvPPA; however, their clinical application lies in their ability to differentiate PPA subtypes, particularly nfvPPA and lvPPA. While this study was likely underpowered to observe such differences, the speech timing metrics have demonstrated capacity to differentiate these two variants in similar studies (Ballard et al., 2014). Chapters Six and Seven demonstrated the utility of speech timing measures for tracking progression of speech decline in bvFTD and nfvPPA, with greater rates of decline observed for a bvFTD participant with concomitant dysarthria, and different rates of decline observed for two nfvPPA participants.

DDK rate and period metrics were sensitive to the disease processes, and were impaired in all pathological groups compared to healthy controls. Only the nfvPPA group demonstrated significant differences from other pathological groups, likely due to prominent AOS. DDK production was associated with lesser cortical thickness at the superior temporal gyrus, which may reflect the impact of deficits of phonological processing and attention (Menon & Uddin, 2010; Vigneau et al., 2006). However, this finding should be considered in the context of the relatively large number of lvPPA participants in correlational analysis of cortical thickness and speech. DDK metrics were sensitive to disease progression in nfvPPA (Chapter Six), and may therefore be a useful adjunct to perceptual ratings when monitoring progression in a clinical setting.

The PVI metric differentiated participants with nfvPPA from other clinical variants. These findings are consistent with the application of PVI to identify progressive AOS in other studies (Ballard et al., 2014; Duffy et al., 2015). Similarly, PVI tracked the progression of one of two nfvPPA participants in Chapter Six. Importantly, only the durational PVI measure was successful, as opposed to the PVI metric based on intensity, which did not demonstrate group difference (Chapter Four) nor successfully track progression of AOS (Chapter Six).

Therefore the PVI metric based on duration should be selected in clinical settings, rather than measures of intensity. The PVI metric has potential to be applied clinically using freely available software such as Praat (Boersma & Weenink, 2001), provided clinicians are trained in the manual calculation of vowel durations.

Voice metrics did not differentiate clinical subtypes in Chapter Four, and the metrics did not reliably track speech decline in Chapters Six and Seven. It is apparent that the disease process in this cohort did not affect voice quality to a greater extent than changes associated with ageing, and is therefore not a good candidate for classification of clinical variant in clinical or research settings (Dehqan et al., 2013; Ferrand, 2002).

Vowel articulation measured with FCR, like voice quality, did not significantly differentiate between groups. We hypothesised that FCR would be affected by dysarthria or AOS, which meant that evaluation of this measure in particular was underpowered due to the low number of nfvPPA participants. Considering this limitation, FCR could be considered in future studies of PPA for evaluation of nfvPPA.

8.3 Limitations

The low number of participants (n = 67) limited the statistical power of the ANOVA in Chapter Four, particularly for post hoc comparisons between each of the PPA groups, which had fewer participants than the bvFTD and control groups. In particular, the nfvPPA group had only four participants, which suggests that the group cannot be considered fully representative of the range of nonfluent and agrammatic presentations that have been described (Josephs et al., 2013; Rohrer, Rossor, et al., 2010b). For example, all participants with nfvPPA presented with AOS at the time of their participation in the study. The low number of nfvPPA participants meant that some metrics could not be explored fully. The timing metrics from the reading and monologue tasks, for example, could not be conducted as two participants could not complete this task due to the severity of their speech impairments (Chapter Four). nfvPPA is the subtype that presents with the most overt motor speech disorder, meaning that this lack of analysis placed a significant limitation on our ability to explore the relative influence of cognition, language and motor speech on the speech timing metrics. Similarly, the utility of the FCR may be undervalued by these findings, as it is the

nfvPPA group that has presented with vowel distortions in this study (perceptually) and earlier investigations (Ash et al., 2010).

The relatively low number of participants limited our capacity to investigate brain-behaviour associations in each subtype separately. Instead, all subtypes were included in a single correlation analysis. As a result, regions of lesser cortical thickness in groups with greater numbers, in this case bvFTD and lvPPA, were more likely to be correlated with speech features, which may partly explain correlations between speech and the right precentral gyrus and left superior temporal gyrus. The number of participants who were assessed at multiple time points also limited the longitudinal investigations. Chapters Six and Seven can therefore only be considered exploratory proofs of concept. Larger studies are required to establish the range of progressions that exist in each subtype.

While the findings of the study elucidate differences between clinical variants, many participants were recruited after their initial presentation to a diagnostic clinic, and we therefore cannot draw conclusions about the measures' capacity to identify the emergence of speech abnormalities in neurodegenerative syndromes. Disease duration for each of the subtypes ranged from 2 to 5.4 years after onset in the current study. Future studies, in which recruitment is limited to participants at their initial clinical presentation, are required to identify early speech features that are salient for diagnosis.

It should also be noted that the FCR summates the three iterations of each of the three selected vowels into a single metric, which results in loss of information regarding direction and magnitude of differences for each of the three vowels (Karlsson & Doorn, 2012). Karlsson and Doorn (2012) propose a vector based method to calculation of vowel space area which has demonstrated greater statistical stability than the FCR, and this could be used to support evaluation of vowel articulation in future studies.

The FCR may have been a more reliable measurement of vowel articulation had a flexible measurement point for formant calculation been utilised, as opposed to selection of the midpoint of the vowel. It has been suggested that a flexible measurement point would more accurately reduce the impact of the place of articulation (e.g., alveolar, velar) of preceding consonants on the vowel formants (Fletcher, McAuliffe, Lansford, & Liss, 2015; Hillenbrand, Clark, & Nearey, 2001). While at the time of study design there was no data to support the notion of a flexible measurement point for assessment of motor speech disorder, a recent study has indicated that articulatory-based selection of formant extraction better correlates

with perceived severity of dysarthria than extraction at the vowel mid-point (Fletcher et al., 2017).

8.4 Future directions

8.4.1 Clarification of the diagnostic accuracy of speech acoustic measures

In the above limitations, I noted that the relatively long average disease duration in this study limits our ability to draw conclusions about the capacity of acoustic measures to support clinical diagnosis of a neurodegenerative syndrome. In this study, participants were recruited at several stages of their disease in order to investigate the salient features of speech that differed between subtypes. Future studies, which limit recruitment to participants in the early disease stage may elucidate whether early changes are identifiable acoustically. Furthermore, larger longitudinal studies of the syndromes may allow for statistical investigation of change between time points, and this would likely assist in the identification of the most salient metrics that should be applied to track disease progression. Tracking of speech decline over shorter time periods (e.g., three-month periods) could help to establish the shortest time period required to identify neurodegenerative speech changes.

8.4.2 Differentiation between deficits of speech, language and cognition

Evaluation of the speech timing measures (e.g. syllables per second, mean pause length) raised discussion about the relative influence of frontal dysfunction (e.g., aspontaneity, apathy, disinhibition), aphasia (e.g., word finding difficulty, agrammatism, phonological encoding), and/or motor speech impairment. While preliminary comparisons to language data from the PALS were made in this study, these distinctions could be explored further. Several studies have been conducted to investigate the quantity of speech and language based errors in samples of connected speech (Ash et al., 2013; Fraser et al., 2014; Gunawardena et al., 2010; Silveri et al., 2014; Wilson et al., 2010), and similar approaches could be used to investigate the influence of linguistic errors on the automated speech timing metrics. Furthermore, the influence of cognition could be explored through more comprehensive cognitive and language assessments.

8.4.3 Tracking treatment effectiveness

In this study, we presented two case series which suggested that acoustic measures are able to track disease progression. Acoustic measures could be applied to treatment studies in which researchers aim to track improvements or reduced deterioration of speech. There is potential for measures of lexical stress (PVI) and DDK production to be applied to evaluation of treatments targeting progressive AOS. Currently, only one trial has targeted improved prosodic range following repetitive oral reading, and outcomes were measured with perceptual rating scales (Henry et al., 2013). The lexical stress metric of PVI provides a more objective outcome measure free from potential bias. Similarly, as disease-modifying treatments are developed in the future, acoustic measures of speech production could provide researchers with objective outcome measures to track their effectiveness in the progressive aphasias.

8.5 Conclusions

The results of these studies support the use and further evaluation of speech acoustic measures for the assessment of speech in PPA and FTD. Their use in clinical classification of speech phenotypes is supported by significant differences between subtypes. Application of acoustic measures to longitudinal analysis of speech decline was explored in case studies of nfvPPA and FTD-MND, and several metrics were sensitive to different rates of progression. The findings highlight the measures that could be used in future research of syndrome characterisation and outcome measurement, and in clinical settings to support perceptual evaluation of speech.

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10 Supplemental Material S1 (Chapter 2)

Table 10-1: Key behavioural speech findings of studies included in the systematic review

Author (year)	Participants	Assessments	Findings
Ackermann et al. (1997)	1 nfvPPA, 16 HC, and 3 pseudobulbar palsy as controls	Phonologically contrastive short and long vowels assessed perceptually and with acoustic temporal measurement	Decreased difference between long and short vowels for nfvPPA participant. 77% of vowels produced were incorrectly perceived by raters.
Ash et al. (2009)	11 nfvPPA, 12 svPPA and 12 bvFTD and 10 HC	Words/min and speech errors per utterance	All pathological groups slower than controls. NfvPPA significantly slower than svPPA. nfvPPA group had significantly more speech errors compared to all other groups.
Ash et al., (2010)	16 nfvPPA and 10 HC	Connected speech quantified for: words/min, hesitation markers, phonetic and phonemic errors.	The nfvPPA group had significantly slower speech rate and greater number of phonemic errors compared to controls. The majority (82%) of speech errors in the nfvPPA group were phonemic rather than phonetic.

Ash et al. (2013)	15 nfvPPA, 29 lvPPA, 18 svPPA, 17 bvFTD, and 12 HC	Connected speech quantified for: words/min, phonemic and phonetic errors and dysfluencies	Speech rate (words per minute) was reduced in all PPA groups compared to controls, as well as in nfvPPA group compared to all other pathological groups. nfvPPA had more phonemic errors compared to controls, whereas lvPPA had a greater incidence of dysfluencies compared to both controls and bvFTD.
Ballard et al. (2014)	41 PPA (21 lvPPA, 20 nfvPPA) and 17 HC	Connected speech quantified for: proportion of silence time, median duration of silences, and variability of silence duration. PVI measured lexical stress with multisyllabic words	Median silence duration was higher, while PVI duration was lesser for the nfvPPA group compared to both controls and lvPPA. A model (Model 1) diagnosed 83% of patients with measures of PVI duration, variability of silence duration and proportion of silence time. A second model (Model 2) accurately diagnosed 84% of the group with PVI only.
Botha et al. (2014)	55 PPA (9 nfvPPA, 41 lvPPA, 5 svPPA) and 34 PAOS	ASRS	PAOS participants with NVOA had significantly greater AOS severity than PAOS participants without NVOA. NVOA was not seen in svPPA or lvPPA and was not associated with severity of AOS in nfvPPA.
Botha et al. (2015)	130 PPA (40 PAOS, 12 nfvPPA, 9 svPPA, 52 lvPPA, 4 PFA, 13 unclassified)	ASRS and four-point dysarthria and apraxia severity scales	Dysarthria present in nfvPPA and PAOS groups only with no significant difference in severity. AOS significantly more severe (on ASRS) in PAOS and nfvPPA compared to all other groups.

Brambati et al. (2015)	8 PPA (8 nfvPPA, 13 svPPA, 7 lvPPA) and 29 HC	MSE	Statistically significant increase in MSE rating over one year for the nfvPPA group.
Caso et al. (2013)	1 nfvPPA	MSE	Participant first observed with slowing of speech which progressed until she was functionally mute.
Caso et al. (2014)	11 nfvPPA (9 nfvPPA-tau, 2 nfvPPA-TDP)	MSE	No statistical comparisons made for motor speech evaluation. Both dysarthria and AOS were reported in both nfvPPA-tau and nfvPPA-TDP groups.
Caramazza, Papagno, and Ruml (2000)	1 fluent PPA	Speech errors counted by category	Majority of participant's errors involved substitutions of phonemes.
Code, Ball, Tree, and Dawe (2013)	1 nfvPPA and 5 HC	Words/min	Words/min markedly reduced for nfvPPA participant.
Croot et al. (2012)	9 nfvPPA and 14 lvPPA	Phonetic distortions, phonemic errors and prosodic disruption each rated on a 4 point scale.	Presence of AOS in speech tasks 100% sensitive in identifying participants with nfvPPA with 71% specificity. Phonological errors were 86% sensitive in identifying lvPPA with only 56% specificity. AOS characteristics were not exclusive to nfvPPA, nor were phonological errors exclusive to lvPPA.

Diehl and Kurz (2002)	50 bvFTD and 30 AD as controls	Speech abnormalities rated on three point scale. Types of speech abnormalities were not described.	58% of participants rated as moderate and 16% rated as severe on a scale of 'speech abnormalities'.
Duffy et al. (2015)	2 PPAOS assessed longitudinally and 13 controls (5 with mild aphasia)	ASRS, 5 point AOS and dysarthria severity scales, 10 point functional severity rating, and an articulation error score, syllables/sec, DDK rate, PVI.	Both participants had greater severity on AOS and articulatory error measures at second time point compared to the first. Both were rated as having equivocal spastic dysarthria at the second but not first time point. PVI measure was attenuated compared to controls at both time points. Syllables/sec and DDK slowed over time.
Fraser et al. (2014)	24 PPA (14 nfvPPA, 10 svPPA) and 16 HC	Connected speech quantified for: fillers, occurences of "um", speech rate.	Speech rate was slower in nfvPPA and svPPA compared to controls, and productions of "um" was higher in the svPPA than nfvPPA participants.
Gorno-Tempini et al. (2008)	4 lvPPA	MSE	None of the four participants showed signs of AOS or dysarthria.
Gorno-Tempini, Murray et al. (2004)	1 nfvPPA progressing to CBS	MSE conducted in 3rd and 4th year of longitudinal study.	Both AOS and dysarthria severities increased from the 3rd to 4th year of the study. The patient developed CBS symptoms in the fourth year of the study.

Gorno-Tempini, Dronkers et al. (2004)	31 PPA (11 nfvPPA, 10 svPPA, 10 lvPPA) and 10 HC	MSE	Apraxia of speech rating was more severe in nfvPPA compared to lvPPA. Four nfvPPA participants had mild dysarthria. There were no significant differences between groups based on dysarthria ratings.
Graff-Radford et al. (2012)	23 PPA (11 lvPPA, 12 nfvPPA)	Speech and facial expression subscale UPDRS (Part 3).	50% of the nfvPPA group was noted to have dysarthria. nfvPPA was more severely impaired than lvPPA on the speech/facial expression subscale.
Graham et al. (2004)	14 nfvPPA and 11 HC	Words/min	NfvPPA significantly slower than controls.
Gunawardena et al. (2010)	16 nfvPPA, 12 bvFTD and 13 HC	Connected speech quantified for: words/min and % speech sound errors.	Words/min significantly reduced in nfvPPA compared to controls and bvFTD.
Josephs et al. (2013)	18 PPAOS, 9 nfvPPA, 10 dominant AOS (PAOS) and 30 HC	ASRS and 4 point dysarthria severity scale. Participants classified as AOS Type 1 if sound errors dominated and AOS type 2 if prosodic errors dominated.	Dominant AOS has a significantly higher number of people with AOS type 2 compared to nfvPPA. There was no difference in AOS type between dominant AOS and PPAOS. Dominant AOS group had a significantly higher ASRS score than both PPAOS and nfvPPA. Dysarthria was observed in all three groups however there were no group differences of severity.

Josephs, Duffy, Strand, Machulda, Senjem, et al. (2014)	13 PPAOS	ASRS and 5-point dysarthria severity scale. Subjects assessed at baseline and follow up, with a mean time to follow up of 2.4 years.	Median increase per year in ASRS score was 4.5. Median increase in dysarthria rating was 0.3. At baseline, two subjects had spastic dysarthria. At follow up there were five subjects with spastic dysarthria, one with hypokinetic dysarthria and three with equivocal signs of dysarthria. All subjects developed parkinsonian features and 5 developed a syndrome similar to PSP.
Josephs, Duffy, Strand, Machulda, Vemuri, et al. (2014)	6 lvPPA	ASRS and presence of phonological errors rated on a 5-point scale.	Mean of 0.8 (out of 60) on the ASRS (SD=0.9). No participants had unequivocal evidence of AOS. Mean of 1.2 on rating of phonological errors (scored out of 5).
Knibb et al. (2009)	15 progressive aphasia (excluding svPPA, MND and CBS) and 15 HC	Connected speech quantified for: words/min and speech errors per word.	NfvPPA group had significantly lower words/min and significantly higher speech sound errors per word compared to controls.
Laganaro, Croisier, Bagou, and Assal (2012)	1 PAOS	Length of syllables, words/min and syllables/sec assessed annually for three years.	Statistically significant effect of time on syllable duration. Words/min and syllables/sec decreased over time.

Mandelli et al. (2014)	25 PPA (9 nfvPPA, 8 svPPA, 8 lvPPA) and 21 HC	A composite 'speech production score' was calculated from the MSE and WAB fluency rating.	nfvPPA group was more impaired on the MSE AOS Rating Scale than all other groups, and more impaired on the MSE dysarthria scale compared to controls and svPPA. nfvPPA group with significantly higher speech production score compared to all other pathological groups.
Mendez, Clark, Shapira, and Cummings (2003)	15 nfvPPA, 15 AD and 15 HC	7-point dysarthria severity scale.	Speech rate was significantly more impaired for nfvPPA group compared to both AD and controls.
Mendez, Joshi, Tassniyom, Teng, and Shapira (2013)	95 clinical bvFTD grouped by pathology: 23 FTLD tau-positive, 51 FTLD tau-negative and 21 AD	UPDRS scale, with speech subscale examined as a separate item.	56.8% of the FTLD group had speech abnormalities. Tau negative FTLD participants had more speech abnormalities (70.6%) than the t-positive patients (28.6%).
Mesulam et al. (2012)	25 PPA (9 nfvPPA, 1 PAOS, 4 svPPA, 6 lvPPA, 5 mixed) and 12 HC	Words/min	NfvPPA and mixed PPA (agrammatism and word comprehension impairment) had the lowest words/min.

Miller et al. (2013)	122 PPA (41 nfvPPA, 61 svPPA, 20 lvPPA)	MSE	Dysarthria and AOS significantly more severe for nfvPPA group.
Ogar et al. (2007)	18 nfvPPA	MSE	Participants divided into two groups based on whether they had AOS and dysarthria (60%) or AOS only (40%). The AOS+dysarthria group demonstrated more severe speech impairment. Spastic features were the most common features of dysarthria (with or without hypokinetic features). One patient had hypokinetic dysarthria only.
Pakhomov et al. (2010)	38 with FTLD (bvFTD, svPPA, nfvPPA) and lvPPA	Natural language processing and automated speech recognition.	Pause to word ratio and normalized dysfluent event were significantly different for nfvPPA group compared to the other three groups.
Rabinovici et al. (2008)	15 PPA (4 lvPPA, 6 nfvPPA, 5 svPPA)	MSE	NfvPPA participants had significantly higher severity ratings on both dysarthria and AOS subscales of the MSE compared to lvPPA and svPPA.
Rohrer, Rossor, & Warren (2010a)	16 nfvPPA	Subtests from the ABA-2, DDK rate, 5-point orofacial apraxia severity rating.	All participants scored within the abnormal DDK range, with the majority (69%) mildly impaired. (19% moderate, 13% severe).

Rohrer et al. (2010b)	24 PPA (10 AOS + agrammatism, 4 AOS - agrammatism, 3 agrammatism - AOS, 7 lvPPA) and 18 HC	Speech errors/min, words/min and mean pause length.	All nonfluent groups had slower speech rate than lvPPA and HC. Speech production errors were worst in the agrammatism with AOS and agrammatism without AOS groups. Mean pause length was greater for the agrammatic (without AOS) group.
Silveri et al. (2014)	42 PPA or PAOS (11 svPPA, 3 lvPPA, 21 nfvPPA, 4 PAOS, 3 NC) and 10 HC	Connected speech quantified for: words/min, fragments (% words without syntactic structure)	SvPPA produced significantly fewer fragments than the nfvPPA group and all other pathological groups combined. Speech rate lower for lvPPA and AOS than svPPA.
Spinelli et al. (2015)	1 nfvPPA progressing to CBS	Articulation and prosody rated on 6 point severity scale in the AAT	Progressive decline in articulation and prosody from 4/6 to 2/6 over four years.
Thompson et al. (2012)	37 PPA (11 nfvPPA, 20 lvPPA, 6 svPPA) and 13 HC	Motor speech scored on 50 point scale on tests of repetition of syllables of varying complexity.	Minor motor speech impairments identified for all pathological groups. No statistical comparison.

Wicklund et al. (2014)	84 PPA (23 nfvPPA, 6 svPPA, 29 lvPPA, 26 unclassified PPA) and 21 PPAOS as controls	ASRS and three 5-point severity scales for AOS, dysarthria and phonologic errors.	ASRS rating and dysarthria rating was significantly higher for both nfvPPA and PPAOS compared to lvPPA, svPPA and unclassified PPA. The logopaenic group had a more severe rating of phonological errors than nfvPPA and PPAOS. The unclassified PPA group had a significantly higher phonologic error rating than PPAOS.
Wilson et al. (2009)	86 PPA (32 nfvPPA, 38 svPPA, 16 lvPPA) and 115 HC	MSE dysarthria and AOS rating scales.	No statistical comparisons reported for speech assessments. NfvPPA mean severity of 2.4 on dysarthria scale and 3.1 on AOS scale. No dysarthria detected in svPPA of lvPPA. Mean AOS score for lvPPA was 0.6. No AOS detected in svPPA.
Wilson et al. (2010)	10 bvFTD, 50 PPA (14 nfvPPA, 25 svPPA, 11 lvPPA) and 10 HC	MSE dysarthria and AOS rating scales. Connected speech quantified for: words/min, maximum speech rate (words/min for three quickest utterances), distortions, phonological paraphasias, dysfluencies.	NfvPPA significantly more severe on AOS scale compared to bvFTD and svPPA. NfvPPA more severe on dysarthria scale compared to svPPA and lvPPA. NfvPPA had significantly slower speech rates than other PPA groups, while lvPPA was slower than svPPA and controls. Measures of dysfluency identified impairments in each PPA variant depending on the specific measurement.

Yunusova et al. (2016)	9 bvFTD, 9 nfvPPA 83 ALS and 32 HC	Words/min, syllables/min, mean and CoV of phrase duration, number of pauses, % pause time, mean and CoV of pause duration.	bvFTD showed reduced speech rate (words/min) and increased pauses and % of pauses, but no impairment of articulatory rate (syllables/min) compared to controls. All measures, except for mean and CoV of pause duration were reduced in nfvPPA.

AAT = Aachener Aphasia Test; ABA-2 = Apraxia Battery for Adults 2; AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; AOS = apraxia of speech; ASRS = Apraxia of Speech Rating Scale; bvFTD = behavioural variant FTD; CBS = corticobasal syndrome; CoV = coefficient of variation; DDK = diadochokinesis; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; HC = healthy controls; lvPPA = logopaenic variant primary progressive aphasia; MND = motor neuron disease; MSE = Motor Speech Evaluation (7 point severity scale); NC = not classifiable; nfvPPA = nonfluent variant primary progressive aphasia; NVOA = non-verbal oral apraxia; PAOS = progressive apraxia of speech; PPA = primary progressive aphasia; PPAOS = primary progressive apraxia of speech; PVI = Pairwise variability index; svPPA = semantic variant primary progressive aphasia; UPDRS = Unified Parkinson's Disease Rating Scale; VBM = voxel based morphometry; WAB = Western Aphasia Battery

11 Supplemental Material S2 (Chapter 2)

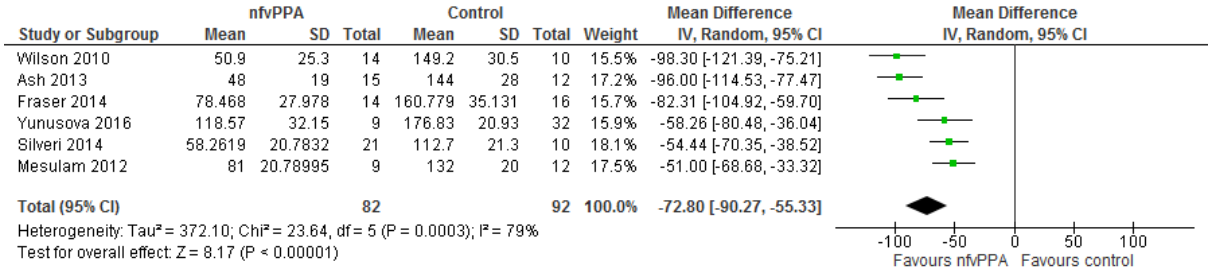

Figure 11-1: Forest plot of comparison: 1 Control vs nfvPPA, outcome: 1.1 words/minute.

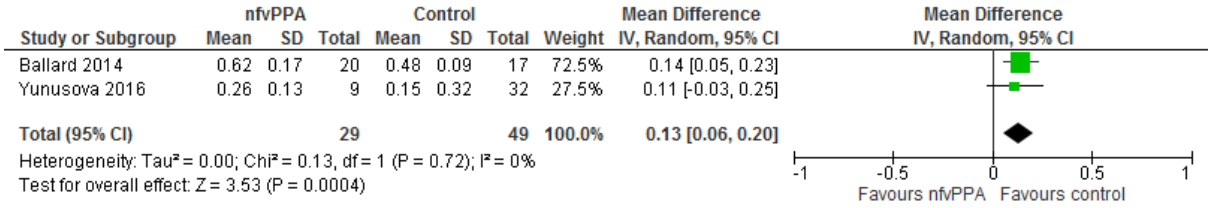

Figure 11-2: Forest plot of comparison: 1 Control vs nfvPPA, outcome: 1.2 Proportion of silence time.

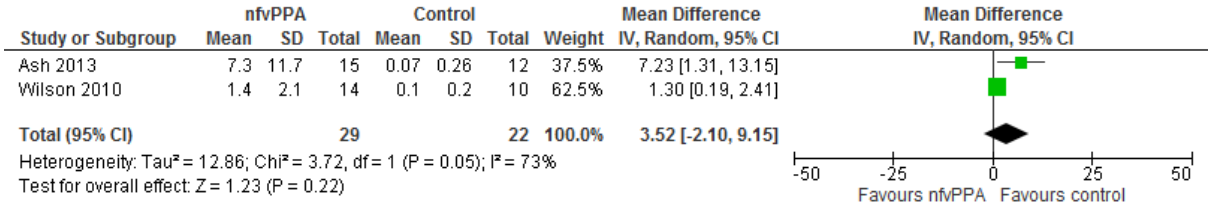

Figure 11-3: Forest plot of comparison: 1 Control vs nfvPPA, outcome: 1.3 Phonemic errors per 100 words.

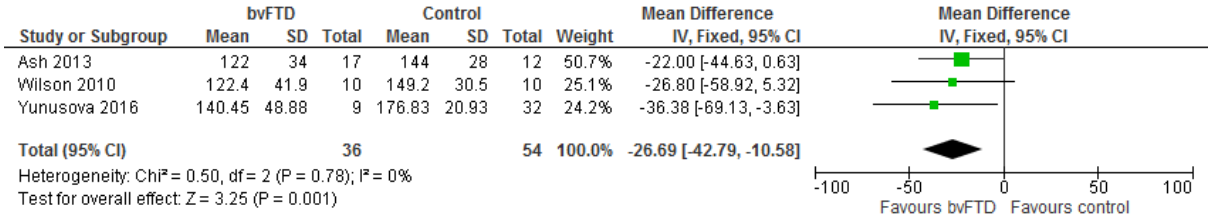

Figure 11-4: Forest plot of comparison: 2 Control vs bvFTD, outcome: 2.1 words/minute.

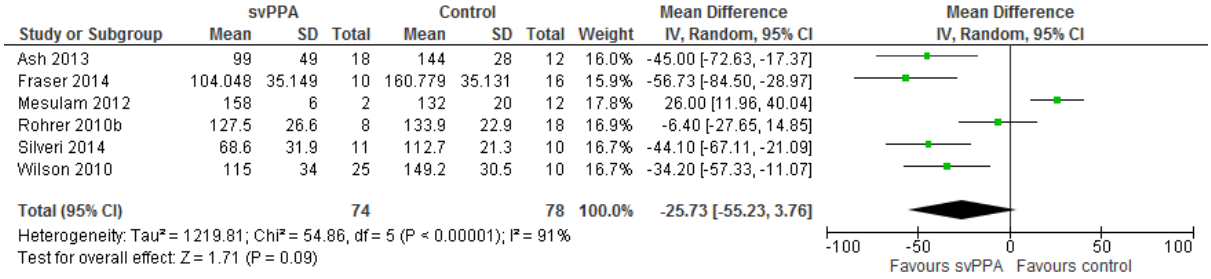

Figure 11-5: Forest plot of comparison: 3 Control vs svPPA, outcome: 3.1 words/minute.

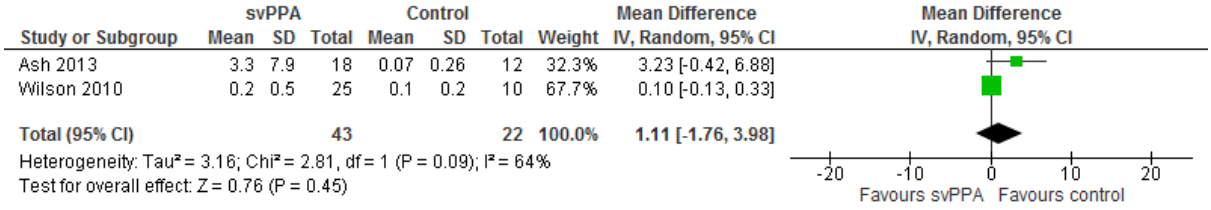

Figure 11-6: Forest plot of comparison: 3 Control vs svPPA, outcome: 3.2 Phonemic errors per 100 words.

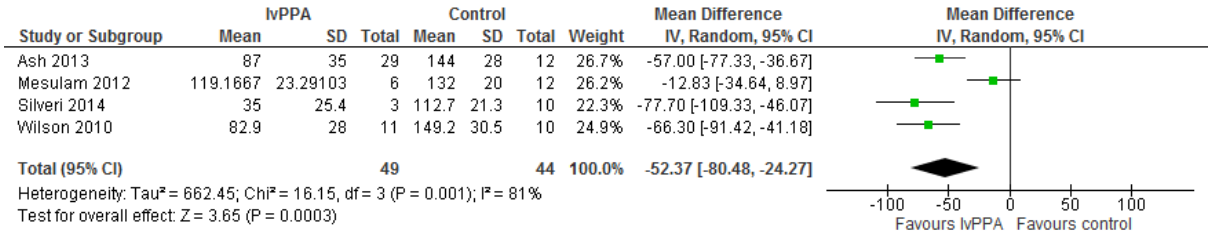

Figure 11-7: Forest plot of comparison: 4 Control vs lvPPA, outcome: 4.1 words/minute.

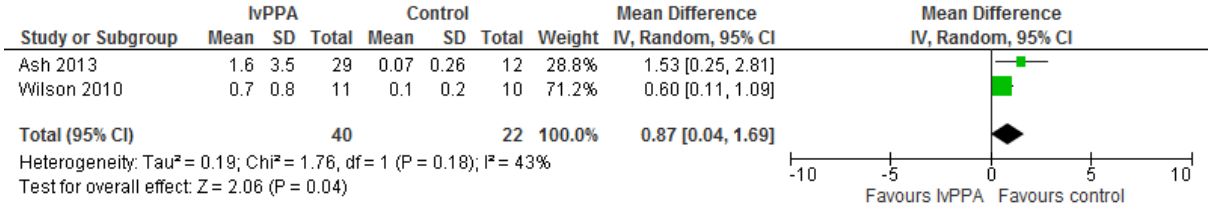

Figure 11-8: Forest plot of comparison: 4 Control vs lvPPA, outcome: 4.2 Phonemic errors per 100 words.

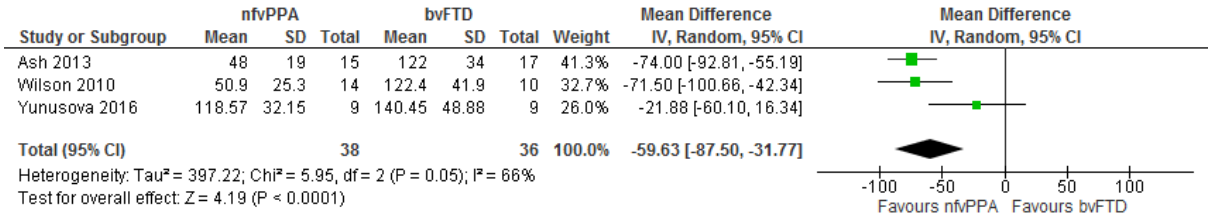

Figure 11-9: Forest plot of comparison: 5 nfvPPA vs bvFTD, outcome: 5.1 words/minute.

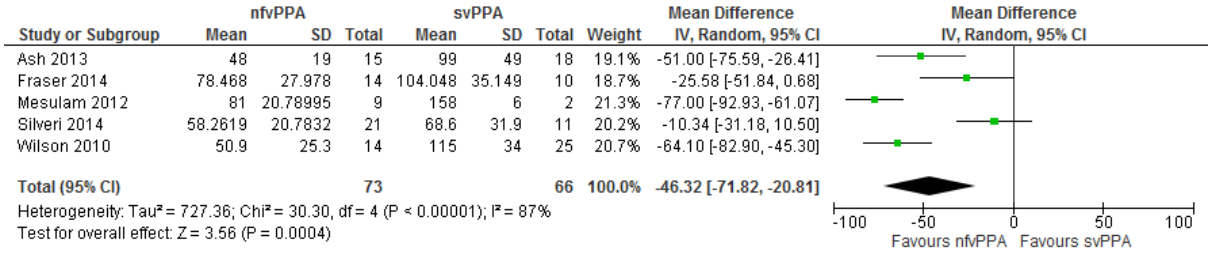

Figure 11-10: Forest plot of comparison: 6 nfvPPA vs svPPA, outcome: 6.1 words/minute.

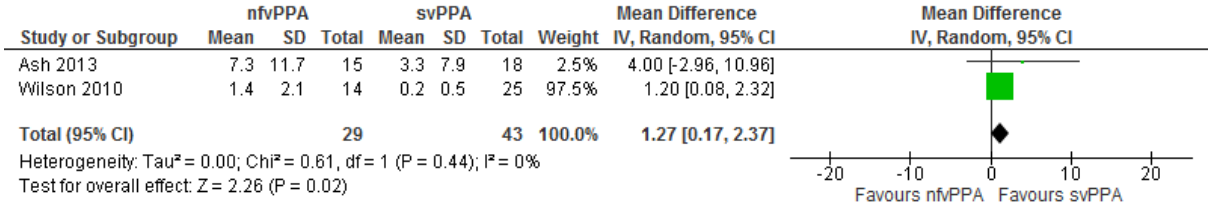

Figure 11-11: Forest plot of comparison: 6 nfvPPA vs svPPA, outcome: 6.2 Phonemic errors per 100 words.

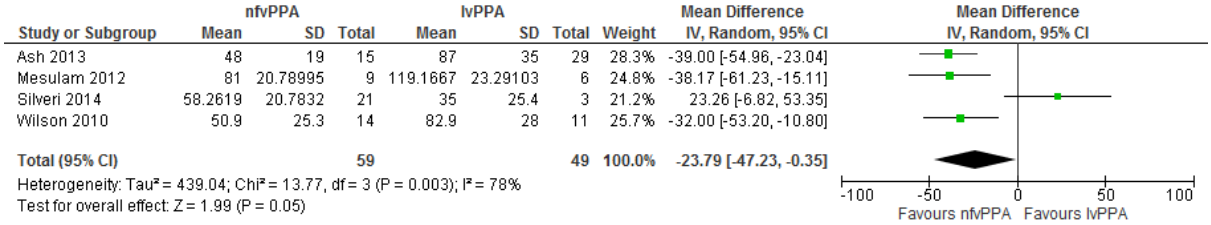

Figure 11-12: Forest plot of comparison: 7 nfvPPA vs lvPPA, outcome: 7.1 words/minute.

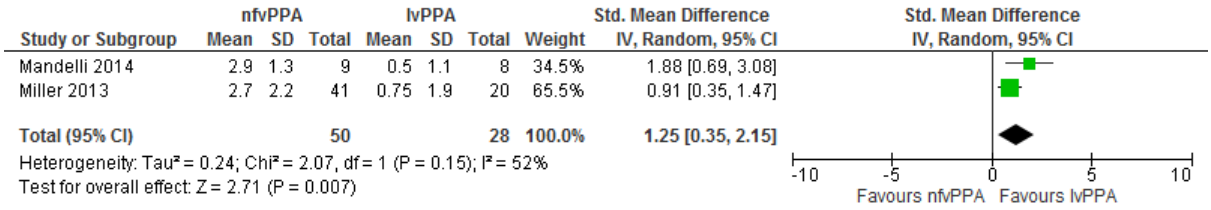

Figure 11-13: Forest plot of comparison: 7 nfvPPA vs lvPPA, outcome: 7.2 MSE AOS rating scale.

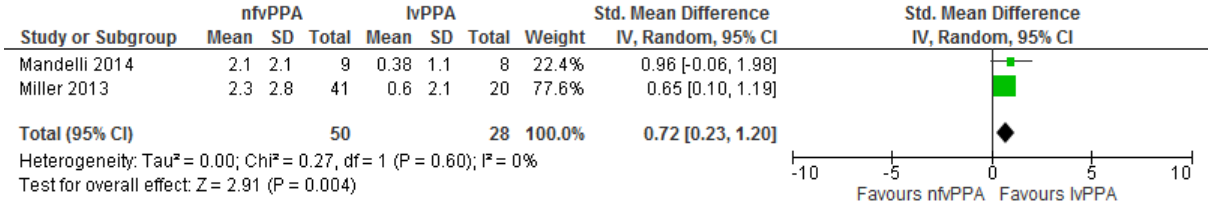

Figure 11-14: Forest plot of comparison: 7 nfvPPA vs lvPPA, outcome: 7.3 MSE Dysarthria Rating Scale.

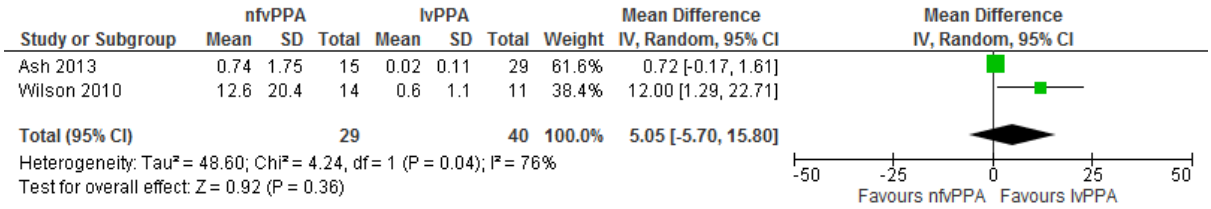

Figure 11-15: Forest plot of comparison: 7 nfvPPA vs lvPPA, outcome: 7.4 Phonetic errors per 100 words.

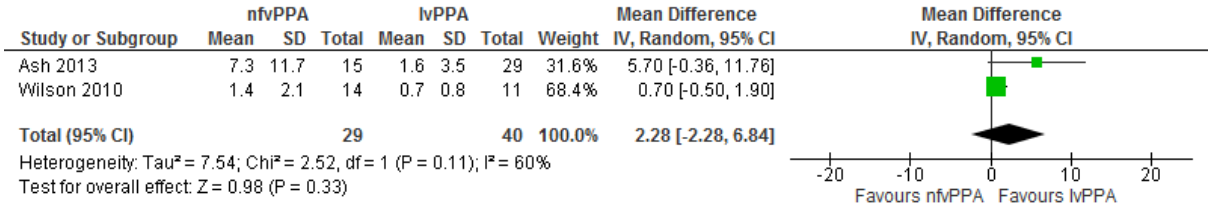

Figure 11-16: Forest plot of comparison: 7 nfvPPA vs lvPPA, outcome: 7.5 Phonemic errors per 100 words.

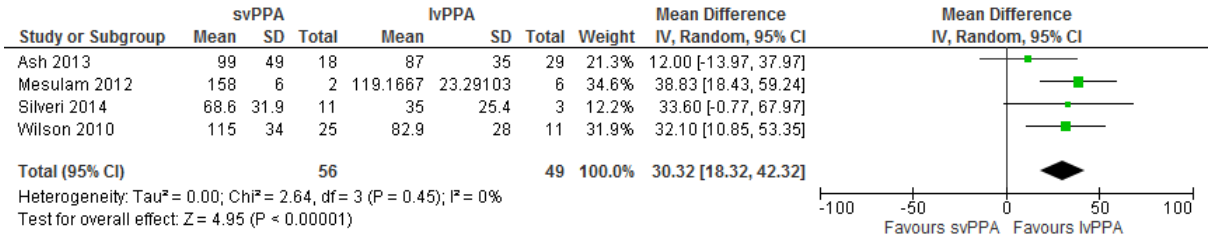

Figure 11-17: Forest plot of comparison: 8 svPPA vs lvPPA, outcome: 8.1 words/minute.

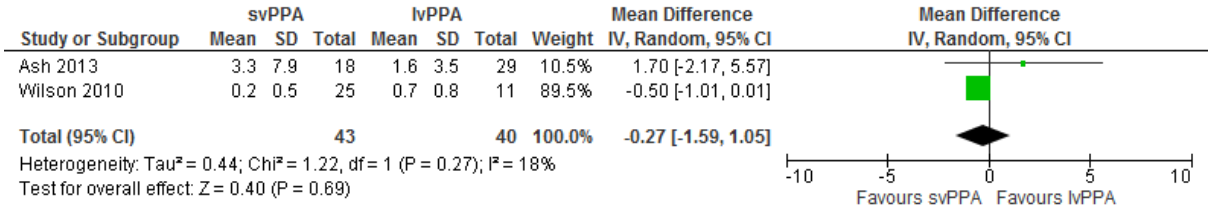

Figure 11-18: Forest plot of comparison: 8 svPPA vs lvPPA, outcome: 8.2 Phonemic errors per 100 words.

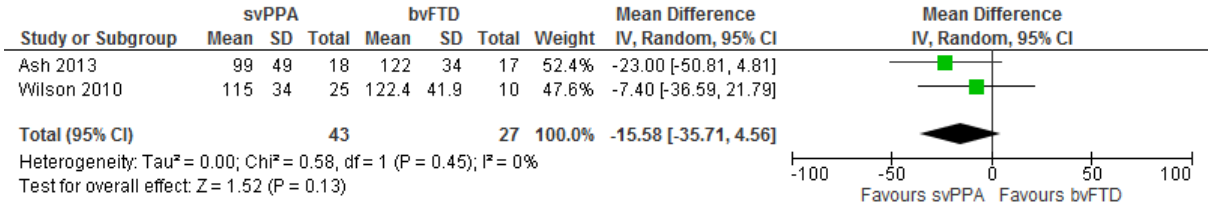

Figure 11-19: Forest plot of comparison: 9 svPPA vs bvFTD, outcome: 9.1 words/minute.

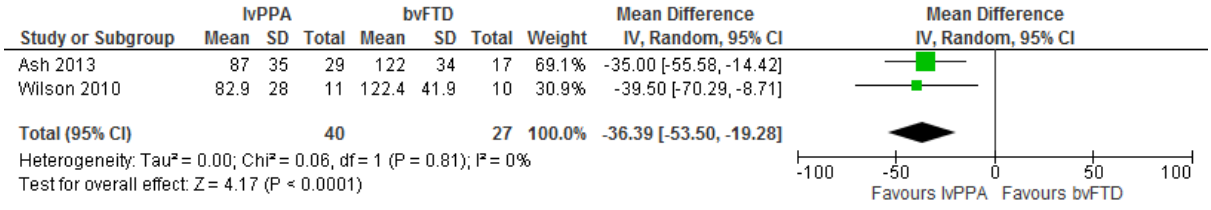

Figure 11-20: Forest plot of comparison: 10 lvPPA vs bvFTD, outcome: 10.1 words/minute.

12 Appendix A – Perceptual ratings of each subgroup

Table 12-1: Frequency and severity of abnormal speech characteristics in healthy controls

Speech subsystem and feature	Frequency (%)	Unremarkable	Subclinical	Mild	Moderate	Severe
Pitch						
Monopitch	9 (38)	15	8	1	0	0
Pitch breaks	0 (0)	24	0	0	0	0
Voice tremor	4 (17)	20	3	1	0	0
Respiration						
Audible inspiration	0 (0)	24	0	0	0	0
Loudness						
Monoloudness	5 (21)	19	3	2	0	0
Loudness decay	0 (0)	24	0	0	0	0
Prosody						
Speech rate ϕ	1 (4)	23	1	0	0	0
Variable rate	1 (4)	23	1	0	0	0
Short phrases	1 (4)	23	1	0	0	0
Reduced stress	3 (13)	21	3	0	0	0
Prolonged intervals	0 (0)	24	0	0	0	0
Equal and excess stress	0 (0)	24	0	0	0	0
Voice						
Hoarse	11 (46)	13	6	4	1	0
Breathy	6 (25)	18	4	2	0	0
Strained-strangled	3 (13)	21	3	0	0	0
Articulation/phonology						
Imprecise consonants	1 (4)	23	1	0	0	0
Prolonged phonemes	0 (0)	24	0	0	0	0
Repeated phonemes	1 (4)	23	0	1	0	0
Irregular articulatory breakdowns	2 (8)	22	2	0	0	0
Vowel distortions	0 (0)	24	0	0	0	0
Increasing errors with increasing length	3 (13)	21	2	1	0	0
Groping	0 (0)	24	0	0	0	0
Phonemic errors	0 (0)	24	0	0	0	0
Fluency						
False starts	2 (8)	22	1	1	0	0
Resonance						
Hypernasality	9 (38)	15	8	1	0	0
Hyponasality	2 (8)	22	2	0	0	0
DDK						
Speed	11 (46)	13	10	1	0	0
Regularity	7 (29)	17	7	0	0	0

Note: DDK = diadochokinetic rate; ϕ = Ratings of severity refer to reduced rate of speech – 2 HC participants presented with subclinical increased speech rate

Table 12-2: Frequency and severity of abnormal speech characteristics in bvFTD

Speech subsystem and feature	Frequency (%)	Unremarkable	Subclinical	Mild	Moderate	Severe
Pitch						
Monopitch	12 (52)	10	6	2	4	0
Pitch breaks	0 (0)	22	0	0	0	0
Voice tremor	5 (22)	17	3	1	1	0
Respiration						
Audible inspiration	1 (4)	21	1	0	0	0
Loudness						
Monoloudness	11 (48)	11	6	4	1	0
Loudness decay	0 (0)	22	0	0	0	0
Prosody						
Speech rate ϕ	12 (55)	10	7	4	1	0
Variable rate	7 (30)	15	3	3	1	0
Short phrases	11 (48)	11	5	3	3	0
Reduced stress	10 (43)	12	3	6	1	0
Prolonged intervals	15 (65)	7	7	5	2	1
Equal and excess stress	4 (17)	18	2	2	0	0
Voice						
Hoarse	17 (74)	5	11	4	2	0
Breathy	10 (43)	12	9	1	0	0
Strained-strangled	12 (52)	10	8	3	1	0
Articulation/phonology						
Imprecise consonants	8 (35)	14	6	0	2	0
Prolonged phonemes	5 (22)	17	1	3	1	0
Repeated phonemes	5 (22)	17	2	2	1	0
Irregular articulatory breakdowns θ	2 (9)	18	2	0	0	0
Vowel distortions	3 (13)	19	1	1	1	0
Increasing errors with increasing length θ	5 (22)	16	3	2	0	0
Groping	3 (13)	19	3	0	0	0
Phonemic errors	5 (22)	17	5	0	0	0
Fluency						
False starts	5 (22)	17	3	1	1	0
Resonance						
Hypernasality	9 (39)	13	5	3	1	0
Hyponasality	2 (9)	20	1	1	0	0
DDK						
Speed	17 (77)	5	8	6	3	0
Regularity	13 (57)	9	8	3	2	0

Note: Asterisks denote significantly more severe impairment at * $p<0.05$, ** $p<0.01$, *** $p<0.001$ than $^{\beta}$healthy controls, ^{a}bvFTD, ^{b}svPPA, ^{c}nfvPPA, ^{d}lvPPA; ϕ = Ratings of severity refer to reduced rate of speech – 2 bvFTD participants presented with subclinical increased speech rate; DDK = diadochokinetic rate

Table 12-3: Frequency and severity of abnormal speech characteristics in svPPA

Speech subsystem and feature	Frequency (%)	Unremarkable	Subclinical	Mild	Moderate	Severe
Pitch						
Monopitch θ	4 (50)	3	2	2	0	0
Pitch breaks	0 (0)	8	0	0	0	0
Voice tremor	1 (13)	7	0	1	0	0
Respiration						
Audible inspiration	1 (13)	7	1	0	0	0
Loudness						
Monoloudness θ	4 (50)	3	2	2	0	0
Loudness decay	0 (0)	8	0	0	0	0
Prosody						
Speech rate θ	3 (57)	4	3	0	0	0
Variable rate θ	2 (25)	5	2	0	0	0
Short phrases θ	4 (50)	3	4	0	0	0
Reduced stress θ	4 (50)	3	2	2	0	0
Prolonged intervals θ	6 (75)	1	4	2	0	0
Equal and excess stress θ	0 (0)	7	0	0	0	0
Voice						
Hoarse	3 (38)	5	2	1	0	0
Breathy	4 (50)	4	2	2	0	0
Strained-strangled	2 (25)	6	2	0	0	0
Articulation/phonology						
Imprecise consonants	1 (13)	7	1	0	0	0
Prolonged phonemes	1 (13)	7	1	0	0	0
Repeated phonemes	2 (25)	6	2	0	0	0
Irregular articulatory breakdowns	1 (13)	7	1	0	0	0
Vowel distortions	2 (25)	6	2	0	0	0
Increasing errors with increasing length	2 (25)	5	2	0	0	0
Groping	0 (0)	8	0	0	0	0
Phonemic errors	1 (13)	7	1	0	0	0
Fluency						
False starts	4 (50)	4	3	1	0	0
Resonance						
Hypernasality	5 (63)	3	3	2	0	0
Hyponasality	0 (0)	8	0	0	0	0
DDK						
Speed	7 (88)	1	5	2	0	0
Regularity	7 (88)	1	5	2	0	0

Note: Asterisks denote significantly more severe impairment at * $p<0.05$, ** $p<0.01$, *** $p<0.001$ than [β]healthy controls, [a]bvFTD, [b]svPPA, [c]nfvPPA, [d]lvPPA; θ = Analysis of feature limited to seven participants due to severity of impairment of one participant; DDK = diadochokinetic rate

Table 12-4: Frequency and severity of abnormal speech characteristics in nfvPPA

Speech subsystem and feature	Frequency (%)	Unremarkable	Subclinical	Mild	Moderate	Severe
Pitch						
Monopitch θ	3 (75)	0	0	1	1	1
Pitch breaks θ	0 (0)	3	0	0	0	0
Voice tremor θ	0 (0)	3	0	0	0	0
Respiration						
Audible inspiration θ	2 (50)	1	1	0	1	0
Loudness						
Monoloudness θ	3 (75)	0	0	2	0	1
Loudness decay θ	3 (75)	0	2	1	0	0
Prosody						
Speech rate θ	3 (100)	0	0	1	2	0
Variable rate θ	0 (0)	3	0	0	0	0
Short phrases θ	2 (66.6)	1	0	0	2	0
Reduced stress θ	3 (100)	0	1	0	2	0
Prolonged intervals θ	2 (66.6)	1	0	1	1	0
Equal and excess stress θ	2 (66.6)	1	0	0	2	0
Voice						
Hoarse	3 (75)	1	0	1	2	0
Breathy	3 (75)	1	2	1	0	0
Strained-strangled	1 (25)	3	1	0	0	0
Articulation/phonology						
Imprecise consonants	3 (75)	1	0	0	2	1
Prolonged phonemes	4 (100)	0	1	0	3	0
Repeated phonemes	1 (25)	3	0	1	0	0
Irregular articulatory breakdowns	1 (25)	3	0	0	1	0
Vowel distortions	3 (75)	1	0	1	2	0
Increasing errors with increasing length θ	2 (66.6)	1	0	1	1	0
Groping θ	2 (66.6)	1	1	1	0	0
Phonemic errors θ	0 (0)	3	0	0	0	0
Fluency						
False starts θ	0 (0)	3	0	0	0	0
Resonance						
Hypernasality	2 (50)	2	0	0	2	0
Hyponasality	1 (25)	3	1	0	0	0
DDK						
Speed	4 (100)	0	0	1	2	1
Regularity	3 (75)	1	1	1	1	0

Note: Asterisks denote significantly more severe impairment at * $p<0.05$, ** $p<0.01$, *** $p<0.001$ than [β]healthy controls, [a]bvFTD, [b]svPPA, [c]nfvPPA, [d]lvPPA; θ = Analysis of feature limited to three participants due to severity of impairment of one participant; DDK = diadochokinetic rate

Table 12-5: Frequency and severity of abnormal speech characteristics in lvPPA

Speech subsystem and feature	Frequency (%)	Unremarkable	Subclinical	Mild	Moderate	Severe
Pitch						
Monopitch	5 (56)	4	3	2	0	0
Pitch breaks	1 (11)	8	1	0	0	0
Voice tremor	0 (0)	9	0	0	0	0
Respiration						
Audible inspiration	2 (22)	7	2	0	0	0
Loudness						
Monoloudness	4 (44)	5	2	2	0	0
Loudness decay	1 (11)	8	0	1	0	0
Prosody						
Speech rate	5 (56)	4	4	0	1	0
Variable rate	4 (44)	5	2	2	0	0
Short phrases	4 (44)	5	1	1	2	0
Reduced stress	4 (44)	5	2	2	0	0
Prolonged intervals	3 (33)	6	1	1	1	0
Equal and excess stress	2 (22)	7	2	0	0	0
Voice						
Hoarse	7 (78)	2	5	2	0	0
Breathy	6 (67)	3	3	2	1	0
Strained-strangled	5 (56)	4	3	1	1	0
Articulation/phonology						
Imprecise consonants	4 (44)	5	2	1	1	0
Prolonged phonemes	3 (33)	6	2	0	1	0
Repeated phonemes	7 (78)	2	2	4	1	0
Irregular articulatory breakdowns	4 (44)	5	2	1	1	0
Vowel distortions	1 (11)	8	0	0	1	0
Increasing errors with increasing length θ	5 (56)	3	1	2	2	0
Groping	4 (44)	5	2	1	1	0
Phonemic errors	6 (67)	3	2	3	1	0
Fluency						
False starts	8 (89)	1	2	4	2	0
Resonance						
Hypernasality	2 (22)	7	2	0	0	0
Hyponasality	1 (11)	8	1	0	0	0
DDK						
Speed	9 (100)	0	7	1	1	0
Regularity	5 (56)	4	2	1	1	1

Note: Asterisks denote significantly more severe impairment at * $p<0.05$, ** $p<0.01$, *** $p<0.001$ than $^{\beta}$healthy controls, ^{a}bvFTD, ^{b}svPPA, ^{c}nfvPPA, ^{d}lvPPA; DDK = diadochokinetic rate

13 Appendix B – Percent agreement of perceptual ratings

Table 13-1: Percent agreement between two blind raters prior to consensus ratings

Speech subsystem and feature	Percent agreement (%)
Pitch	
Monopitch	57.75
Pitch breaks	98.63
Voice tremor	87.67
Respiration	
Audible inspiration	90.41
Loudness	
Monoloudness	63.01
Loudness decay	94.52
Prosody	
Speech rate	61.64
Variable rate	79.45
Short phrases	68.49
Reduced stress	75.34
Prolonged intervals	65.75
Equal and excess stress	87.67
Voice	
Hoarse	52.05
Breathy	52.05
Strained-strangled	60.27
Articulation/phonology	
Imprecise consonants	79.45
Prolonged phonemes	84.93
Repeated phonemes	80.82
Irregular articulatory breakdowns	84.93
Vowel distortions	84.93
Increasing errors with increasing length	80.82
Groping	83.56
Phonemic errors	83.56
Fluency	
False starts	83.56
Resonance	
Hypernasality	67.12
Hyponasality	93.15
DDK	
Speed	69.86
Regularity	80.82

Note: DDK = diadochokinetic rate.