Mechanisms of auditory signal decoding in the progressive aphasias

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Declaration

I, Christopher J. D. Hardy, confirm that the work presented in this thesis is my own. Where information is derived from other sources I confirm that this has been referenced appropriately.

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Abstract

The primary progressive aphasias (PPA) are a diverse group of neurodegenerative disorders that selectively target brain networks mediating language. The pathophysiology of PPA remains poorly understood, but emerging evidence suggests that deficits in auditory processing accompany and may precede language symptoms in these patients. In four studies, I have probed the pathophysiology of auditory signal decoding in patient cohorts representing all major PPA syndromes – nonfluent variant PPA (nfvPPA), semantic variant PPA (svPPA), and logopenic variant PPA (lvPPA) – in relation to healthy age-matched controls. In my first experiment, I presented sequences of spoken syllables manipulated for temporal regularity, spectrotemporal structure and entropy. I used voxel-based morphometry to define critical brain substrates for the processing of these attributes, identifying correlates of behavioural performance within a cortico-subcortical network extending beyond canonical language areas. In my second experiment, I used activation functional magnetic resonance imaging (fMRI) with the same stimuli. I identified network signatures of particular signal attributes: nfvPPA was associated with reduced activity in anterior cingulate for processing temporal irregularity; lvPPA with reduced activation of posterior superior temporal cortex for processing spectrotemporal structure; and svPPA with reduced activation of caudate and anterior cingulate for processing signal entropy. In my third experiment, I manipulated the auditory feedback via which participants heard their own voices during speech production. Healthy control participants spoke significantly less fluently under delayed auditory feedback, but patients with nfvPPA and lvPPA were affected significantly less. In my final experiment, I probed residual capacity for dynamic auditory signal processing and perceptual learning in PPA, using sinewave speech. Patients with nfvPPA and lvPPA showed severely attenuated learning to the degraded stimuli, while patients with svPPA showed intact early perceptual processing, but deficient integration of semantic knowledge. Together, these experiments represent the most concerted and comprehensive attempt to date to define the pathophysiology of auditory signal decoding in PPA.

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Abbreviations

$A\beta_{1-42}$	Amyloid-$Beta_{1-42}$ protein
AAF	Altered auditory feedback
ACC	Anterior cingulate cortex
AD	Alzheimer's disease
AFC	Alternative forced-choice
AG	Angular gyrus
ANOVA	Analysis of variance
Ant	Anterior
ASA	Auditory scene analysis
BA	Broca's aphasia
BNT	Boston naming test
BOLD	Blood oxygen level dependent
BPVS	British picture vocabulary scale
BST	Baxter spelling test
bv/bvFTD	behavioural variant frontotemporal dementia
C	Controls
C9orf72	Chromosome 9 open reading frame 72
Caud	Caudate
CBD	Corticobasal degeneration
CI	Confidence interval
CSF	Cerebro-spinal fluid
DAF	Delayed auditory feedback
DARTEL	Diffeomorphic anatomical registration through exponentiated lie algebra
dB	Decibel
DLPFC	Dorsolateral prefrontal cortex
EPI	Echo planar image
fMRI	Functional magnetic resonance imaging
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
FUS	Fused in sarcoma
FWE	Family-wise error
FWHM	Full-width-half-maximum
GDA	Graded difficulty arithmetic
GNT	Graded naming test
GRN	Granulin
HG	Heschl's gyrus
IFG	Inferior frontal gyrus
ISE	Irrelevant sound effect
ITS	Inferior temporal sulcus
LH	Left-handed
lv/lvPPA	logopenic variant primary progressive aphasia
M1	Primary motor cortex
MEG	Magnetoencephalography
Mil	Mild
MMN	Mismatch negativity
MMSE	Mini-mental state examination
MNI	Montreal neurological institute
MNI	Montreal Neurological Institute
Mod	Moderate
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
MRT	Modified rhyme test
MTG	Middle temporal gyrus
MTL	Medial temporal lobe

N	Normal
NA	Not available
NAF	Natural auditory feedback
nfv/nfvPPA	nonfluent variant primary progressive aphasia
OFC	Orbitofrontal cortex
PAC	Primary auditory cortex
PALPA	Psycholinguistic assessments of language processing in aphasia
PCC	Posterior cingulate cortex
PCu	Precuneus
PD	Parkinson's disease
PET	Positron emission tomography
PHW	Per hundred words
PIQ	Performance IQ
PPA	Primary progressive aphasia
PPA-NOS	Primary progressive aphasia – not otherwise specified
PrG	Precentral gyrus
PSP	Progressive supranuclear palsy
PT	Planum temporale
PTA	Pure tone audiometry
PWM	Phonological working memory
RH	Right-handed
rms	Root mean square
RMT	Recognition memory test
ROI	Region of interest
SD	Semantic dementia
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SPECT	Single-photon emission computed tomography
SPL	Superior parietal lobule
SPM	Statistical parametric mapping
STM	Short-term memory
STS/G	Superior temporal sulcus/gyrus
sv/svPPA	semantic variant primary progressive aphasia
SVC	Small volume correction
tAD	typical Alzheimer's disease
TDP-43	Transactive response DNA-binding protein 43
TIV	Total intracranial volume
TPO	Temporo-parieto-occipital junction
TSA	Transcortical sensory aphasia
tvPPA	temporal variant primary progressive aphasia
VBM	Voxel-based morphometry
VIQ	Verbal IQ
VOSP	Visual object and space perception
WA	Wernicke's aphasia
WASI	Wechsler abbreviated scale of intelligence
WM	Working memory
WPM	Words per minute

1. General introduction

1.1. The challenge of diagnosis and stratification in primary progressive aphasia

"An account of aphasia … must go beyond the description of pathological phenomena and their grouping into clinical types … It must be an attempt, through an increasingly deeper-penetrating description of phenomenology, to achieve an understanding of the pathological processes and their relationships".

Arnold Pick, 1931 (published posthumously)

'Aphasia' is a broad term, defined as a language and communication disorder caused by damage to the brain. Broadly, the syndrome can be caused by an acute episode, such as a traumatic brain injury or a stroke, or by an underlying neurodegenerative process. This thesis attempts to extend current understanding of the major neurodegenerative processes associated with aphasia: the primary progressive aphasias (PPA). These are typically, and unsurprisingly, characterised as 'language-led dementias', and the earliest medical observation of PPA came around 125 years ago, with the French psychiatrist Paul Sérieux (1864-1947) describing for the first time a case of dementia that seemed specifically to manifest in problems with language (Sérieux, 1893). The Czech psychiatrist Arnold Pick (1851-1924) saw similar cases and wrote extensively on 'amnestic aphasia': a syndrome that he linked to left temporal lobe atrophy and that we recognise today as the semantic variant of PPA or semantic dementia (see below). Their contemporary, the English neurologist Henry Head (1861-1940), studied aphasia expansively and again used a framework of classifications that are still recognised today (e.g. "semantic aphasia").

Our understanding of the degenerative aphasias has improved dramatically over the last century, helped by incredible improvements in neuroimaging and molecular techniques. Importantly, however, the approach taken by these three pioneering clinicians is just as relevant today as it was in their own time. Arnold Pick and Henry Head, in particular, took a very physiological approach to language disorders, delineated clearly in Pick's writings on aphasia, an excerpt from which I have included at the beginning of this Chapter. He argued that in order for us to fully understand aphasia, it is crucial to go beyond the basic clinical phenotype: to characterise the entire disease entity and to relate these deficiencies

to their pathophysiological underpinnings. One-hundred and twenty-five years later, this is the argument that I am attempting to develop in relation to the PPAs in this thesis. These disorders are typically defined as 'language-led', but there is now a large body of literature emerging, suggesting that in fact these may be disorders of generic signal processing which go beyond language.

Forty years ago, Elizabeth Warrington wrote the first description of semantic dementia, now known as semantic variant PPA (svPPA) (Warrington, 1975). In 1982, Marsel Mesulam wrote a seminal paper of 8 cases with PPA (Mesulam, 1982), in which he made the distinction between fluent (i.e. svPPA) and nonfluent variants (i.e. nfvPPA). The logopenic variant was most recently described as a separate entity from nfvPPA for the first time (Gorno-Tempini *et al.*, 2004, 2008), and consensus criteria written in 2011 are the current 'gold-standard' for diagnosis of PPA (Gorno-Tempini *et al.*, 2011). According to these criteria, PPA comprises these three major syndromes (Gorno-Tempini *et al.*, 2011): nfvPPA, presenting with impaired speech production and/or agrammatism; svPPA, presenting with impaired single word comprehension and vocabulary loss due to progressive erosion of conceptual knowledge; and lvPPA, presenting with word-finding difficulty and impaired phonological verbal working memory. An experienced neurologist is usually required for an accurate diagnosis of one of the PPA variants to be made, and there are considerable problems with nosology and classification associated with each syndrome. As a consequence of this, PPA is probably under-diagnosed and under-recognised, especially in the early stages. Accurate and early identification is the key for prognostication, molecular stratification, research, and recommendation of appropriate therapies. In particular, molecular stratification will become crucial with putative future clinical trials of new medicines on the horizon (Croot, 2009; Spinelli *et al.*, 2017).

Critically, a significant proportion of cases presenting with a primary progressive aphasic syndrome do not fit any of the current consensus criteria and therefore are labelled as primary progressive aphasia – not otherwise specified (PPA-NOS). Estimates vary across case series, but a substantial minority of patients are consistently put into this PPA-NOS category (Rohrer *et al.*, 2011; Mesulam *et al.*, 2012, 2014b; Harris *et al.*, 2013; Matias-Guiu *et al.*, 2014; Wicklund *et al.*, 2014; Botha *et al.*, 2015). Automatic clustering algorithms fail to

accurately differentiate between lvPPA and nfvPPA on the basis of semantic, language, and non-linguistic cognitive scores (Hoffman *et al.*, 2017). One series noted that 41.3% of their 46 patients with PPA did not meet diagnostic criteria for any of the major syndromes (Sajjadi *et al.*, 2012), and my own impression is that between 10 and 20% of patients I have seen with PPA are unclassifiable according to the current criteria.

These problems with classification are significant, as they imply that standard linguistic tests may not be sufficient or adequate to capture the phenomenology and pathophysiology of these heterogeneous syndromes. These leaves open the possibility that the language symptoms regarded until now as cardinal features of the syndromes may in fact be downstream corollaries of a more fundamental mechanism: auditory processing. In this introduction, I will briefly describe each of the main syndromes in relation to the current consensus criteria, with reference to clinical presentation, neuropsychological features, neuroanatomy and molecular and genetic pathologies. I will then turn to consideration of the neuroanatomy and neuropsychology of auditory processing in the healthy brain, before briefly synthesising the literature on auditory processing deficits in the PPA syndromes. My central tenet is this: the PPAs are general disorders of auditory signal processing, rather than specific disorders of language processing.

1.1.1. Diagnosis of semantic variant PPA

Semantic variant PPA is characterised by a generic loss of multimodal conceptual knowledge (Knibb & Hodges, 2005; Garrard & Carroll, 2006), reflected by anomia, single-word comprehension deficits and impaired object knowledge. Semantic deficits in svPPA have been shown across the full range of conceptual and sensory modalities, including olfaction (Luzzi *et al.*, 2007; Piwnica-Worms *et al.*, 2010), flavour (Piwnica-Worms *et al.*, 2010), faces and names (Snowden, 2004), object use (Hodges, 2000), and nonverbal sounds (Bozeat *et al.*, 2000; Goll *et al.*, 2012b).

A key feature of svPPA is in asking the meaning of previously familiar words, and patients tend to have fluent, garrulous, circumlocutory speech that can be strikingly devoid of content. Analysis of their speech shows reliance on high-frequency words as well as frequent use of demonstratives (Wilson *et al.*, 2010b; Fraser *et al.*, 2014). Surface dyslexia is a common feature of svPPA, reflecting an intact phonological route to reading

compensating for the impaired semantic route that stores irregular word knowledge in the healthy brain (Woollams *et al.*, 2007). This will manifest in patients making 'regularisation errors', for instance reading /'aɪlənd/ ("island") as /'ɪzlənd/.

For a diagnosis of svPPA to be made, the current diagnostic criteria stipulate that the patient must present with two main deficits: impaired confrontation naming and impaired single-word comprehension. If the patient presents with isolated problems with naming, this would be regarded as an atypical form of PPA: primary progressive anomia (Ingles *et al.*, 2007). If both impairments are present, the criteria stipulate that the patient must have three of the following four symptoms: i) impaired object knowledge (particularly for low-frequency items); ii) surface dysgraphia/ dyslexia; iii) spared repetition; and iv) spared grammar and motor speech production (see Table 1.1).

Both of: 1. Impaired confrontation naming 2. Impaired single-word comprehension
3 of: 1. Impaired object knowledge, particularly for low-frequency or low-familiarity items 2. Surface dyslexia or dysgraphia 3. Spared repetition 4. Spared speech production (grammar and motor speech)
At least 1 of: 1. Predominant anterior temporal lobe atrophy 2. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

Table 1.1. Consensus criteria for a diagnosis of svPPA.

Hallmark atrophy associated with svPPA is knife-blade anterior temporal lobe damage lateralised to the dominant hemisphere that is particularly severe at the temporal pole and fusiform cortex, also affecting mesial temporal structures. (Fletcher & Warren, 2011; Gorno-Tempini *et al.*, 2011) (Figure 1.1). Large case studies consistently report that the vast majority of patients with svPPA have FTLD TDP-43 pathology at post-mortem (Rohrer *et al.*, 2011; Harris *et al.*, 2013; Chare *et al.*, 2014; Spinelli *et al.*, 2017). Pick's disease, FUS, Alzheimer's and tau represent the significant minority of alternative pathologies (Rohrer *et al.*, 2011; Chare *et al.*, 2014). Neurofilament light chain concentration is elevated in FTD phenotypes as compared to Alzheimer's and other neurodegenerative diseases in cerebrospinal fluid (Scherling *et al.*, 2014) and serum (Rohrer *et al.*, 2016).

Cases of svPPA are rarely genetic, though a similar syndrome can occur with MAPT mutations, which are typically associated with behavioural variant FTD. This syndrome is associated with a specific language phenotype that is qualitatively similar to that seen in svPPA (Hardy *et al.*, 2015), and while the leading symptoms are usually behavioural, there are instances in which language decline can be the leading symptom.

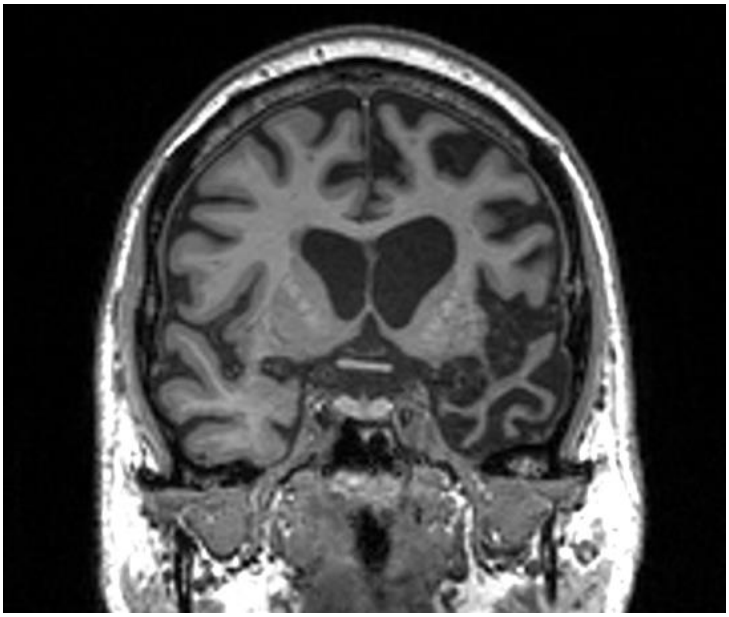

Figure 1.1. Coronal volumetric T1-weighted MRI of a patient with svPPA. The scan shows characteristic knife-blade atrophy of the left anterior lobe. The left hemisphere is on the right side.

1.1.2. Diagnosis of nonfluent variant PPA

The speech of patients with nfvPPA is characteristically hesitant and malformed, with frequent stuttering and phonological speech errors (Gunawardena *et al.*, 2010; Wilson *et al.*, 2010b; Yunusova *et al.*, 2016; Cordella *et al.*, 2017). Agrammatism is also common in expressive speech production, and while the two cardinal features of speech apraxia and agrammatism are typically comorbid, primary progressive apraxia of speech is sometimes recognised as a separate entity to the agrammatic variant of nonfluent aphasia (Southwood & Chatterjee, 1998; Ricci *et al.*, 2008; Josephs *et al.*, 2012). Speech is typically devoid of function words and contains inappropriate verb usage, both of which are typical of the grammatical errors made by patients (Wilson *et al.*, 2010b).

Patients may show impairment at the level of sentence comprehension (Grossman *et al.*, 2005; Peelle *et al.*, 2007, 2009). Spared single-word comprehension is emphasised in the criteria, but can in fact be impaired in nfvPPA, particularly in patients with high levels of agrammatism (Rohrer *et al.*, 2010d). Similarly, confrontation naming can be affected in nfvPPA (McMillan *et al.*, 2004), perhaps disproportionately for verbs relative to nouns (Thompson *et al.*, 2012) but object knowledge should be preserved.

According to the current consensus criteria for nfvPPA, the patient must present with either agrammatism in spoken or written language production, or apraxia of speech (defined as effortful, halting speech with inconsistent speech sound errors and distortions). If one of these main features is present, they must also show two of the following three subsidiary features: i) impaired comprehension of syntactically complex sentences; ii) spared single-word comprehension; or iii) spared object knowledge (see Table 1.2).

Table 1.2. Consensus criteria for a diagnosis of nfvPPA.

1 of: 1. Agrammatism in language production 2. Effortful, halting speech with inconsistent speech sound errors and distortions (AOS)
2 of: 1. Impaired comprehension of syntactically complex sentences 2. Spared single-word comprehension 3. Spared object knowledge
At least 1 of: 1. Predominant left posterior fronto-insular atrophy on MRI 2. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET

Estimates vary, but a significant proportion of patients with nfvPPA develop symptoms of Parkinsonism (Kremen *et al.*, 2011; Graff-Radford *et al.*, 2012; Doherty *et al.*, 2013; Park *et al.*, 2017) that overlap with progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Many patients with nfvPPA present with orofacial apraxia – an inability of the mouth to form movements like coughing, yawning or whistling on demand (Rohrer *et al.*, 2010c; Botha *et al.*, 2014).

nfvPPA is associated with atrophy of the dominant hemisphere along a fronto-insular gradient (Grossman *et al.*, 1996; Gorno-Tempini *et al.*, 2011) (Figure 1.2). The underlying proteinopathy is more heterogeneous than seen in svPPA. One recent case

series suggested that 88% of cases with nfvPPA had underlying tau pathology (Spinelli *et al.*, 2017), but other series have reported more balanced representations of tau and TDP-43 pathologies (Rohrer *et al.*, 2011). The nature of the clinical phenotype can to an extent predict the molecular pathology: presence of motor symptoms like orofacial apraxia or Parkinsonism is more likely to be indicative of underlying tau pathology (Deramecourt *et al.*, 2010; Gorno-Tempini *et al.*, 2011).

A minority of cases of nfvPPA have a relevant family history of a disorder in the frontotemporal lobar degeneration (FTLD) spectrum (Snowden *et al.*, 2006; Mesulam *et al.*, 2007; Beck *et al.*, 2008; Rohrer *et al.*, 2009a). Mutations in the *GRN* gene are the most common cause, and there is some speculation that PPA-GRN may represent a distinct clinical phenotype characterised by severe agrammatism without apraxia of speech, and anomia and prominent word-finding pauses (Snowden *et al.*, 2007; Rohrer *et al.*, 2010a). Mutations in the *C9ORF72* gene account for a smaller number of cases of nfvPPA (Hsiung *et al.*, 2012; Mahoney *et al.*, 2012; Simon-Sanchez *et al.*, 2012).

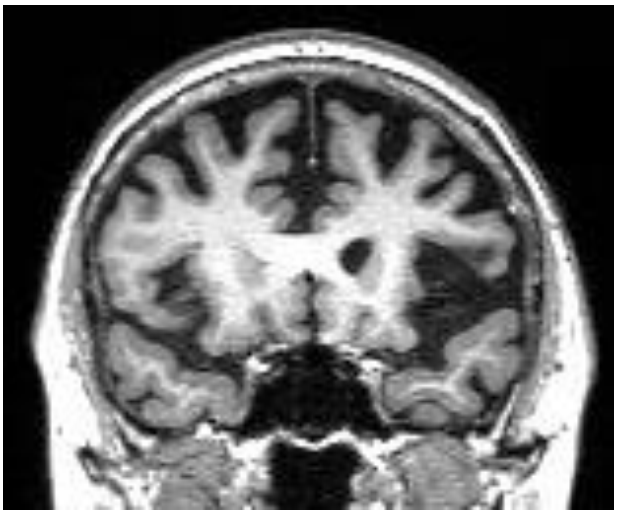

Figure 1.2. Coronal volumetric T1-weighted MRI of a patient with nfvPPA. The scan shows typical asymmetric atrophy of left insula and opercular inferior frontal gyrus. The left hemisphere is on the right side.

1.1.3. Diagnosis of logopenic variant PPA

The spontaneous speech of somebody with lvPPA is characterised by word-finding pauses and phonemic paraphasias. In this sense, it is dissociable from the fluent speech of someone with svPPA, and the severely distorted motor speech of somebody with nfvPPA:

the speech phenotype falls somewhere between the two in terms of fluency, distortions and syntactic errors (Wilson *et al.*, 2010b). Phonemic paraphasias can induce morphological grammatical errors in speech and indeed written sentences, but crucially these grammatical errors are not typically representative of frank agrammatism. Impaired repetition of sentences and phrases is emphasised in the consensus criteria for lvPPA.

Table 1.3. Consensus criteria for a diagnosis of lvPPA.

Both of: 1. Impaired single-word retrieval in spontaneous speech and naming 2. Impaired repetition of sentences and phrases
3 of: 1. Speech (phonologic) errors in spontaneous speech and naming 2. Spared single-word comprehension and object knowledge 3. Spared motor speech 4. Absence of frank agrammatism
At least 1 of: 1. Predominant left posterior perisylvian or parietal atrophy on MRI 2. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

The cardinal deficit in lvPPA is arguably still yet to be defined. Current research, however, emphasises the role of phonological working memory – the short-term storage system for auditory information. This manifests in a dissociation between relatively intact repetition for single words, and poorer performance for longer words and sentences, when this phonological store is over-burdened. This deficit is likely to be attributable to temporo-parietal junction damage (Rohrer *et al.*, 2010b; Henry *et al.*, 2016), and consensus criteria emphasise that atrophy should occur in dominant posterior peri-Sylvian cortex (Gorno-Tempini *et al.*, 2011); see Figure 1.3. The phenotype of lvPPA is considered as an atypical form of Alzheimer's disease, reflecting the fact that the pathology associated with lvPPA is most likely to be the amyloid plaques and tau tangles that are hallmarks of Alzheimer's pathology (Henry & Gorno-Tempini, 2010; Rohrer *et al.*, 2011; Matías-Guiu *et al.*, 2015; Magnin *et al.*, 2016; Spinelli *et al.*, 2017). Cerebrospinal fluid profiles of patients with lvPPA are also typically consistent with Alzheimer's pathology (Ikeda *et al.*, 2014).

The consensus criteria for lvPPA emphasise impaired single-word retrieval in spontaneous speech/ naming, together with impaired repetition of sentences and phrases: both must be present. Additionally, the patient must have three of the following four

symptoms: i) speech (phonologic) errors in spontaneous speech and naming; ii) spared single-word comprehension and object knowledge; iii) spared motor speech; and iv) absence of frank agrammatism; see Table 1.3.

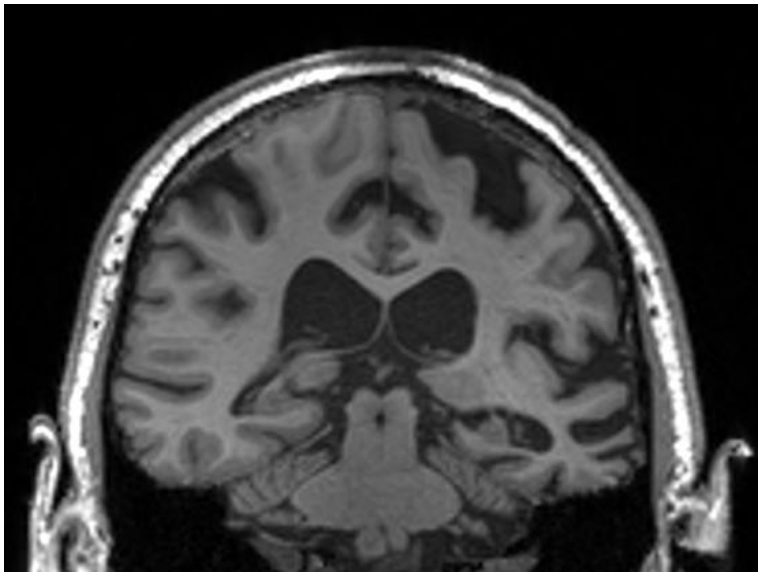

Figure 1.3. Coronal volumetric T1-weighted MRI of a patient with lvPPA. The scan shows characteristic asymmetric atrophy of left tempoparietal cortex. The left hemisphere is on the right side.

1.1.4. The relationship between primary progressive and stroke aphasia

A comprehensive account of the relationship between the degenerative aphasia subtypes and aphasias caused by strokes is beyond the scope of this thesis. Moreover, contrasting the two syndromes is perhaps artificial: comparing a focal lesion (as in stroke) with network-level breakdown (as in PPA) is by no means a direct comparison. However, the fact that constellations of similar symptoms can arise from ostensibly different diseases is of relevance.

First, nfvPPA is broadly comparable to Broca's aphasia (BA) (Broca, 1861), which is characterised by nonfluent speech, agrammatism and relatively intact comprehension. BA is associated, not unsurprisingly, with a lesion to Broca's area: the same IFG region that is affected early on in nfvPPA. lvPPA has no direct counterpart in stroke, although it has been argued that it is most similar to conduction aphasia arising from stroke (Gorno-Tempini *et al.*, 2008). Conduction aphasia is associated with a repetition deficit comparable to that seen in lvPPA, with problems emerging for sentences and phrases. Comprehension of spoken language is also intact, and naming is affected too, which is again consistent with lvPPA

(Mesulam, 2009). The lesion implicated in conduction aphasia affects the arcuate fasciculus, sparing Broca's and Wernicke's areas, but ultimately resulting in a functional disconnection between the two regions. Speech in conduction aphasia is typically fluent (albeit paraphasic), again distinguishing it from the 'nonfluent' logopenic variant.

On anatomical grounds, Wernicke's aphasia (WA) more closely resembles the pattern of atrophy seen (at least initially) in lvPPA: Wernicke's area comprises an area in posterior STG that is completely consistent with lvPPA (see Figure 1.3). However, there are phenotypical differences between WA and lvPPA too: WA is associated with comprehension deficits in spoken and written language, problems with repetition, but fluent spontaneous speech production that is highly paraphasic and circumlocutious (Mesulam, 2009) – making it unlike the speech of somebody with lvPPA which is characterised by frequent word-finding pauses. Indeed, a key difference here is in terms of self-monitoring: patients with lvPPA are typically able to monitor their speech and correct for errors, whereas patients with WA are not. As the syndrome of lvPPA develops, however, this self-monitoring can be lost; 'jargon aphasia' syndromes have been reported to develop in the context of lvPPA (Rohrer *et al.*, 2009b; Caffarra *et al.*, 2013) and patients often lose insight into the fact that what they are saying is incomprehensible to the listener. In WA, research has shown that comprehension deficits are associated with lesions extending to posterior MTG and other extra-Sylvian areas (Robson *et al.*, 2012).

Intriguingly, recent work suggests that the auditory comprehension deficit observed typically in WA may not be limited to linguistic stimuli. One case study observed that a stroke in Wernicke's area resulted in the patient having a remarkable dissociation in terms of intact speech processing relative to severely impaired nonverbal auditory processing (Saygin *et al.*, 2010). Another observed an equally remarkable case of amusia characterised by arrhythmia in a professional musician that was associated with a stroke in left temporo-parietal cortex (Di Pietro *et al.*, 2004). Most recently, Robson and colleagues demonstrated that patients with WA had normal frequency discrimination but significant impairments in terms of frequency and dynamic modulation detection (Robson *et al.*, 2013). The authors argue that the auditory language comprehension impairment that is a cardinal feature of WA

could be subserved by this core auditory processing deficit for temporal and spectrotemporal nonverbal stimuli.

Semantic variant PPA is broadly comparable to the syndrome of transcortical sensory aphasia (TSA). This is characterised by impaired auditory comprehension with intact repetition and fluent speech, arising from posterior temporal lobe atrophy (not implicating Wernicke's area). svPPA, by contrast, is associated with a pan-modal degradation of semantic and conceptual knowledge, and so the specificity of the deficit in TSA to the auditory domain is not comparable here. Phonological processing is assumed to be broadly intact in both svPPA and TSA, distinguishing it from WA (Robson *et al.*, 2012). One additional important point is that despite the similar terminologies, svPPA and semantic aphasia are not synonymous either in terms of their clinical phenotype or neuroanatomical profiles (Jefferies & Lambon Ralph, 2006; Jefferies *et al.*, 2010).

Thus, consideration of the stroke aphasias raises three conclusions that are of central importance to this thesis: i) damage to key areas in the language network results in specific clinical phenotypes; ii) there are broad similarities in terms of language phenotypes with the PPA syndromes; and iii) there is some evidence to suggest that a core auditory processing deficit may subserve some of the language symptoms associated with the stroke aphasias.

1.2. Auditory processing

I now turn to a brief consideration of auditory processing in the healthy brain. This will outline the neuroanatomical and neuropsychological hierarchies that are used for auditory perception, and outline different stages at which impairments can arise, with important corollaries for my consideration of the PPA syndromes in section 1.3.

1.2.1. Auditory processing neuroanatomy

The earliest level of processing of acoustic stimuli begins in the inner ear. Hair cells in the cochlea convert the mechanical energy of sound into electrical impulses in the auditory nerve. Problems at this stage of processing reflect 'peripheral' hearing loss typically associated with deficient hair cell function, and are distinct from 'central' hearing loss that is associated with damage to the cortex itself. From the auditory nerve, information is then

transmitted as neuroelectrochemical activity through a succession of neurons to auditory receptive areas in the cortex. Here, the medial portion of the transverse gyrus of Heschl (Heschl's gyrus; HG) in the superior temporal plane comprises the primary auditory cortex (PAC). There is, however, considerable variability across individuals: PAC accounts for between 16-90% of HG depending upon the individual (Rademacher *et al.*, 2001). The auditory processing pathway then extends laterally through HG into planum temporale (PT), which lies posterior to HG on the superior temporal plane. Both regions show plasticity in relation to auditory experience, e.g. increased grey matter volume of HG (Schneider *et al.*, 2002) with musical training and PT (Zatorre *et al.*, 1998) with absolute pitch.

As auditory processing becomes more complex, two streams are thought to emerge that are analogous to those propounded by the dual stream hypothesis that is widely accepted to apply to the visual system (Mishkin *et al.*, 1983; Goodale & Milner, 1992). For auditory processing, the dorsal and ventral streams are proposed to focus on 'where' and 'what', respectively (Rauschecker & Tian, 2000); a division that has been supported in human studies (Clarke *et al.*, 2000, 2002; Alain *et al.*, 2001; Adriani *et al.*, 2003; Hart *et al.*, 2004). The auditory dorsal 'where' stream, broadly implicated in space and motion processing, extends from the planum temporale to inferior and superior parietal regions, and then on to dorsal frontal areas. The ventral 'what' stream, preferentially involved in processing auditory objects for meaning, projects more anteriorly along the STG and STS to the IFG (Bizley & Cohen, 2013).

Considering speech processing, which might be regarded as a highly specialised form of auditory processing, the ventral stream is thought to be critical for speech recognition and comprehension (Hickok & Poeppel, 2007). The left ventral stream is particularly involved in phonetic discrimination, phonological processing, lexical, semantic and combinatorial processes, whereas the right ventral stream is more associated with voice identification and processing of prosody (Specht, 2014). The dorsal stream is critical for translating speech signals into articulatory representations in the inferior frontal lobe (thus making it critical for speech production as well as speech perception) (Hickok & Poeppel, 2007), and it has been argued that the dorsal stream also contains an auditory feedback loop allowing for online monitoring of speech production (Warren *et al.*, 2005); see Figure 1.4. There is still some

controversy as to whether there are just two streams for auditory processing, or a series of parallel streams (Rauschecker & Scott, 2009), but it is widely accepted that there is a degree of functional specialisation for the processing and production of speech.

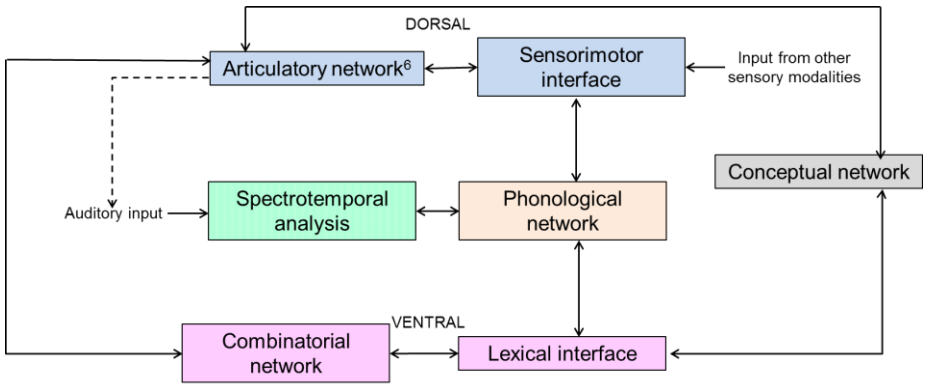

Figure 1.4. Schematic diagram of the dual-stream model of the functional anatomy of language. Early spectrotemporal analysis is carried out in auditory cortices bilaterally in the supratemporal plane. Phonological-level processing and representation occurs in middle and posterior portions of the STS bilaterally, with a slight left-hemispheric bias. The hierarchy then diverges into a ventral stream (pink) that maps sensory/ phonological representations onto lexical conceptual representations, and a dorsal stream (blue) that maps sensory/ phonological representations onto motor representations (adapted from Hickok & Poeppel, 2007). The dotted arrow represents an addition made to the dual streams model, incorporating auditory feedback into the model (Warren *et al.*, 2005). This is critically relevant to the work described in Chapter 5.

More recently, the temporal domain has been integrated into speech processing models. Oscillatory neural activity is ubiquitous, and in the auditory cortex, these oscillations 'phase-lock' (entrain) to temporally regular acoustic cues. All sounds are inherently temporal, but speech perception is relatively more dependent upon fine temporal discrimination: low-frequency information in the range of 4-8Hz provides rhythmic scaffolding for the processing of spoken language. A wealth of recent research suggests that oscillations in the human auditory cortex entrain to speech rhythm. Importantly, this entrainment goes beyond processing of acoustic characteristics: phase-locking is enhanced by intelligibility of the speech signal (Peelle & Davis, 2012; Peelle *et al.*, 2013), although these results have not been replicated universally (Millman *et al.*, 2015).

1.2.2. Neuropsychology of auditory object processing

The neuropsychological hierarchy by which we are able to process auditory information has been aligned with other complex neuropsychological processes such as vision (Goll *et al.*, 2010b; Cope *et al.*, 2015). Speech, music and environmental sounds are

extremely different in terms of their acoustic properties. Such sounds can be considered as 'auditory objects' (Griffiths & Warren, 2004) – collections of acoustic data bound into cohesive and coherent perceptual representations that are disambiguated from the auditory background (Goll *et al.*, 2010b). Stages of this neuropsychological hierarchy therefore comprise early perceptual spectrotemporal analysis (i.e. encoding features like rhythm, timbre, and pitch); auditory scene analysis (i.e. deconstructing the acoustic environment to identify and track sounds of interest); apperceptive processing (i.e. identifying sound characteristics under varying listening conditions); and associative processing (i.e. recognising and ascribing meaning to the sound). Below I briefly consider each stage of the hierarchy and its relevance to auditory processing as a whole; a summary is given in Figure 1.5.

1.2.2.1. Sub-object level processing

Certain acoustic characteristics, such as pitch, modulation, and timbre, are features of all auditory objects. Processing of these elements is thought to involve brain mechanisms separable from those involved in formation of whole-object-level representations. Importantly, these properties represent auditory precepts, rather than physical sound attributes, and are most likely processed in primary auditory cortex and beyond.

1.2.2.2. Auditory scene and spatial analysis

Auditory scene analysis (ASA) is the process by which we parse auditory information into single auditory objects for further analysis. Critical examples include segregating a specific sound object from a wider auditory background (e.g. disambiguating one's own name from a background of voices in a noisy room: the so-called 'cocktail party' effect (Cherry, 1953)), and grouping temporally separated sounds into a single object (e.g. notes in a musical melody). Auditory spatial analysis represents a core component of auditory scene analysis, allowing the listener to identify the location and motion of sounds in space.

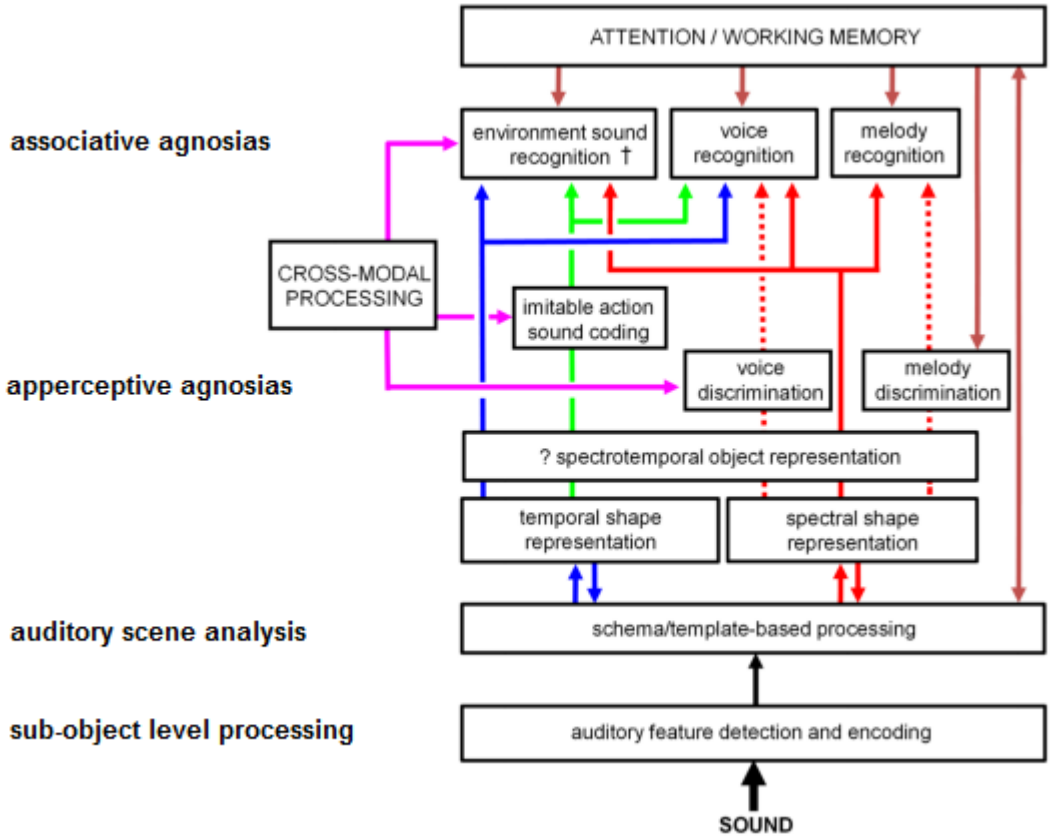

Figure 1.5. A simplified hierarchical neuropsychological model of auditory processing. Arrows delineate the likely directionality of information flow between processing modules in the hierarchy, though most connections are probably reciprocal. Arrows are colour-coded as follows: black = basic acoustic features; blue = temporal properties; green = temporal properties relevant to encoding of imitable action sounds; red = spectral properties; magenta = cross-modal sensory processing; brown = executive processes. Solid arrows show obligatory processes, and dotted arrows are processes that may be engaged in some circumstances (e.g. increased perceptual load). Adapted from Goll et al., 2010.

1.2.2.3. Apperceptive processing

The next stage is representation of whole auditory objects (i.e. collections of sub-object properties bound together in coherent auditory objects). The formation of whole-object-level representations requires the brain to process incoming sensory data corresponding to particular auditory objects under widely varying conditions, for instance the same phoneme spoken by different voices or the same tune played by different instruments. Apperceptive sound agnosias are difficult to differentiate from higher-level associative deficits. Auditory templates representing the sound structures of particular auditory objects might facilitate discrimination of familiar sounds under degraded listening conditions

1.2.2.4. Associative processing

Auditory object recognition – the level of associative processing – is the process by which the successfully parsed auditory object is matched to the conceptual mental lexicon. This manifests in recognition and identification of a song from hearing its melody, or a person from hearing their voice. We are able to ascribe meaning to environmental sounds, such as running water or a door shutting, that facilitate appropriate navigation.

1.3. Auditory processing in primary progressive aphasia

Prevailing recent evidence suggests that cognitive deterioration may be predicted, or even accelerated, by hearing loss (Hardy *et al.*, 2016), although the vast majority of literature refers to typical AD (Lin *et al.*, 2011a, 2011b, 2014). Below I briefly describe issues around peripheral and central hearing loss in the context of neurodegeneration, before turning my attention to focus on central hearing loss exclusively in PPA.

1.3.1. The challenge of peripheral vs central hearing loss

'Hearing loss' can be used ubiquitously to refer to any phenotype of auditory deafferentation, but it is crucial to make a distinction between peripheral (i.e. damage to structures of the ear) and central (i.e. damage to the cortex) levels. Differentiating between the two can be extremely difficult in patients with PPA, and it is crucial that peripheral hearing function is assessed in conjunction with central auditory processing.

Around 40% of people over the age of 65 have significant peripheral hearing loss (Gates & Mills, 2005), which has important links to cognitive impairment and dementia. Presbycusis (age-related hearing loss) most commonly arises from cochlear dysfunction, although central auditory involvement is relevant and has probably been under-recognised in the past (Panza *et al.*, 2015). Across studies, epidemiological evidence is in accord that hearing loss is associated with cognitive decline, therefore constituting a risk factor for development of AD and other dementias, although the strength of this association does vary dramatically across studies (Panza *et al.*, 2015; Taljaard *et al.*, 2015). In the Baltimore Longitudinal Study of Aging hearing loss of 25dB had an effect on cognition equivalent to around seven years of aging (Lin *et al.*, 2011a), and risk of dementia onset correlated with severity of hearing impairment (Lin *et al.*, 2011b). Tissue volume loss in auditory cortex in

older adults correlates with hearing loss (Peelle *et al.*, 2011), as well as in temporal lobe and whole brain (Lin *et al.*, 2014).

However, the mechanism accounting for the association between peripheral hearing loss and cognitive decline is unresolved. One possibility is that hearing impairment could compound sensory and social isolation and increase cognitive load, exhausting the brain's capacity for compensatory cognitive reallocation (Panza *et al.*, 2015). The association between peripheral hearing and cognition, however, remains even after controlling for various demographic and comorbidity factors (Lin *et al.*, 2011b; Dawes *et al.*, 2015). The link between peripheral hearing loss and neurodegeneration may therefore be more direct. Many major auditory relay nuclei are affected in AD (Sinha *et al.*, 1993; Parvizi *et al.*, 2001), and animal models have suggested there is a causal link between peripheral deafferentation and hippocampal function (Liu *et al.*, 2016; Park *et al.*, 2016). These studies have been almost exclusively undertaken in the context of AD. One study linked peripheral hearing impairment to general disability (i.e. not specifically cognitive dysfunction) in patients with Parkinson's disease (Vitale *et al.*, 2012), but to my knowledge, no studies have systematically explored peripheral hearing alongside central auditory processing in PPA.

In AD, central auditory deficits may be disproportionate to abnormalities in sound detection or otological markers (Strouse *et al.*, 1995; Gates *et al.*, 1996, 2011; Idrizbegovic *et al.*, 2011; Quaranta *et al.*, 2014; Panza *et al.*, 2015), and young carriers of pathogenic AD mutations show abnormal auditory cortical evoked potentials that predate their clinical symptoms (Golob *et al.*, 2009). Indeed, the presenting clinical feature in any neurodegenerative syndrome is rarely auditory dysfunction, but significant histopathological involvement of auditory cortices has been described across the major dementia syndromes (Sinha *et al.*, 1993; Baloyannis *et al.*, 1995, 2011a, 2011b; Baloyannis, 2005). Patients with svPPA often report tinnitus, which has been linked to structural alterations in a fronto-temporo-subcortical network, and patients may also show 'hyperacusis', or increased sensitivity to sound (Mahoney *et al.*, 2011).

Below, I discuss the literature on central auditory processing dysfunction in PPA, using the neuropsychological hierarchy outlined in Section 1.2.2: first contemplating the important role of working memory and very early sub-object level processing, then turning to

auditory scene analysis before considering apperceptive and associative agnosias for particular classes of sounds.

1.3.2. Working memory

Working memory refers to the short-term rehearsal of information in a temporary store that is then available for subsequent processing (Baddeley, 2010). One important consideration is that working memory is not a unitary store: there is in fact a heterogeneity of working memory storage systems distributed throughout the brain that subserve short-term storage of information in a number of different sensory modalities. Dissociations between visual, phonological and visuospatial working memory systems are well documented (Warrington & Rabin, 1971; Warrington & Shallice, 1972).

These systems are cognitively and neuroanatomically dissociable: visuospatial STM is putatively processed in right parietal regions (Chechlacz et al., 2014); visual-verbal STM is left-lateralized to a temporo-parietal-occipital region (Warrington & Rabin, 1971; Shallice & Saffran, 1986), and auditory-verbal information is processed in left temporo-parietal junction (Warrington et al., 1971, 1986). The insidious pathological spread of atrophy extending posteriorly in the left temporal and parietal lobes in nfvPPA and lvPPA is therefore consistent with the deficits in phonological working memory that have been widely observed in nfvPPA and lvPPA (Greene *et al.*, 1996; Grossman *et al.*, 1996, 2005; Code *et al.*, 2006; Gorno-Tempini *et al.*, 2008, 2011; Leyton *et al.*, 2014; Whitwell *et al.*, 2015; Hardy *et al.*, 2015, 2016; Henry *et al.*, 2016): indeed, PWM impairment is often regarded as the defining feature of lvPPA (Gorno-Tempini *et al.*, 2004, 2008; Rohrer *et al.*, 2010b). This has important implications for assessing auditory cognition and accounting for phonological working memory capacity is often critical in designing novel psychoacoustic tests.

1.3.3. Sub-object level processing

Early spectrotemporal auditory processing deficits of pitch direction perception and timbre processing have been identified across the PPA syndromes. Timbre processing is affected in nfvPPA but not in svPPA (Goll *et al.*, 2010a, 2011), and is also affected in lvPPA – with the important consideration that this is not accounted for by reduced working memory capacity (Goll *et al.*, 2011). Deficits in lvPPA for processing of pitch direction and auditory

size perception are attributable to reduced working memory capacity, while in nfvPPA auditory size perception appears to be unaffected relative to impaired pitch direction perception (Goll *et al.*, 2011).

However, despite the small number of studies in this area, results are not entirely consistent. Recently, Grube and colleagues constructed a novel psychoacoustic battery of tasks probing auditory processing in PPA still further. They found that patients with nfvPPA were particularly impaired on tasks requiring rhythm and pitch processing, while patients with lvPPA did not show any significant impairments (Grube *et al.*, 2016). The rhythm perception deficit in nfvPPA here could be indicative of altered auditory timing pathways in this group, manifesting in the speech production problems inherent to the disease and deficient processing of acoustic sequence structures. A subset of patients in the svPPA group was also impaired, but this was not universal across the whole cohort, and they were relatively less impaired than patients in the nfvPPA group. The results here should be interpreted with some caution, especially with regard to the null effect in the lvPPA group, as they only had four patients, with mean symptom duration of one-and-a-half years.

Taken together, the available literature suggests that patients with nfvPPA have a deficit at the sub-object level of early spectrotemporal processing, and that those with lvPPA may be similarly impaired. By contrast, patients with svPPA are relatively unaffected at this level of processing.

1.3.4. Impaired perception of auditory scenes

Deficits with auditory scene analysis have been associated with disintegration of a core parieto-temporal network in typical AD and posterior cortical atrophy (Goll *et al.*, 2012a; Golden *et al.*, 2015a, 2015c). Comparatively little research has been undertaken in PPA, although the temporo-parietal cortical hub regions implicated in parsing the acoustic stream into constituent sound objects are contiguous with the classic pattern of atrophy typically reported in lvPPA (Gorno-Tempini *et al.*, 2011), and one would predict similar deficits associated with the underlying AD pathology.

1.3.5. Speech processing

Speech represents a major auditory signal carrying a wealth of nonverbal and metalinguistic information before even being mapped onto the mental lexicon. In this section, I review literature on metalinguistic speech processing, considering auditory agnosia for speech (word deafness), voice processing, accent processing and receptive prosody.

1.3.5.1. Word deafness

Word deafness is a selective auditory agnosia for speech, characterized by an inability to understand spoken language in the context of intact peripheral hearing and retained comprehension of written language. The specificity of the deficit for speech is crucial: auditory agnosia for any sound reflects general cortical deafness. Cases in a neurodegenerative context are relatively rare (see Table 1.4): one study of 100 consecutive patients with PPA observed that only three patients presented with pure word deafness as the leading symptom (Senaha *et al.*, 2013). Intriguingly, a higher number of cases seem to be reported in Japanese and Korean patients (Otsuki *et al.*, 1998; Kuramoto *et al.*, 2002; Kaga *et al.*, 2004; Iizuka *et al.*, 2007; Kim *et al.*, 2011)[1] which could potentially reflect some aspect particular to these languages that is especially vulnerable, though cases in the context of European languages have also been reported (Sérieux, 1893; Jörgens *et al.*, 2008; Gibbons *et al.*, 2012): see Table 1.4.

The case described by the French neurologist Sérieux in the paper "Sur un case de surdité verbale pure" (Sérieux, 1893) is often hailed as one of the first descriptions of a PPA. However, the patient presented with word deafness and contemporary neurologists have suggested that his patient might be better characterised as a case of primary progressive auditory agnosia (Ceccaldi *et al.*, 1996), which raises the intriguing possibility that one of the most widely-known and earliest descriptions of PPA would not meet the consensus criteria used today, and suggests that progressive pure word deafness represents an exception syndrome outside of the consensus criteria. Remarkably, one of the eight patients in Mesulam's original case series of PPA was a 17 year-old girl who presented with word deafness (Mesulam, 1982). This case was extremely atypical, however, in terms

[1]Note that the patient described by (Kim *et al.*, 2011) is described as having a clinical phenotype consistent with atypical early-onset Alzheimer's disease. The clinical syndrome they describe, however, is in keeping with a language-led, i.e. logopenic-type primary progressive aphasia syndrome.

of her age at presentation and the fact that she did not deteriorate over time. Later testing of the same patient revealed that her auditory agnosia for words was more likely attributable to cranial nerve or cerebellar, rather than cortical, dysfunction (Pinard *et al.*, 2002).

Table 1.4. Documented cases of word deafness in the context of PPA

Authors	Participant	Key findings
(Croisile *et al.*, 1991)	1 PPA-NOS (NA): 69, RH, M, French	Word deafness with reduced spontaneous speech, anomia, spared single word repetition relative to poor sentence repetition. **Left temporal lobe atrophy with widening of the peri-Sylvian fissure.**
(Gibbons *et al.*, 2012)	1 PPA-NOS (PPA): 57, RH, M, English	Word deafness accompanied by other language deficits that were limited to the verbal domain: written testing showed adequate performance.
(Iizuka *et al.*, 2007)	1 PPA-NOS (FTD): 66, RH, M, Japanese	Word deafness was the presenting symptom, followed by speech production problems one year later. **Severe atrophy of left peri-Sylvian cortex.**
(Jörgens *et al.*, 2008)	1 PPA-NOS (NA): 71, RH, F, German	Word deafness with all other language functions relatively intact. **Bilateral atrophy of Heschl's gyrus and peri-Sylvian cortex.**
(Kaga *et al.*, 2004)	1 PPA-NOS (PPA): 70, NA, F, Japanese	Progressive word deafness that affected environmental sound processing on later testing. **Bilateral peri-Sylvian hypometabolism and atrophy of primary auditory and temporoparietal areas.**
(Kim *et al.*, 2011)	1 PPA-NOS (AD): 59, RH, F, Korean	Word deafness was the presenting symptom, followed by poor repetition and phonemic paraphasias in speech. **Bilateral temporo-parietal hypometabolism left > right.**
(Kuramoto *et al.*, 2002)	1 PPA-NOS (PPA): 68, RH, Japanese	Word deafness in conjunction with jargon aphasia. **Widening of peri-Sylvian fissure and atrophy along a frontotemporal network.**
(Otsuki *et al.*, 1998)	1 PPA-NOS (PPA): 67, RH, M, Japanese	Word deafness that eventually affected environmental sound processing and temporal auditory discrimination. **Atrophy in left STG likely responsible for phenotype of word deafness.**
(Sérieux, 1893)	1 PPA-NOS (PPA): 55, RH, F, French	Isolated progressive word deafness with eventual progression to Wernicke-type aphasia. **Bilateral temporal lobe atrophy.**

The Table shows all cases of progressive word deafness in the context of a PPA syndrome. Note that here I have described each case as PPA-NOS, reflecting the fact that none would meet a diagnosis for one of the major PPA syndromes according to current consensus criteria. The original clinical label ascribed to each case is given in parentheses if available. Demographic information for each case is given in the format age at case study, handedness, gender, native language. If neuroimaging correlates were reported, they are summarised in **bold.**

1.3.5.2. Voice processing

A person's voice conveys a wealth of information about the speaker, such as their accent (see below), gender, age, and emotional state. Voice identification is thought to depend upon a fine-grained spectrotemporal representation (at the early perceptual level), followed by speaker discrimination (the apperceptive level), and then attribution of meaning (the associative level); this is in line with the broad neuropsychological processing hierarchy summarised earlier in this Chapter, and with the formulation described by Hailstone and colleagues, depicted in Figure 1.6 (Hailstone, 2012).

Impaired recognition of familiar voices in the context of intact apperceptive processing has been consistently identified in the temporal variants of FTD (see Table 1.5). In two cases with right temporal lobe damage, one had a relatively selective deficit for voices (progressive associative phonagnosia), while the other had a deficit for voices consistent with a general decline in person knowledge characterised by progressive prosopagnosia (Hailstone *et al.*, 2010). In a VBM study of a combined cohort of 22 patients with AD and 14 with temporal variant FTD (13 of which had svPPA), patients with svPPA were found to have a voice recognition deficit above that seen in the AD group that was associated with atrophy of the right temporal pole and anterior fusiform gyrus (Hailstone *et al.*, 2011). Therefore, voice processing is affected in svPPA at the level of associative processing, reflecting general decline in semantic conceptual knowledge.

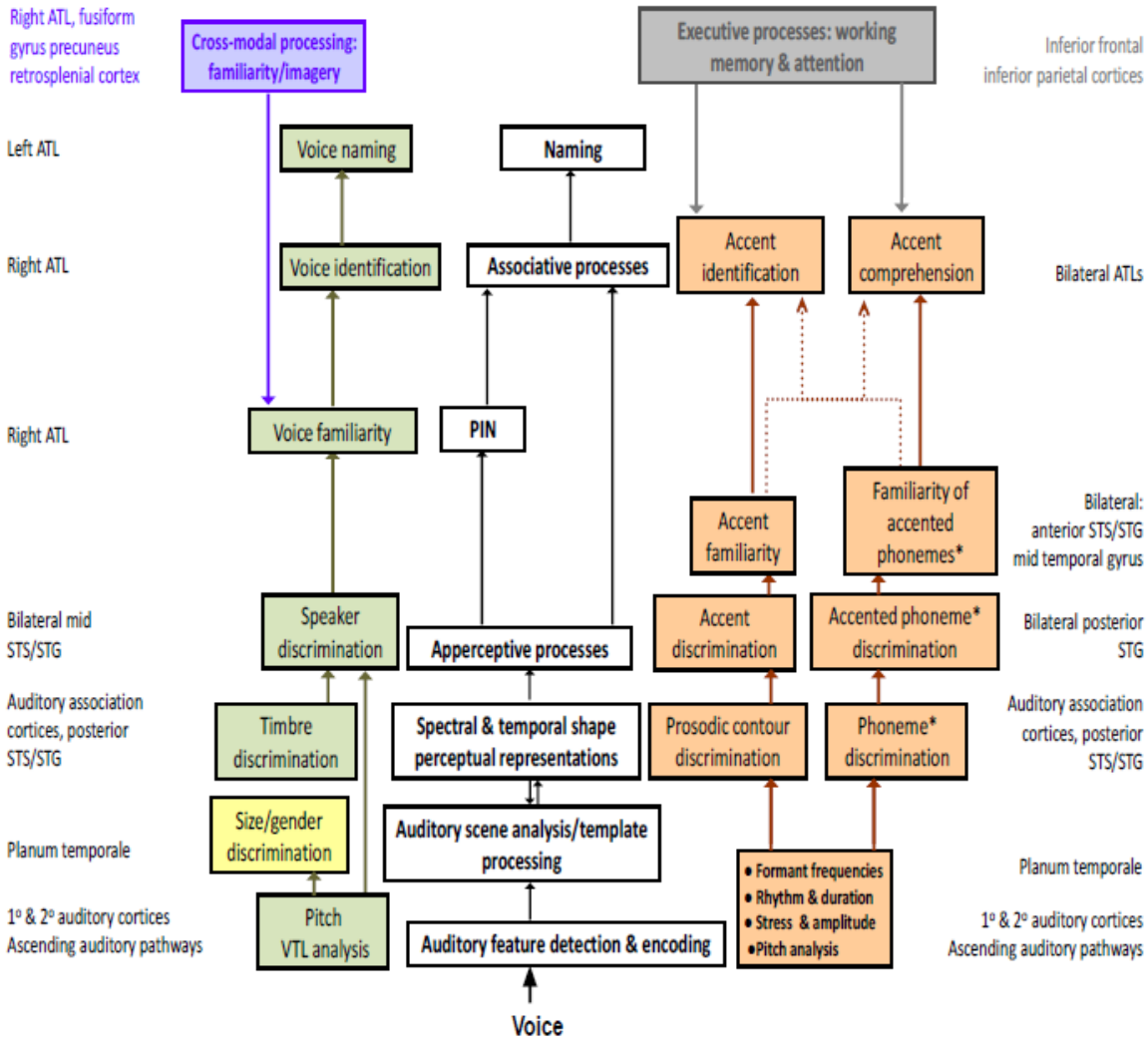

Figure 1.6. A hierarchical model of voice processing. Size/ gender information is indicated in yellow; parallel processing pathways for voice identity and accent processing are given in green and orange, respectively. Putative anatomical substrates are given on the relevant side of the diagram. Accent processing recruits linguistic processing mechanisms possibly at the level of phonemes(*), although this is unclear. Coloured arrows demonstrate the primary direction of communication between stages in the hierarchy; dotted arrows show candidate links between perceptual cues and processes that are less evident than those depicted by solid lines. Arrows linking template processing and spectral and temporal shape representations are bidirectional, emphasising the dynamic updating of these templates via the interaction between incoming information and stored representations. Reproduced from Hailstone (2012).

1.3.5.3. Accent processing

Accented speech is processed routinely by the healthy brain, providing nonverbal information about the speaker, including geographical origin, social milieu and ethnicity. Processing of accents is computationally demanding, relying on neural mechanisms that are anatomically and functionally separable from those concerned with the verbal content of speech. However, impairments of accent processing may

themselves constitute syndrome specific signatures of neurodegenerative diseases: see Table 1.5.

In one group study of 20 patients with AD and six with nfvPPA, both groups were impaired at recognition of both regional and international accents relative to the control participants (Hailstone *et al.*, 2012). Importantly, however, the patterns of impairment were dissociable for each patient group. Whilst patients with AD showed a perceptual cost for comprehension of accented sentences (but not single words), patients with nfvPPA tended to show the opposite effect – a perceptual cost for comprehension of accented words, but not sentences. The nfvPPA group also showed a reduced ability to understand words spoken in international accents as compared to words spoken in a southern English accent.

Fletcher and colleagues have probed the brain basis of accent processing in PPA still further in a study of two patients: one with nfvPPA and one with svPPA (Fletcher *et al.*, 2013). The nfvPPA patient presented with a marked difficulty in understanding non-native accents, whereas the svPPA patient presented with prosopagnosia and phonagnosia, but no reported difficulty in understanding accents. At an apperceptive level, the nfvPPA patient was significantly impaired relative to healthy controls and the svPPA patient on detecting changes in accent, but not on phoneme discrimination or speaker change, suggesting that this was an apperceptive level deficit that was not grounded in a more general deficit of early perceptual coding. By contrast, the svPPA patient was able to perceive changes in phonemes, voices and accents, with a mild impairment in accent identification. Whilst the svPPA patient was unable to identify faces normally, the nfvPPA patient was able to do this, suggesting that whilst the nfvPPA patient had an interacting apperceptive and semantic deficit for accent processing, the svPPA patient had a primary semantic (associative) deficit.

The consensus here, therefore, is that svPPA patients have impairment at the level of associative processing, while patients with nfvPPA have an earlier, apperceptive-level impairment. Accent processing in lvPPA has not yet been studied, though one might predict them to display a pattern of deficits similar to that seen in nfvPPA.

1.3.5.4. Receptive prosody

Prosody represents another metalinguistic, suprasegmental vocal pattern that conveys important information to the listener pertaining to the speaker's affect and intentions. Expressive prosody (the 'melody of speech') has been studied extensively in PPA and is abnormal in many patients (Ghacibeh & Heilman, 2003; Tsao *et al.*, 2004; Josephs *et al.*, 2006; Graff-Radford *et al.*, 2012), but less is known about receptive prosody (see Table 1.5). Rohrer and colleagues conducted a systematic investigation of three different dimensions of receptive prosody processing (acoustic, linguistic and emotional) in a cohort of patients with PPA. lvPPA patients (n = five) performed significantly worse than control participants on all tests of linguistic and acoustic prosody subtests (Rohrer *et al.*, 2012). nfvPPA (n = 11) and PPA-GRN (n = three) participants were significantly worse than controls on all tests except for stress discrimination. Grey matter associations of acoustic and linguistic prosody processing were identified in a distributed cortical network involved in the perceptual analysis of vocalisations (left posterior temporal and inferior parietal cortices) and fronto-parietal circuitry involved in working memory.

In the same study, recognition of vocal emotions was more impaired than recognition of facial emotions in all PPA subgroups studied (svPPA patients were not included), suggesting that this was not representative of a deficit at the level of generic semantic processing, but more likely reflecting the involvement of early perceptual mechanisms that cascade to higher levels of prosodic processing in PPA. VBM revealed atrophy associated with emotional prosody processing for negative emotions (disgust, fear, sadness) in a broadly overlapping network of left frontal, temporal limbic and parietal areas. There is little other research in this area, although four patients with bvFTD or svPPA were relatively unimpaired on an emotional prosody discrimination task compared to an emotional prosody naming task (Perry *et al.*, 2001). Taken together, results suggest that the nonfluent PPA syndromes are impaired at earlier perceptual levels than affected in svPPA, corroborating the characterization of nfvPPA and lvPPA as disorders of generic early perceptual auditory signal processing.

Table 1.5. Case and group studies of voice, accent, and receptive prosody processing deficits in PPA.

Authors	Participant(s)	Key findings
Voice processing		
(Hailstone *et al.*, 2010)	1 tvPPA: 72, LH, M, American	The patient showed severe phonagnosia and prosopagnosia in the context of partly preserved recognition of musical instrument and entirely preserved environmental sound processing. **Bilateral predominantly anterior temporal lobe atrophy R > L.**
(Hailstone *et al.*, 2011)	13 svPPA	svPPA patients were not impaired at level of vocal gender perception or voice perception but were severely affected at voice recognition, reflecting general semantic decline. **Combined with an AD cohort, voice recognition was associated with GM volume in right temporal pole and anterior fusiform gyrus**
(Omar *et al.*, 2011)	10 svPPA	svPPA patients showed significantly impaired emotion recognition from voices, as well as from faces and music.
Accent processing		
(Fletcher *et al.*, 2013)	1 nfvPPA: 67, RH, F, English; 1 svPPA: 71, RH, F, English.	The nfvPPA patient showed an apperceptive and associative accent agnosia; the svPPA patient only had an associative deficit. **The nfvPPA patient had left peri-Sylvian atrophy while the svPPA patient had relatively focal asymmetric right temporal lobe atrophy.**
(Hailstone *et al.*, 2012)	6 nfvPPA	nfvPPA patients showed deficits of non-native accent recognition, and reduced comprehension of words spoken in international accents.
Receptive prosody		
(Perry *et al.*, 2001)	4 tvFTD	Patients were relatively unimpaired on an emotional prosody discrimination task compared to much poorer performance on an emotional prosody naming task.
(Rohrer *et al.*, 2012)	11 nfvPPA; 5 lvPPA; 3 PPA-GRN	Broadly comparable profiles across the three syndromes in terms of receptive acoustic, linguistic and affective prosodic processing deficits. **Acoustic and linguistic deficits were associated with posterior temporal and inferior parietal cortices, and fronto-parietal circuitry.**

The table shows group and case studies of voice, accent and receptive prosody processing in PPA. For individual case studies, demographic information is given in the format: age at case study, handedness, gender, native language. If neuroimaging correlates were reported, they are summarised in **bold**.

1.3.6. Environmental and nonverbal sound processing

Here, I characterise environmental and nonverbal sounds as auditory objects that potentially carry meaning (e.g. a horse neighing; a hammer striking a nail; water trickling). A summary of research into environmental and nonverbal sound processing in PPA is given in Table 1.6.

In svPPA, nonverbal sound recognition is impaired, reflecting general decline in conceptual knowledge that is not limited to the verbal domain. This was first put on record at the turn of the century (Bozeat *et al.*, 2000), and has subsequently been replicated many times (Yamamoto *et al.*, 2004; Adlam *et al.*, 2006; Garrard & Carroll, 2006; Uttner *et al.*, 2006; Goll *et al.*, 2010a, 2012b; Hsieh *et al.*, 2011; Golden *et al.*, 2015b), and activation fMRI work suggests that altered bilateral networks involving the superior and middle temporal lobes are implicated in the altered semantic processing of environmental sounds in svPPA (Goll *et al.*, 2012b). Physiological responses to salient stimuli may also be attenuated in svPPA (Fletcher *et al.*, 2015b). Intriguingly, recent research manipulating the semantic and emotional congruity of constituent sounds in auditory scenes suggested that patients with svPPA and bvFTD had impaired processing of these complex auditory environments, possibly reflecting a deficit at the level of decoding auditory signal relatedness (Clark *et al.*, 2017).

Broadly, evidence suggests that patients with semantic dementia develop deficits of nonverbal sound recognition (auditory associative agnosias) as part of a pan-modal erosion of semantic memory, linked to antero-mesial temporal lobe dysfunction (Bozeat *et al.*, 2000; Goll *et al.*, 2010a; Golden *et al.*, 2015b). In the nonfluent variants, patients with nfvPPA may also have associative deficits for nonverbal sound processing, with relatively unaffected apperceptive processing (Goll *et al.*, 2011). Deficits across both levels have been reported in lvPPA, but these are likely both accounted for to a large extent by their phonological working memory deficit (Goll *et al.*, 2011).

Table 1.6. Studies of environmental sound processing in PPA.

Authors	Participant(s)	Key findings
(Adlam *et al.*, 2006)	7 svPPA	Patients were impaired on a range of semantic associative tasks, including nonverbal sound recognition. **Task performance related to left inferior temporal lobe volume.**
(Bozeat *et al.*, 2000)	10 svPPA	Patients were impaired on environmental sound recognition and association tasks.
(Clark *et al.*, 2017)	10 svPPA	Patients were impaired on processing semantic and emotional components of complex incongruent auditory scenes. **Semantic: prefrontal, parieto-temporal, insular; Emotional: insular and striatal.**
(Fletcher *et al.*, 2015c)	12 nfvPPA; 10 svPPA	Autonomic reactivity to salient environmental, animal, human and mechanical sounds was reduced in svPPA.
(Garrard & Carroll, 2006)	12 svPPA	Patients performed equally poorly on tasks assessing knowledge of environmental sounds, colours, contexts and motions.
(Goll *et al.*, 2010a)	12 nfvPPA; 8 svPPA	Both groups showed an associative deficit for environmental sounds that was specific to the auditory modality in nfvPPA and reflective of general semantic degradation in svPPA.
(Goll *et al.*, 2011)	5 nfvPPA; 7 lvPPA; 1 PPA-GRN: 64, RH, M, English	Patients with nfvPPA were impaired on an associative, but not apperceptive, level of environmental sound processing. Patients with lvPPA were impaired at both levels but PWM performance accounted for these deficits. The PPA-GRN patient was impaired on an apperceptive level.
(Goll *et al.*, 2012b)	9 svPPA	Patients were impaired on recognition of animal and tool sounds. **fMRI showed differential activation of areas around the STS for perceptual and semantic processing of sounds compared to controls.**
(Golden *et al.*, 2015b)	9 svPPA	Patients showed impaired performance on within-modality environmental sound matching tasks.
(Hsieh *et al.*, 2011)	13 svPPA	Patients were profoundly impaired on recognition of every day environmental sounds.
(Uttner *et al.*, 2006)	1 lvPPA (PPA): 65, ?, F, German	Environmental sound agnosia in the context of word-finding difficulties and repetition problems with long words. **Atrophy of Wernicke's area and inferior parietal cortex; hypometabolism of right temporal and frontal regions.**
(Yamamoto *et al.*, 2004)	1 PPA-NOS (PPA): 60, RH, M, Japanese	Progressive environmental sound agnosia accompanied by speech production problems. **Atrophy to secondary auditory area in right temporal lobe.**

The table shows group and case studies of nonverbal sound processing in PPA. Note that I have classified each case study according to the 2011 consensus criteria: the original clinical label ascribed to each case is given in brackets if available. Demographic information for individual case studies is given in the format age at case study, handedness, gender, native language. If neuroimaging correlates were reported, they are summarised in **bold.**

1.3.7. Music processing

Music is a powerful nonverbal signal, and several studies have reported music processing to be impaired at some level across typical and atypical FTD and PPA syndromes (Confavreux *et al.*, 1992; Gentileschi *et al.*, 2001; Hailstone *et al.*, 2009; Matthews *et al.*, 2009; Barquero *et al.*, 2010; Omar *et al.*, 2011, 2010, Hsieh *et al.*, 2011, 2012; Johnson *et al.*, 2011; Golden *et al.*, 2017); see Table 1.7.

In svPPA, evidence points to a dissociation between musical knowledge and music emotion recognition. In a case study, Omar and colleagues found that while their patient with svPPA showed relatively preserved ability to recognise musical symbols and objects, they were severely impaired at recognising musical emotions or identifying musical instruments from their sounds (Omar *et al.*, 2010). Similar findings were reported by Hailstone, who observed that their patient with svPPA was able to continue singing well-known melodies when given the start of the melody, despite focal atrophy in the left anterior temporal lobe (Hailstone *et al.*, 2009). It is likely that this region is less critical for musical than other forms of semantic memory, and in fact the right temporal lobe may be crucial for the processing of known tunes.

Music recognition impairment in svPPA is consistently associated with atrophy to the right temporal pole (Hsieh *et al.*, 2012). One case study reported on a 60 year old svPPA patient with predominately right temporal lobe atrophy who could only recognise 14 out of 33 previously familiar songs (Gentileschi *et al.*, 2001), and similar findings have been reported elsewhere (Confavreux *et al.*, 1992; Johnson *et al.*, 2011).

Music processing in the nonfluent variants is less well-studied. However, in one group study of music processing, lvPPA patients had deficits of global pitch processing, while nfvPPA patients had both local and global pitch processing deficits (Golden *et al.*, 2017). Local pitch processing is broadly defined as processing the pitch of an individual tone, or the interval size between two adjacent tones, whereas global pitch processing reflects processing of the contour, characterising pitch directions independent of precise pitch values (Peretz, 1990).

Taken together, results suggest that music recognition is impaired in svPPA, but perhaps to a lesser extent than other semantic constructs. This could reflect

localization of music knowledge to the right temporal lobe; damage to this structure is associated with poorer music recognition performance. Work in the nonfluent variants suggests that music recognition is relatively unimpaired, but both syndromes may show impairments in terms of melody processing that is at least partially separable across global and local pitch processing.

1.3.8. Autonomic/ emotional responses to sound in PPA

Altered hedonic (emotional) behavioural responses to sound are common to a number of dementia syndromes. Impaired processing of emotional prosody has been described in tAD (Horley *et al.*, 2010), bvFTD (Dara *et al.*, 2013) and nfvPPA and lvPPA (Rohrer *et al.*, 2012), while patients with svPPA and bvFTD show impaired recognition of musical and nonverbal vocal emotions (Omar *et al.*, 2011).

Across the whole FTD spectrum, many patients exhibit misophonia[2] or sound aversion, while an abnormal craving for music (musicophilia) seems particularly prevalent in svPPA, but not in nfvPPA (Fletcher *et al.*, 2015a). In nfvPPA, however, looming sounds appear to be significantly less alerting than to a healthy control group, and showed abnormal patterns of pupillary responses to looming vs withdrawing sounds, dissociating from patients with svPPA who did not differ from healthy control participants (Fletcher *et al.*, 2015c).

[2]It is worth noting, however, that misophonia has been precisely defined and the phenotype of sound aversion described in patients with PPA does not fit the description of congenital misophonia (Kumar *et al.*, 2017).

Table 1.7. Group and case studies of music processing in PPA.

Authors	Participant(s)	Key findings
(Barquero *et al.*, 2010)	1 PPA-GRN: 53, RH, F, Spanish	The patient worked as a music critic and was unimpaired on tasks requiring processing of melody, pitch or rhythm, but could not differentiate between a piece played by a professional and played by a student (apperceptive processing deficit). **Cortical atrophy in left frontotemporal areas.**
(Confavreux *et al.*, 1992)	1 PPA-NOS: 63, RH, F,	The patient presented with progressive amusia, manifesting in her inability to sing in the choir. She could not recognise well-known tunes or discriminate between simple rhythms. Musical knowledge, however, was preserved. **Right-sided peri-Sylvian and insular atrophy.**
(Fletcher *et al.*, 2015a)	19 svPPA; 15 nfvPPA	Patients with svPPA were more likely to show musicophilia. **Antero-mesial temporal lobe, insula, anterior cingulate and nucleus accumbens.**
(Gentileschi *et al.*, 2001)	1 PPA-NOS (FTD): 60, RH, F, Italian.	The patient presented with a progressive prosopagnosia syndrome that was accompanied by an inability to name famous pieces of music. **Right temporal lobe damage.**
(Golden *et al.*, 2017)	5 lvPPA; 9 nfvPPA	All patients were impaired at global pitch (melody contour) processing; patients with nfvPPA were additionally impaired at local pitch (interval) processing. Neither group was impaired on music temporal processing, timbre processing, musical scene analysis or tune recognition.
(Hsieh *et al.*, 2011)	13 svPPA	Patients with svPPA were profoundly impaired in the recognition of famous tunes. **Correlated with right temporal lobe volume, particularly in the pole.**
(Hsieh *et al.*, 2012)	11 svPPA	Identification of emotions from unknown musical tunes was impaired in svPPA, particularly for negatively valenced stimuli. **Correlated with right temporal pole, insula and amygdala volumes.**
(Johnson *et al.*, 2011)	20 svPPA	Patients with svPPA were not different from controls on basic pitch and melody discrimination tasks. They had difficulties naming familiar melodies and were less able to identify pitch errors in the same melodies. **This pitch identification error correlated with right temporal lobe while naming correlated with bilateral temporal lobes and inferior frontal gyrus.**
(Omar *et al.*, 2010)	1 svPPA: 56, RH, M, English	Severely impaired recognition of musical emotions and identification of musical instruments from sounds, with relatively preserved recognition of musical compositions and musical symbols. **Anterior temporal lobe involvement.**

The table shows group and case studies of music sound processing in PPA. Note that I have classified each case study according to the 2011 consensus criteria: the original clinical label ascribed to each case is given in brackets if available. Demographic information for individual cases is given in the format age at case study, handedness, gender, native language. If neuroimaging correlates were reported, they are summarised in **bold.**

1.4. Key experimental questions motivating this thesis

This thesis addresses the neuropsychological and neuroanatomical mechanisms of impaired auditory signal decoding in the PPAs. A wealth of evidence suggests that nfvPPA and lvPPA are impaired at early perceptual and apperceptive levels of auditory processing, while patients with svPPA typically have problems with associative auditory processing, reflecting the pan-modal nature of their disease. In light of the nosological difficulties that surround PPA, and mounting neuropsychological and functional neuroanatomical evidence for nonverbal auditory impairment in these syndromes, it may be timely to re-evaluate the 'language-led' dementias as more fundamental disorders of auditory signal decoding. There is considerable interest in identifying psychoacoustic measures that could stratify patients by syndrome, and allow for greater understanding of the auditory signal processing impairments previously identified, with a view to measuring and tracking disease evolution in relation to the development and evaluation of therapies. Broadly, I use the hierarchy of auditory processing outlined in Figure 1.5 as a neuropsychological model in which to probe deficits at different levels across the PPA syndromes.

Here I report the results of four linked experiments conducted with a well-characterised cohort of patients with PPA in relation to healthy older individuals (Chapters 3-6) and to neurodegenerative control groups (Chapters 5 and 6). Psychoacoustic tests were used to define auditory deficits behaviourally (Chapters 3-6), and structural/ functional imaging techniques then used to establish neuroanatomical associations with these behavioural deficits (Chapters 3-4, 6).

Experiment 1: Behavioural and neuroanatomical correlates of auditory speech analysis

The PPA syndromes are associated with impaired decoding of auditory speech signals. The deficits displayed by each patient group are, to some extent, non-contiguous and different syndromes will be associated with specific speech signal processing deficits. In this experiment, I manipulate non-linguistic speech stimuli (sequences of spoken syllables) for three basic characteristics: temporal regularity; pitch

sequence entropy (information content); and phonemic structure, and assess patients' ability to process these sequences. Behavioural performance is then used in a voxel-based morphometry (VBM) analysis. Based on previous literature discussed in this Chapter, I predict that patients with nfvPPA and lvPPA will show early perceptual deficits characterised by impaired processing of temporal regularity and phonemic structure, while patients with svPPA will show impaired processing of entropy, and that these behavioural deficits will correlate with grey matter volume in dissociable brain regions (frontotemporal-subcortical for temporal regularity/ entropy; temporo-parietal cortex for phonemic structure).

Experiment 2: Functional neuroanatomy of speech signal decoding

Here, I extend the work presented in Chapter 3, as participants with PPA and healthy controls listened to auditory sequences manipulated for the same basic characteristics (temporal regularity, pitch sequence entropy, and phonemic structure) in an activation fMRI paradigm. I predict that the functional substrates of temporal regularity will lie within a distributed frontotemporal-subcortical network, while the substrate of phonemic processing will lie within posterior superior temporal cortex. I further predict that each of the PPA syndromes will have separable functional neuroanatomical signatures of abnormal speech signal decoding relative to healthy older individuals.

Experiment 3: Delayed auditory feedback

In my third experiment, I focus on the interaction between speech perception and speech production, using the paradigm of delayed auditory feedback in a cohort of patients with PPA, bvFTD and AD and healthy control participants. DAF has been used therapeutically in the context of developmental stammering, but has a paradoxically negative effect on speech output in healthy individuals. Here, I predict that healthy controls and patients with svPPA, bvFTD and AD will show significant impairment in terms of spoken speech production under DAF, while patients with nfvPPA and lvPPA will show the opposite result, speaking faster and with fewer speech errors.

Experiment 4: Degraded speech signal processing

In my final experiment, I use linguistic speech stimuli, as participants with PPA, tAD and healthy controls listened to speech signals that had been dramatically distorted using the paradigm of sinewave speech. The sinewave transformation used here initially renders speech unintelligible, but over time healthy individuals adjust through perceptual learning to the degraded stimuli. Here, I predict that patients with lvPPA and nfvPPA will show early perceptual speech processing deficits that would correlate in a VBM analysis with neuroanatomical substrates in early speech areas including posterior superior temporal gyrus and planum temporale, while patients with svPPA will show rapid adaptation to the distorted speech stimuli, but exhibit reduced top-down associative integration of content.

2. Methods overview

This Chapter provides an overview of the experimental methods employed in performing the work described in this thesis. Where individual experiments deviate from the procedures and protocols described here, further information will be given in the specific Chapter.

2.1.1. Participants

Participants were recruited over a three-year period from October 2014–March 2017 from the tertiary specialist cognitive clinic at the National Hospital for Neurology and Neurosurgery (NHNN), London. A minority of patients were referred from external consultants. All patients had neuroimaging findings compatible with their clinical syndromic diagnosis and conformed to consensus criteria for their respective diagnoses. Ethical approval for all studies included in this thesis was obtained from the University College London and NHNN Research Ethics Committees, in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants. Where patients were adjudged not to have capacity to consent to participate in the study themselves, a carer or guardian consented on their behalf, affirming that it was the express wish of the participant that they would participate in research at our Centre before losing capacity to consent themselves.

Demographic information was collected from each participant, including gender, handedness, age, and years of education. Patients' symptom duration was calculated from the date of symptom onset as reported by their principal caregiver. All patients and controls underwent a full neurological examination during which a mini-mental state examination (MMSE) (Folstein *et al.*, 1975) was conducted.

Syndromic group characteristics for each of the three main PPA syndromes are clearly outlined in Chapter 1. In Chapters 5 and 6, I recruited a cohort of patients with typical Alzheimer's disease (AD) as a disease control group, and in Chapter 5, I additionally studied patients with behavioural variant frontotemporal dementia (bvFTD). Both of these additional groups met consensus criteria for a diagnosis of Alzheimer's disease (Dubois *et al.*, 2007) or bvFTD (Rascovsky *et al.*, 2007). Healthy control participants were recruited from a local research database and screened to ensure that

they had no history of neurological or psychiatric illness. Supplementary Table 1 in the Appendix to this thesis lists individual participants by involvement in each experiment.

2.1.2. Peripheral audiometry

Pure tone audiometry was performed using an Otovation Roto audiometer (www.otovation.com) in a quiet room. Five frequency levels were tested (500, 1000, 2000, 4000, 6000 Hz). At each frequency, the participant was played three tones, starting at 20dB. If the participant indicated correctly that they had heard at least two of the three tones, this was recorded as the threshold for that frequency; if not, the level was increased in increments of 5dB up to 70dB. Hearing was assessed in both ears for each participant. I created a composite pure tone average score based on the average volume (dB) required for tone detection at 500, 1000, and 2000 Hz, for each ear separately. Using data from the best ear for each participant, scores within the range of 0-25dB were categorised as 'normal', scores between 26-40dB were classified as 'mild hearing loss', and scores between 40-70dB as 'moderate hearing loss', consistent with previously established protocols (Lin *et al.*, 2011c).

2.1.3. Neuropsychological assessment

All participants had a comprehensive general neuropsychological assessment including standardised measures of general intellect, visuoperceptual, executive and linguistic functions that are summarised in Table 2.1. Additional tasks probing linguistic psychometry more deeply were administered to all healthy controls and patients with PPA.

Table 2.1. Summary of general neuropsychological tasks used in this thesis

	C	sv	nfv	lv	AD	bv	Reference	Notes
General intellect								
MMSE (/30)	✓	✓	✓	✓	✓	✓	(Folstein *et al.*, 1975)	Used widely as a quick test of global cognition
PIQ	✓	✓	✓	✓	✓	✓	(Wechsler, 1981)	Generated from WASI Block Design and WASI Matrices
VIQ	✓	✓	✓	✓	✓	✓	(Wechsler, 1981)	Generated from WASI Vocabulary and WASI Similarities
Episodic memory								
RMT Words (/50)	✓	✓	✓	✓	✓	✓	(Warrington, 1984)	The 25-item version of this task was used with AD patients.
RMT Faces (/50)	✓	✓	✓	✓	✓	✓	(Warrington, 1984)	The 25-item version of this task was used with AD patients.
Working memory								
Digit span forward (max)	✓	✓	✓	✓	✓	✓	(Wechsler, 1987)	The participant is given two attempts at each span length
Spatial span forward (max)	✓	✓	✓	✓			(Wechsler, 1987)	The participant is given two attempts at each span length
Executive skills								
Digit span reverse (max)	✓	✓	✓	✓	✓	✓	(Wechsler, 1987)	The participant is given two attempts at each span length
Spatial span reverse (max)	✓	✓	✓	✓			(Wechsler, 1987)	The participant is given two attempts at each span length
Letter fluency (F)	✓	✓	✓	✓	✓	✓	in-house	Maximum time limit of 60 seconds
Category fluency (animals)	✓	✓	✓	✓	✓	✓	in-house	Maximum time limit of 60 seconds
Trails A (s)	✓	✓	✓	✓	✓	✓	(Tombaugh, 2004)	Maximum time limit of 150 seconds
Posterior cortical skills								
GDA Calculation (/24)	✓	✓	✓	✓	✓	✓	(Jackson & Warrington, 1986)	Administered with 10 second time limit for each item
VOSP (/20)	✓	✓	✓	✓	✓	✓	(Warrington & James, 1991)	4AFC
Auditory input processing								
PALPA-3 (/36)	✓	✓	✓	✓			(Kay *et al.*, 1992)	2AFC
Naming								
GNT (/30)	✓	✓	✓	✓	✓	✓	(Mckenna & Warrington, 1980)	Written answers accepted from patients with nfvPPA
BNT (/30)	✓	✓	✓	✓			(Kaplan *et al.*, 1983)	I used a reduced (30-item) version of the BNT
Comprehension								
BPVS (/51)	✓	✓	✓	✓	✓	✓	(Dunn, L & Whetton, 1982)	The full task is 150 items long: we use items 100-150.
Concrete synonyms (/25)	✓	✓	✓	✓				
Abstract synonyms (/25)	✓	✓	✓	✓			(Warrington *et al.*, 1998)	A graded difficulty 2AFC task
PALPA-55 (/24)	✓	✓	✓	✓			(Kay *et al.*, 1992)	3AFC
Speech repetition								
Polysyllabic words (/45)	✓	✓	✓	✓			(Mccarthy and Warrington, 1984	The examiner covered their mouth to prevent lip-reading
Graded sentences (/10)	✓	✓	✓	✓			(Mccarthy & Warrington, 1984)	Included to probe difference between nfvPPA and lvPPA
Spelling								
BST (/30)	✓	✓	✓	✓			(Baxter & Warrington, 1994)	I used List A here: all target words were given orally

2.2. Presentation of auditory stimuli

All experimental sound stimuli were stored as wavefiles at a 44100Hz sampling rate. Within each test, sounds were matched for root-mean-square (rms) intensity over trials, and all sounds created in MATLAB were windowed with 20ms onset-offset temporal ramps to prevent click artefacts. All sound stimuli were played binaurally via ATH-M50X Audio-Technica headphones through a MacBook computer at a comfortable listening level (at least 70dB).

2.3. Ancillary/ Molecular techniques

All patients were asked if they would be willing to give a sample of cerebrospinal fluid (CSF) via lumbar puncture, allowing stratification of underlying AD from non-AD pathologies. Results were interpreted based on local laboratory reference ranges for known neurodegenerative markers: normal ranges were considered as total tau < 320, Amyloid-Beta$_{1\text{-}42}$ (A$\beta_{1\text{-}42}$) 220-2000, and a tau: A$\beta_{1\text{-}42}$ ratio of above 0.8 was considered as predictive of underlying AD pathology.

Genetic screening was performed using a panel of mutations in major causative dementia genes including *C9orf72, MAPT, PRGN, presenilin 1 and 2 (PS1 and PS2), TBK1, and pathogenic mutations in amyloid precursor protein (APP).*

2.4. Structural MRI acquisition

Participants underwent volumetric brain MRI on a 3Tesla scanner for all of the experiments reported in Chapters 3, 4, and 6. The scanner model changed in March 2016, so the different acquisition strategies are outlined below in relation to the relevant chapters. All structural MRI data reported in Chapters 3 and 4 were acquired in a 3T Siemens Tim Trio MRI scanner, using a 32-channel receiver array head-coil and a T1-weighted sagittal 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (TE = 2.9msec, TI = 900msec, TR = 2200msec), with dimensions 256 x 256 x 208 and voxel size 1.1 x 1.1 x 1.1 mm. Note that the functional data reported in Chapter 4 were obtained using different parameters, and these are described in full in that Chapter.

All MRI data reported in Chapter 6 were acquired in a 3T Siemens Magnetom Prisma MRI scanner, using a 64-channel head-and-neck receiver array

coil and a T1-weighted sagittal 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (TE = 2.93ms, TI = 850ms, TR = 2000ms), with matrix size 256x256x208 and voxel dimensions 1.1x1.1x1.1mm. Parallel imaging was used (GRAPPA with acceleration factor 2), resulting in an overall scan time of five minutes six seconds.

2.5. Structural MRI preprocessing

All structural brain imaging data were preprocessed using statistical parametric mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm) running under MATALB R2014b (The Mathworks, Inc).

Images were segmented, bias corrected and spatially normalized using the 'Segment' procedure in SPM12 and a smoothing Gaussian full-width-half-maximum (FWHM) kernel of 6mm. This step outputs data for each participants in a number of user-specified tissue types. Native space grey matter, white matter and CSF volumes were used to calculate total intracranial volume (TIV) by summing them together for each participant. TIV was later used as a nuisance covariate to control for individual differences in head size in subsequent analyses. The number of Gaussians used to represent the intensity distribution for grey matter, white matter and CSF was set to 2.

DARTEL processes were implemented in SPM for inter-subject registration of brain images. The Run Dartel (create Template) tool computes an initial template from the imported data (the rigidly-aligned images) which incorporates a smoothing procedure. This template is then iteratively performed on each of the participants' scans in turn. The Normalise to Montreal Neurological Institute (MNI) Space tool was then used to spatially normalise the scans into standard (MNI) space using an affine transformation that maps from the Dartel Template average (i.e. sample-specific space) to the MNI space.

Study-specific mean structural brain images were created by calculating the average (mean) of the brain images generated after the DARTEL steps. Statistical parametric maps were then overlayed on the study-specific mean brain image.

2.6. Small volume generation

Small volume corrections were used in the testing of study-specific *a priori* hypotheses relating to both functional and structural imaging. Volumes were derived from Oxford-Harvard cortical (Desikan et al., 2006) and Jülich histological (Eickhoff et al., 2005) atlases via FSLview (Jenkinson *et al.*, 2012). Where appropriate, these maps were manually edited in MRICron (Rorden *et al.*, 2007). Further details of small volumes are outlined in the relevant chapters.

2.7. Statistical analysis

Statistical analyses on behavioural data were performed in Stata v14 (StataCorp, 2015). Brain imaging analyses were performed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) in MATLAB R2014b (The Mathworks, Inc.).

2.7.1. Demographic, neuropsychological and behavioural analyses

Typically, parametric regression models were initially employed, and residuals of the applied statistical models were assessed for skewness and kurtosis to ensure that they approximated a normal distribution. Heteroscedasticity was assessed using Levene's test and visual inspection of a spread of residuals versus predicted values. Where these assumptions were violated, nonparametric equivalents were adopted: Wilcoxon rank-sum tests were substituted for independent sample t-tests, Wilcoxon signed-rank tests for one-sample t-tests, and Kruskal-Wallis tests for analyses of variance (ANOVAs). Categorical variables were compared using χ^2 or Fisher's exact tests. Pearson's correlation coefficient was used to assess degree of correlations between certain variables, used particularly with measures of disease severity and experimental task scores.

For background demographic and neuropsychological data, I used an omnibus test (ANOVA/ Kruskal-Wallis) looking for a main effect of diagnosis. If this was significant, I used post-hoc follow-up t-tests (or Wilcoxon rank-sum tests when appropriate) to compare groups. In Chapters 3 and 4 it was possible to compare each participant group to each other group; in Chapters 5 and 6, the additional neurodegenerative control groups made this untenable, so each patient group was

compared to the healthy control group only, in order to reduce the number of comparisons being made.

2.7.2. Voxel-based morphometry analyses

The analysis framework employed by SPM12 is based on the general linear model, which makes the assumption that intensity within a given voxel (i.e. grey matter volume) can be to some extent explained by (a) certain predictor variable(s) plus a degree of error. This is expressed by the equation: $y_i = \text{intercept} + \beta x_i + \varepsilon_i$ where y represents a matrix of observed data (i.e. voxel intensity), β represents each parameter to be estimated, x is a variable of interest or nuisance covariate, and ε denotes error, representing the difference between the observed data, and the data predicted by the model (Ridgway *et al.*, 2008).

VBM was used for two separate purposes in this thesis: i) to examine associations between specific experimental task performance and grey matter atrophy in patient groups; and ii) to create 'disease-maps' representing areas of high atrophy in patient groups relative to healthy age-matched controls.

In the task-volume regression analyses (i), individual voxel grey matter volume was modelled as a function of experimental test score. For the patient-control disease maps (ii), groups were compared using voxel-wise two-sample t-tests. The standard procedure was to incorporate nuisance covariates of age, gender and TIV; deviations from this approach are reported in individual chapters. In healthy control participants, total brain volume varies with head size (Acer *et al.*, 2007), and adjusting for TIV controls for this (Whitwell *et al.*, 2001). In the studies reported in this thesis, TIV was always calculated by adding together the volumes of the grey matter, white matter, and CSF generated during the initial segmentation process (Malone *et al.*, 2015).

To limit the number of multiple comparisons and to ensure that only voxels inside the brain were included in the analyses, I used an automatic mask creation strategy designed to find an optimal threshold at which to binarise an average image (Ridgway *et al.*, 2009). Traditional explicit mask creation strategies commonly exclude voxels in areas of the brain that are most vulnerable to atrophy, and using this automatic

mask creation approach reduces the possibility of false negatives arising from masking out critical areas of atrophy (Ridgway *et al.*, 2009).

For all studies reported in this thesis, I used the SPM default uncorrected cluster-defining threshold of $p < 0.001$ at voxel level, which is widely accepted as an appropriate primary threshold (Woo *et al.*, 2014) followed by a correction for multiple comparisons at peak-level for voxel-based morphometry and cluster level for functional magnetic resonance imaging.

Controlling for multiple comparisons protects against the possibility of making a Type 1 error (obtaining 'false-positive' results), and in this thesis I consistently use a family-wise error (FWE) correction (Worsley *et al.*, 1996), either across the whole brain or within Chapter-specific small volumes. In behavioural statistics, the problem of multiple comparisons can be overcome with Bonferroni corrections, where the accepted alpha level for significance is divided by the number of tests conducted (Benjamini & Hochberg, 1995). Such an approach is not appropriate for use with VBM or fMRI because the tests are not independent: if one voxel is heavily atrophied, or shows heightened activation, it is likely that the surrounding voxels will be too. The methodology proposed by Worsley and colleagues employs random-field theory to limit the Type 1 error rate, by assuming that the distributions of statistics in the imaging data follow a smoothly varying random field. This approach requires the neuroimaging data to have a minimum level of smoothness, and this is why I consistently use a Gaussian smoothing kernel of 6mm in preprocessing. Essentially, this approach is then able to estimate the likelihood of voxels (or clusters of voxels) with particular statistical values occurring by chance in data of that smoothness (Worsley *et al.*, 1996; Nichols, 2012). However, FWE corrections over the whole brain are still stringent and small volume corrections represent an appropriate way of reducing the number of multiple comparisons being made, if defined *a priori* on the basis of previous reports in the literature.

2.8. Presentation of data

2.8.1. Tables

For all tables containing demographic data in this thesis, mean (standard deviation (SD)) scores are presented, unless otherwise indicated. Maximum possible scores are given in parentheses after the name of each test, and significant group differences from the control cohort are typically indicated in bold. If reduced numbers of participants completed a particular task, this is shown with a footnote to each table.

For tables containing neuroimaging data, peak (local maxima) coordinates are given in MNI standard stereotactic space. Only positive grey matter associations are reported; no negative associations were identified at the prescribed significance thresholds for the contrasts and groups of interest in any of the experimental chapters.

2.8.2. Figures

For behavioural data, scatter plots or box-and-whisker diagrams have been used to give an indication of the variability in performance across groups and tasks.

SPM figures show regional grey matter volume (VBM)/ activation (fMRI) associated with performance on key experimental tasks in particular patient groups. All SPMs have been overlaid on representative sections of the normalised study-specific T1-weighted mean brain MR image in MNI space. Coronal sections show the left hemisphere on the left and axial sections show the left hemisphere at the top. Colour bars code T-values for each SPM, and all SPMs are thresholded at a voxel-level of $p<0.001$ uncorrected for display purposes, while regional local maxima were significant at $p<0.05_{FWE}$ corrected for multiple comparisons at whole brain or within pre-specified regions of interest.

3. Behavioural and neuroanatomical correlates of auditory speech analysis

3.1. Chapter Summary

It is clear from the research discussed in Chapter 1 that the PPA syndromes are associated with core auditory processing deficits. In this experiment, I used auditory sequences manipulated for three core auditory speech signal parameters: temporal regularity, phonemic structure, and entropy. I studied 27 patients with PPA (10 nfvPPA; nine svPPA; eight lvPPA) and 19 healthy controls, and assessed their ability to process these parameters behaviourally using a series of two-alternative, forced-choice tasks. All patient groups showed impaired processing of phonemic structure and entropy, and the nfvPPA and lvPPA groups were also impaired in terms of processing temporal regularity in speech signals. In a VBM analysis across a combined patient cohort comprising patients with nfvPPA and svPPA, performance on the temporal regularity task was associated with grey matter volume in left supplementary motor area and right caudate, while phonemic processing correlated with grey matter in left supramarginal gyrus. Performance on processing of prosodic predictability correlated with grey matter volume in right putamen. My findings here suggest that PPA syndromes may be underpinned by generic deficits of auditory signal analysis, and that these deficits have structural correlates in a distributed network of regions that are crucial for these elements of auditory signal analysis.

3.2. Introduction

The primary progressive aphasias (PPAs) have collectively helped establish the paradigm of selective neural network vulnerability to neurodegenerative pathologies (Mesulam, 1982; Mesulam *et al.*, 2014a). A large body of work discussed in detail in Chapter 1 has identified nonverbal auditory deficits associated with PPA syndromes, and it has been proposed that generic deficits of auditory signal processing may be intrinsic to PPA syndromes, and could underpin the neurolinguistic deficits associated with these diseases (Goll *et al.*, 2010a; Grube *et al.*, 2016), reflecting underlying network pathophysiology.

Consistent with the clinico-anatomical profiles described in Chapter 1, nfvPPA and lvPPA syndromes are associated with more prominent deficits of early perceptual auditory analysis. svPPA, by contrast is particularly associated with auditory associative deficits and impaired sound meaning (Bozeat *et al.*, 2000; Goll *et al.*, 2010a, 2011; Rohrer *et al.*, 2012; Golden *et al.*, 2015b, 2017; Grube *et al.*, 2016; Hardy *et al.*, 2016; Henry *et al.*, 2016).

In this Chapter and in Chapter 4, I explore auditory speech signal processing in patients with nfvPPA, svPPA and lvPPA relative to healthy older individuals, using experimental stimuli based on sequences of spoken syllables. These sequences were manipulated for three generic auditory speech signal characteristics relevant to previously documented neurolinguistic deficits in PPA syndromes: temporal regularity, phonemic structure, and entropy. These "building blocks" of speech signals have not been explored systematically in PPA previously.

Analysis of temporal structure is critical for speech segmentation (and therefore lexical access) in healthy individuals (Dilley & McAuley, 2008; Dilley *et al.*, 2010), and particularly vulnerable in nfvPPA (Grube *et al.*, 2016). Here, I varied the syllabic timing so that the interval between syllables was either regular (isochronous) or irregular (anisochronous).

Phonemes are the smallest intelligible units of spoken language and as such constitute a special category of auditory 'objects' (Griffiths & Warren, 2004): phonemic processing deficits are prominent in lvPPA and nfvPPA (Rohrer *et al.*, 2010b; Hailstone *et al.*, 2012; Hardy *et al.*, 2015; Henry *et al.*, 2016). Here, I manipulated the higher-order spectral structure that distinguishes natural (intelligible) phonemes from complex, but synthetic (unintelligible) speech-like sounds (Blesser, 1972), in order to target a universal neural mechanism of phoneme detection relevant to any language.

'Entropy' is a concept derived from information theory describing the average amount of information carried by any signal (Shannon, 1948; Overath *et al.*, 2007): it measures signal unpredictability, in the sense that an unpredictable signal is less 'redundant' and therefore conveys more information (henceforth I use the term 'information' in this technical sense). I manipulated the information content (entropy) of

the experimental stimuli by varying the predictability of pitch patterns across successive syllables in a sequence: a generic characteristic relevant to speech prosody, but not bound to the prosodic conventions of any particular language. Deficits of pitch pattern processing have been identified in all major PPA syndromes (Hsieh *et al.*, 2011; Rohrer *et al.*, 2012; Golden *et al.*, 2015b, 2017). However, the manipulation used here – unlike those previously employed – was designed to index a brain mechanism responsible for computing the overall statistics of an auditory object (the 'melody' of the syllable sequence). An analogous computational mechanism has been invoked to account for the profile of evolving object recognition deficits across sensory modalities in svPPA (Lambon Ralph *et al.*, 2010).

In this Chapter, I identify behavioural signatures for each syndrome, before exploring the critical structural brain substrates driving performance on the auditory tasks across PPA syndromes. In Chapter 4, I use the same stimuli in the context of a functional magnetic resonance imaging (fMRI) experiment to identify functional neuroanatomical substrates: the mechanisms underpinning deficits for particular PPA syndromes.

3.3. Key predictions

- Patients with nfvPPA and lvPPA will show impaired processing of temporal regularity and phonemic spectral structure (Rohrer *et al.*, 2010b; Hailstone *et al.*, 2012; Hardy *et al.*, 2015; Grube *et al.*, 2016; Henry *et al.*, 2016).
- Patients with svPPA will show impaired processing of predictability (entropy) of speech signals (Hsieh *et al.*, 2011; Golden *et al.*, 2015b, 2017; Lambon Ralph *et al.*, 2016).
- Processing of temporal regularity and signal predictability will correlate with grey matter volume in a distributed frontotemporal-subcortical network comprising posterior temporal, medial prefrontal and striatal cortex (Griffiths & Warren, 2002; Overath *et al.*, 2007; Ide *et al.*, 2013; Cope *et al.*, 2014; Schaeverbeke *et al.*, 2016).

- Processing of phonemic spectral structure will correlate with grey matter volume in temporo-parietal cortex (Liberman & Mattingly, 1989; Scott *et al.*, 2000; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009).

3.4. Materials and methods

3.4.1. Participants

Ten patients with nfvPPA (five female; mean age 71.2 ± 8.9 (SD) years), nine patients with svPPA (three female; mean age 63.8 ± 4.6 years), eight patients with lvPPA (three female; mean age 64.5 ± 6.3 years), and nineteen healthy older individuals (10 female; mean age 69.4 ± 4.5 years) participated in this study. Cerebrospinal fluid tau/ abeta profiles were available for six of the eight patients with lvPPA, all of which were consistent with Alzheimer's pathology based on local reference ranges (total tau: beta-amyloid 1-42 ratio > 1). All participants were recruited in accordance with the procedures described in Section 2.1. Demographic and background clinical information are given in Table 3.1.

Table 3.1. Demographic, clinical and neuropsychological characteristics of participant groups.

Characteristic	Controls	nfvPPA	svPPA	lvPPA
Demographic and clinical				
No. (m:f)	9:10	5:5	6:3	5:3
Age (years)	69.4 (4.5)	71.2 (8.9)	**63.8 (4.6)***	**64.5 (6.3)***
Handedness (R:L)	18:1	8:2	8:1	7:1
Education (years)	15.8 (2.4)	14.8 (2.9)	14.9 (2.9)	14.9 (2.0)
MMSE (/30)	29.7 (0.6)	**25.6 (4.6)**	**19.7 (9.1)**	**17.0 (7.8)**
Symptom duration (years)	-	4.8 (2.8)	5.3 (2.8)	4.4 (1.5)
PTA best ear (N:Mild:Mod)	10:7:0[b]	3:5:1[a]	5:4:0	3:5:0
Background neuropsychology				
General intellect: IQ				
PIQ	125.9 (7.3)	**90.7 (21.4)[a]**	**72.3 (18.9)**	**65.4 (18.8)***
VIQ	124.6 (2.5)	**101.2 (7.0)**	**102.1 (25.6)**	**87.8 (13.9)**
Episodic memory				
RMT words (/50)	49.3 (0.9)	**43.5 (6.3)**	**36.0 (8.0)[c,]***	**34.8 (6.4)[b,]***
RMT faces (/50)	45.2 (3.1)	**39.3 (6.1)**	**33.3 (6.8)[c]**	**32.5 (9.7)**
Working memory				
Digit span forward (max)	7.2 (1.2)	**5.1 (0.8)[b]**	6.0 (1.9)	**3.4 (0.9)*,†**
Spatial span forward (max)	5.5 (0.8)[c]	**4.3 (1.1)[c,†]**	5.4 (0.9)	**3.6 (0.7)†**
Executive skills				
Digit span reverse (max)	5.6 (1.2)	**3.4 (0.9)[b]**	4.4 (2.1)	**2.0 (1.3)*,†**
Spatial span reverse (max)	5.4 (1.0)[c]	4.4 (1.5)[c]	4.9 (2.0)	**3.1 (1.1)*,†**
Letter fluency (total)	16.8 (5.0)	**5.5 (5.8)[d]**	**7.3 (6.5)**	**1.9 (1.7)[a,]*,†**
Category fluency (total)	23.6 (5.5)	**10.7 (4.3)[d]**	**4.9 (5.8)**	**4.1 (3.2)[a,]***
Trails A (s)	34.5 (6.8)[a]	**86.9 (50.0)[b]**	**48.8 (18.2)[a]**	**111.5 (85.7)†**
Posterior cortical skills				
GDA Calculation (/24)	15.3 (5.5)	**5.7 (3.6)[c]**	11.2 (9.8)	**1.6 (2.2)*,†**
VOSP Object Decision (/20)	19.2 (1.3)[a]	**15.1 (4.6)[a]**	**16.8 (3.1)[a]**	**16.9 (2.1)**
Neurolinguistic functions				
Auditory input processing				
PALPA-3 (/36)	35.8 (0.5)[c]	**34.0 (2.6)[c]**	**32 (6.5)**	**31.5 (3.8)**
Word retrieval				
GNT (/30)	26.4 (2.5)	**17.0 (7.1)[a]**	**1.9 (4.6)***	**3.6 (6.4)***
Comprehension				
BPVS (/51)	49.5 (1.3)	**43.4 (5.7)**	**10.1 (14.9)*,‡**	**35.5 (13.0)***
Concrete synonyms (/25)	24.1 (0.8)[c]	21.3 (4.7)[c]	**14.6 (3.2)*,‡**	**17.6 (2.6)[a],***
Abstract synonyms (/25)	24.3 (0.9)[c]	21.1 (5.1)[c]	**15.9 (3.5)[c,]***	14.7 (4.1)[a],*
PALPA-55 sentences (/24)	23.8 (0.6)[e]	22.1 (3.3)[c]	19.7 (6.8)	**15.0 (5.1)***
Speech repetition				
Polysyllabic words (/45)	44.4 (0.9)[e]	**33.2 (12.0)[d,†]**	43.8 (1.6)	**32.0 (7.8)†**
Psychoacoustic tasks**				
Temporal regularity (/20)	19.5 (1.0)	**18.0 (2.3)**	18.6 (2.7)	**17.0 (3.9)**
Phonemic structure (/20)	18.8 (1.6)	**15.3 (3.4)**	**15.6 (1.6)**	**11.8 (2.9)*,†**
Entropy (/20)	19.1 (1.8)	**14.0 (3.1)**	**15.0 (4.0)**	**13.5 (4.1)**

Significant differences ($p<0.05$) from healthy control values are indicated in **bold**; *significantly different from nfvPPA group; †significantly different ($p<0.05$) from svPPA group; ‡significantly different ($p<0.05$) from lvPPA group; **see text for details. Reduced numbers of participants are indicated: [a]n–1; [b]n–2; [c]n–3; [d]n–4; [e]n–5; [f]n–6.

3.4.2. Experimental stimuli

The stimuli used here and in Chapter 4 were based on sequences of spoken syllables comprising consonant-vowel or vowel-consonant phoneme combinations, recorded in a standard southern English accent by a young adult male speaker (myself). The syllables ‘af’, ‘ba’, ‘da’, ‘mo’, ‘om’, ‘or’, ‘po’, and ‘ro’ were selected for high intelligibility and identifiability, based on pilot testing in five young adult listeners in the Dementia Research Centre. In MATLAB R2012a (https://uk.mathworks.com/), recorded syllables were each edited to duration 240 msec and concatenated with random ordering into sequences; each sequence comprised 20 syllables and intervening silent intervals, with fixed overall sequence duration (7.65 seconds) and root-mean-square intensity.

I varied three sequence parameters independently to create the experimental conditions used in these Chapters. Temporal regularity was manipulated by varying the inter-syllable interval within each sequence such that the interval was either kept constant at 150ms (isochronous condition) or randomly allocated in the range 50 to 250 msec around a mean of 150 msec (anisochronous condition), maintaining the same overall sequence tempo.

Phonemic structure was manipulated by spectrally rotating spoken syllables using a previously described procedure (Blesser, 1972); spectral rotation preserves overall acoustic spectral and temporal complexity and bandwidth but radically alters spectral detail, by inverting the acoustic frequency spectrum. This manipulation renders the rotated signal unintelligible as human speech (it is perceived as ‘alien’ or ‘computer speech’) and here enabled me to create stimulus conditions in which the constituent syllables in each sequence were either all unrotated (natural) or all spectrally rotated (unintelligible).

Entropy (or average information content in the sequence) was manipulated by varying fundamental frequency (pitch) of constituent syllables over a half-octave range from a lower fundamental frequency of 100 Hz with a 20-note octave division (i.e., not conforming to the intervals of Western music), adapting a previously described procedure (Overath et al., 2007). Pitch sequences were based on inverse Fourier

transforms of f^n power spectra, using values of n = 0 (no correlation between successive pitch values) for the high entropy condition and n = 4 (high correlation between successive pitch values, approaching a sine wave contour for the low entropy condition. Examples of these stimuli are schematised in Figure 3.1 and included on the enclosed CD in Audio Files 3.1–3.6 (see Supplementary Table 2).

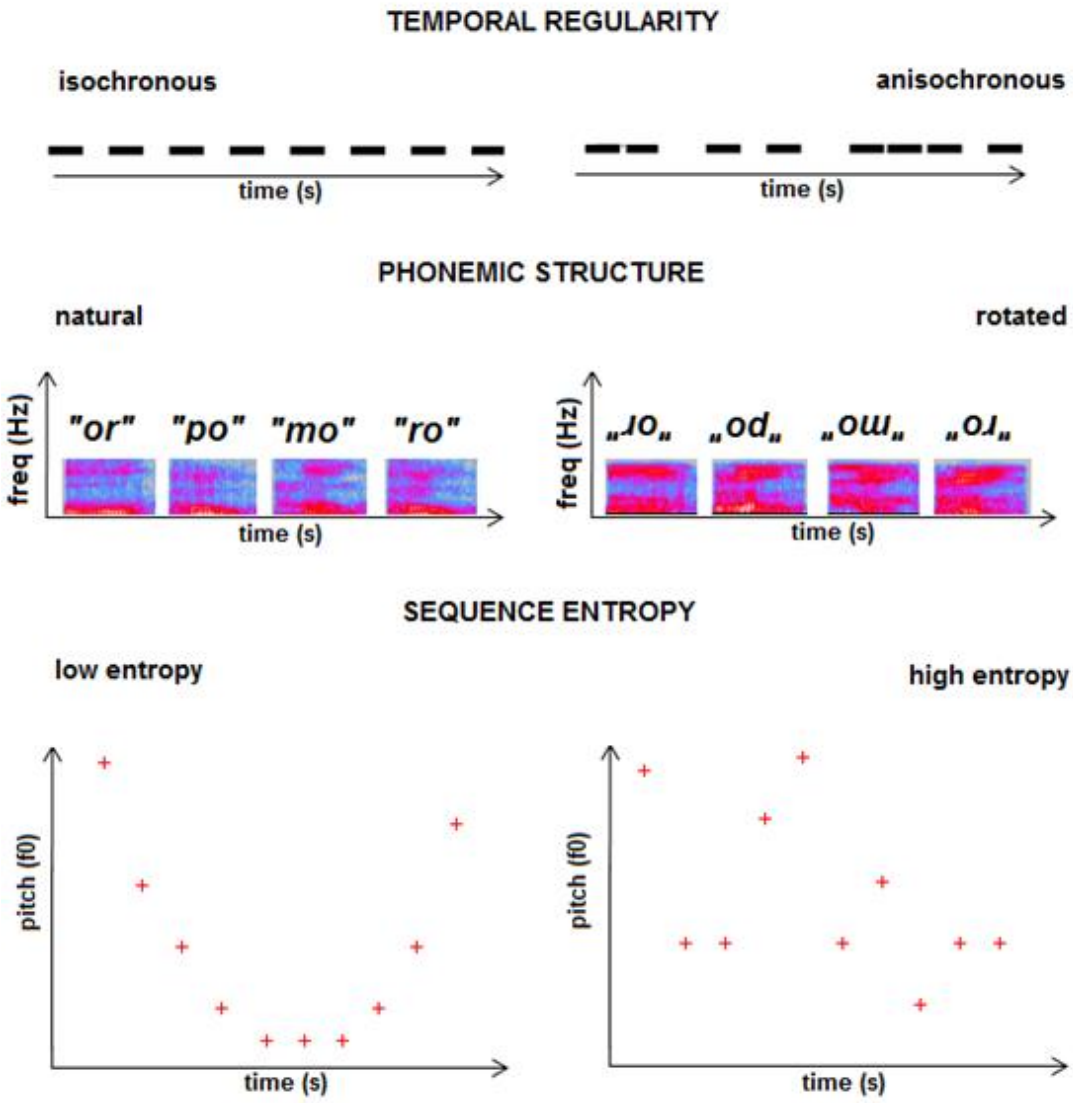

Figure 3.1. Schematic representations of stimulus manipulations used to create the conditions in Chapters 3 and 4. The top panels show examples of isochronous and anisochronous sequences. The middle panels show spectrograms for syllable sequences in the natural and spectrally rotated conditions. The bottom panels show examples of low and high entropy sequences, based on degree of correlation between pitch (fundamental frequency, f0) of successive intervals (highly correlated and approaching a sine wave contour in the low entropy condition; uncorrelated in the high entropy condition).

3.4.3. Experimental psychoacoustic test procedure

Each participant's ability to perceive the key experimental manipulations was determined using psychoacoustic tests employing two-alternative-forced-choice decisions on the syllable sequences described above. Separate tests were administered to assess temporal processing (regular vs irregular sequences), phoneme detection (natural vs artificial [spectrally rotated] phonemes) and pitch pattern detection (low entropy vs high entropy sequences). Pictorial cards were used to ensure all participants understood the task instructions and to allow nonverbal responses where preferred (details of task instructions and aids used are in Figure 3.2). For each test, 20 stimuli (10 representing each of the two conditions of interest) were presented; no feedback was given and no time limits were imposed. Participant responses were recorded for offline analysis.

3.4.4. Analysis of clinical and background neuropsychological data

Clinical and behavioural data were analysed in accordance with the general principles outlined in Section 2.9.1.

3.4.5. Analysis of experimental psychoacoustic data

Here, nonparametric Mann-Whitney U tests were used to compare groups on neuropsychological parameters where residuals were non-normally distributed. In separate regression (Spearman's rank correlation) analyses over the participant cohort, I assessed experimental psychoacoustic task performance against background executive function (WASI Matrices score; a proxy for disease severity) and performance on the experimental phonemic task against a standard measure of phoneme discrimination (PALPA-3 score).

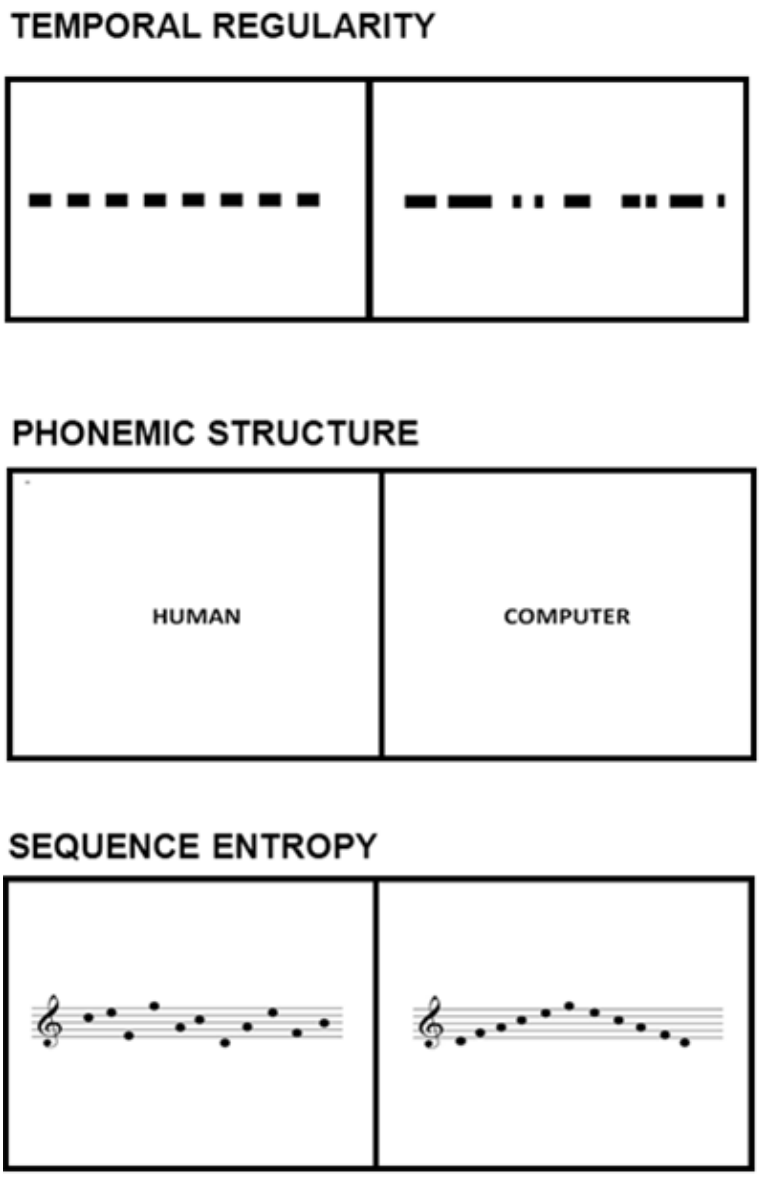

Figure 3.2. Visual aids used in behavioural testing. Pictorial cue cards were used to assist understanding and responding on the behavioural tasks. For the test assessing temporal processing (top panels), on each trial participants were asked to decide whether the sounds they heard came regularly or irregularly. For the test assessing processing of phonemic structure (middle panels), participants were asked to decide whether the sounds were made by a human or by a computer. For the test assessing processing of sequence entropy, participants were asked to decide whether the sounds were arranged randomly or following a pattern. On each trial, participants were able to respond verbally or by pointing to the appropriate cue card.

3.4.6. Brain MRI acquisition and voxel-based morphometry

I first assessed disease-associated atrophy profiles in each patient group; see Section 2.9.2 for a description of the procedure. I also assessed neuroanatomical correlates of experimental behavioural task performance in each syndromic group individually, incorporating age, total intracranial volume (TIV) and symptom duration as nuisance covariates. Correlates of behavioural performance on the temporal regularity and prosodic predictability tests were assessed within a region comprising bilateral posterior superior temporal gyrus, planum temporale, supramarginal gyrus, supplementary motor area, anterior cingulate and striatum (Griffiths & Warren, 2002; Overath *et al.*, 2007; Ide *et al.*, 2013; Cope *et al.*, 2014). Grey matter correlates of performance on the phoneme detection test were assessed with a more restricted subregion comprising left posterior superior temporal gyrus, planum temporale and supramarginal gyrus (Liberman & Mattingly, 1989; Scott *et al.*, 2000; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009). Anatomical regions are depicted in Figure 3.3.

Ultimately, this approach lacked power to detect changes within each syndromic group separately, so I decided to pool just the nfvPPA and svPPA groups (i.e. the syndromes most likely to have FTLD pathology) into a combined cohort. Age, total intracranial volume, symptom duration and group membership were incorporated as nuisance covariates in a multiple regression design, using the same small volumes as described above and depicted in Figure 3.3. All other parameters were consistent with the procedure described in Section 2.9.2.

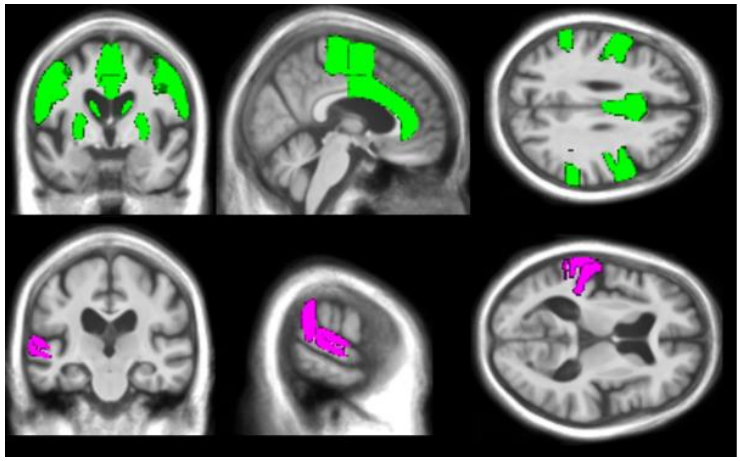

Figure 3.3. Representative sections of small volume corrections. Small volumes are rendered on sections of the mean normalised brain template for the patient cohort. For the contrasts assessing temporal processing and prosodic predictability processing, the anatomical region of interest (green, above) comprised bilateral posterior superior temporal gyrus/sulcus, planum temporale, supramarginal gyrus, striatum (caudate and putamen), supplementary motor cortex and anterior cingulate. For the contrast assessing phonemic processing, the anatomical region for small volume correction (lilac, below) was a subregion comprising left posterior superior temporal gyrus/sulcus, planum temporale and supramarginal gyrus.

3.5. Results

3.5.1. General participant characteristics

Comparisons of general characteristics and neuropsychological performance between participant groups are summarised in Table 3.1.

Patient groups did not differ significantly from healthy controls in terms of gender, handedness or years in formal education (all $p > 0.05$). The svPPA and lvPPA groups were significantly younger than both the healthy control and nfvPPA groups ($p < 0.05$; accordingly, the effect of age as a nuisance covariate of group experimental psychoacoustic task performance was separately assessed). The patient groups had comparable symptom duration ($p = 0.4$), and there were no overall group differences in terms of MMSE score ($p = 0.5$). Participant groups showed no significant differences in peripheral hearing (see Table 3.1).

3.5.2. Experimental psychoacoustic task performance

Group performance profiles on the experimental psychoacoustic tasks are summarised in Table 3.1 and individual data are plotted in Figure 3.4. On the tests of phoneme detection and entropy analysis, all patient groups performed significantly

worse than the healthy control group (all $p < 0.05$). On the test of temporal regularity processing, the nfvPPA and lvPPA groups performed significantly worse than the healthy control participants ($p < 0.05$), whereas the performance of the svPPA group did not differ significantly from controls ($p = 0.07$). The lvPPA group also performed significantly worse than the nfvPPA and svPPA patient groups on this task. This pattern of results was not altered by incorporating age as a nuisance covariate.

Performance on each of the experimental psychoacoustic tasks correlated significantly with a standard index of background executive capacity (WASI Matrices score; all $p<0.01$), an index of overall disease severity. Performance on the experimental phoneme detection task correlated significantly with a standard measure of phoneme discrimination ability (PALPA-3 score; $p = 0.04$).

3.5.3. Neuroanatomical data

Statistical parametric maps of disease-associated atrophy are shown in Figure 3.5. Maps of grey matter regions associated in the combined patient cohort with performance on the experimental psychoacoustic tasks are shown in Figure 3.6.

Local maxima for disease-related atrophy are summarised in Table 3.2; local maxima of grey matter change correlated with experimental psychoacoustic task performance are summarised in Table 3.3.

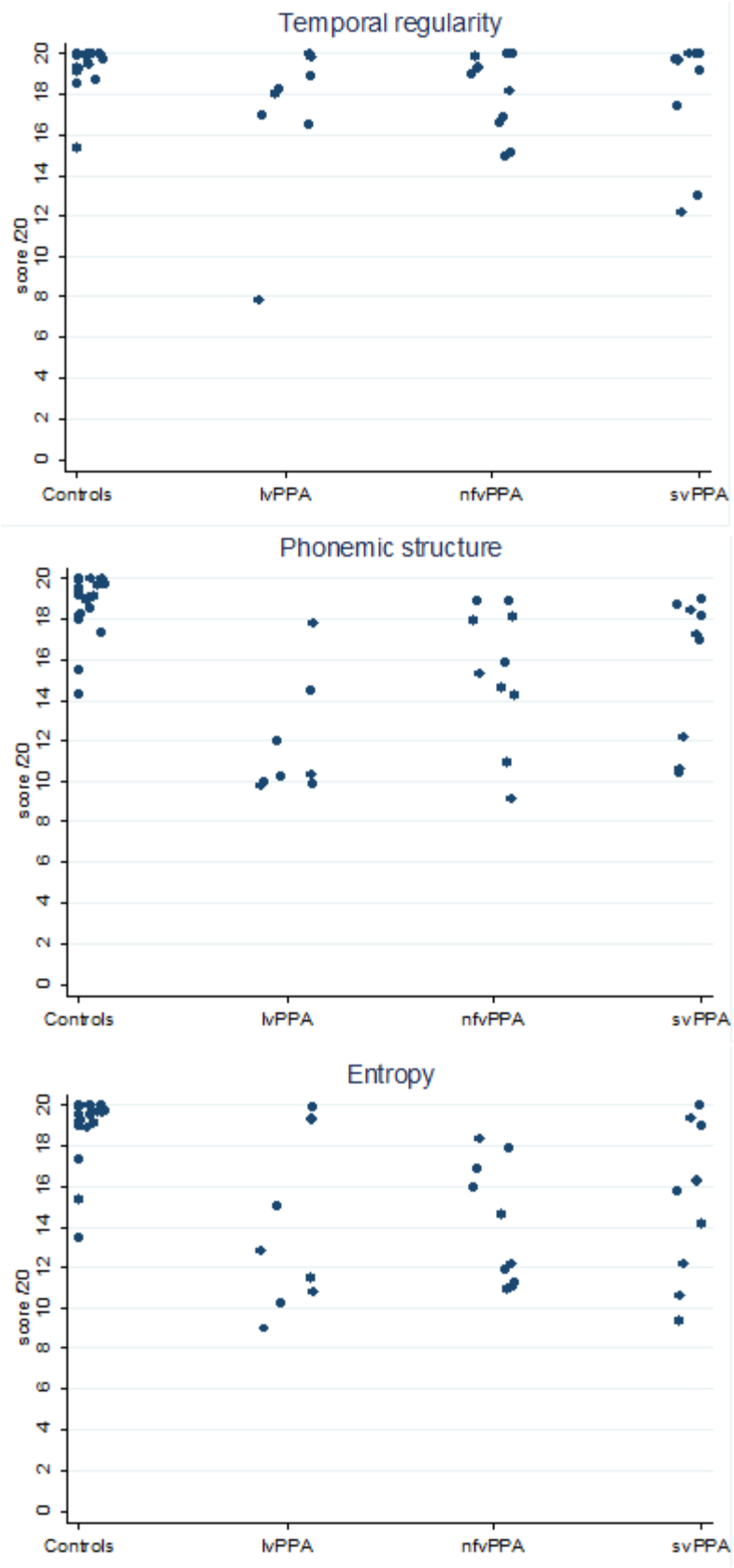

Figure 3.4. Performance on experimental psychoacoustic tasks. Scatter plots showing individual performance on each of the psychoacoustic tasks of interest, by participant group. Note that individual data points have been "jittered" randomly so as to minimise overlap.

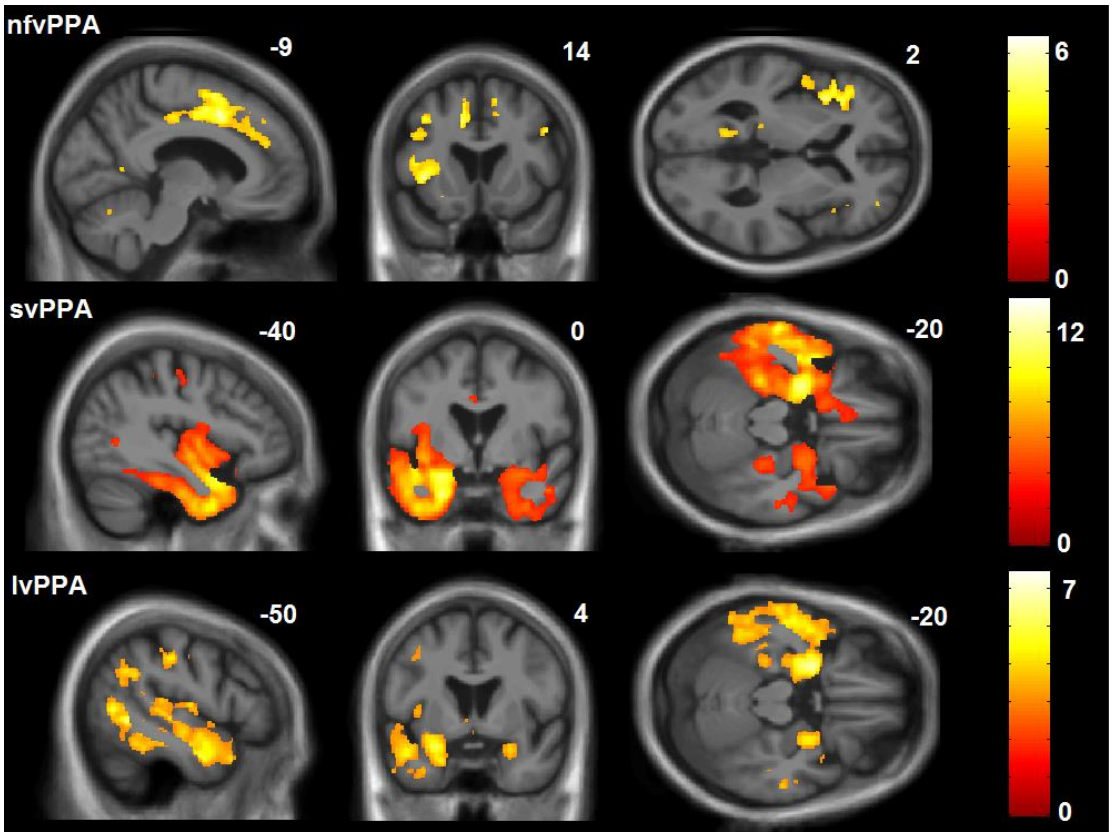

Figure 3.5. Disease-associated grey matter atrophy in each patient group. The Figure shows SPMs of disease-associated grey matter atrophy relative to healthy controls, based on a voxel-based morphometric analysis.

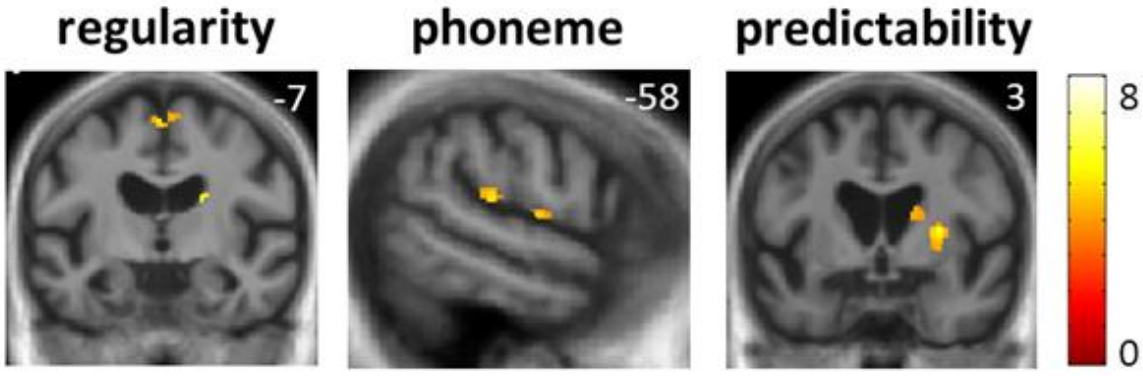

Figure 3.6. Neuroanatomical correlates of performance on speech signal analysis tasks. Statistical parametric maps of regional grey matter volume positively associated with performance on speech signal analysis tasks (assessing processing of temporal regularity, phonemic spectral structure and prosodic predictability, respectively) in the combined nfvPPA and svPPA patient cohort.

Table 3.2. Neuroanatomical associations of disease-related grey matter atrophy

Region	Side	Cluster (voxels)	Peak (mm)			t-value
			x	y	z	
Nonfluent variant						
Supplementary motor cortex*	L	2581	-8	9	48	5.97
Insula/ precentral gyrus	L	4903	-38	14	2	5.80
Lingual gyrus	R	104	21	-48	-4	5.19
Lingual gyrus	L	595	-15	-56	-2	5.05
Middle frontal gyrus	R	108	45	12	34	5.00
Fusiform gyrus	L	185	-28	-12	-33	4.90
Inferior temporal gyrus	L	376	-56	-63	-15	4.87
Supplementary motor cortex	R	141	12	3	60	4.84
Fusiform gyrus	R	279	28	-30	-24	4.78
Thalamus	L	101	-20	-32	-3	4.65
Precentral gyrus	R	304	40	-15	52	4.49
Supramarginal gyrus	R	193	57	-44	39	4.18
Supramarginal gyrus*	L	136	-40	-42	38	4.01
Semantic variant						
Temporal pole	L	29614	-33	14	-32	13.82
Temporal pole	R	8845	39	9	-34	7.79
Anterior cingulate	L	103	-4	-3	33	4.71
Anterior cingulate (separate locus)	L	406	-4	24	32	4.04
Logopenic variant						
Middle/ superior temporal gyrus	L	15162	-60	-12	-12	7.77
Middle/ superior temporal gyrus	R	2246	62	-26	-8	6.36
Supramarginal gyrus	L	738	-36	-46	42	5.83
Middle occipital gyrus	L	363	-27	-86	28	5.72
Angular gyrus	L	384	-45	-48	27	5.55
Hippocampus	R	699	27	-6	-16	5.46
Postcentral gyrus	L	304	-50	-24	40	5.31
Middle frontal gyrus	L	743	-33	50	26	5.31
Superior parietal lobule	L	129	-21	-75	44	5.28
Temporal pole	R	156	40	8	-36	5.03

The Table summarises the distribution of significant disease-related regional grey matter loss, comparing each syndromic group with the healthy control group in separate voxel based morphometric analyses. All values shown were significant at a lenient threshold $p<0.001$ uncorrected over the whole brain volume; clusters >100 voxels in size are included and coordinates of local maxima are in MNI standard space; *region also identified as a significant association of experimental psychoacoustic task performance (see Table 3.3).

Compared with the healthy control group, each syndromic group exhibited the anticipated profile of disease-associated grey matter loss (see Figure 3.5). The nfvPPA group had bilateral, predominantly fronto-insular atrophy that was more marked in the left cerebral hemisphere. The svPPA group showed asymmetric atrophy predominantly involving the antero-mesial and inferior temporal lobes, again more marked in the left cerebral hemisphere. The lvPPA group again showed asymmetric atrophy, predominantly involving the middle and superior temporal lobes, but with considerable parietal extension into supramarginal gyrus and associated structures.

Table 3.3. Neuroanatomical correlates of speech signal analysis.

Contrast	**Region**	**Side**	**Cluster** (voxels)	**Peak** (mm)			**t-value**	**p-value**
				x	y	z		
Temporal regularity	Supplementary motor*	L	427	-2	-9	63	7.93	0.016
	Caudate	R	216	16	-2	20	7.02	0.042
Phonemic structure	Supramarginal gyrus*	L	12	-58	-28	14	5.53	0.026
Prosodic predictability	Putamen	R	289	28	0	6	7.01	0.035

The Table summarises statistically significant positive associations between grey matter volume and performance on psychoacoustic tasks to assess the temporal regularity, phoneme structure and prosodic predictability of experimental speech stimuli (see text for details), based on a voxel based morphometric analysis of brain MR images for the combined nfvPPA and svPPA patient cohort. All values were significant at $p<0.05_{FWE}$ within a prespecified neuroanatomical small volume correction (see Figure 3.1); *local maximum coincident with regional disease-related grey matter atrophy in the nfvPPA group (see Table 3.2).

Performance on the task assessing temporal regularity in speech signals was positively associated with grey matter volume in left supplementary motor area and right caudate (both $p<0.05_{FWE}$ within the pre-specified region of interest). Performance on the task assessing phoneme detection was associated with grey matter volume in left supramarginal gyrus ($p<0.05_{FWE}$ within the pre-specified region of interest). Performance on the task assessing prosodic predictability was associated with grey matter volume in right putamen ($p<0.05_{FWE}$ within the pre-specified region of interest).

3.6. Discussion

Here, I have demonstrated that all three of the major PPA syndromes are associated with core deficits at the level of speech signal decoding, relative to healthy older individuals. Furthermore, I have identified neuroanatomical correlates of the defective analysis of these generic speech signal attributes that extend across the two canonical FTLD PPA syndromes: nfvPPA and svPPA.

Consistent with previous evidence concerning the processing of nonverbal sounds in PPA (Goll *et al.*, 2010a, 2011; Rohrer *et al.*, 2012; Golden *et al.*, 2015b, 2017; Grube *et al.*, 2016; Hardy *et al.*, 2016), processing of speech signal temporal regularity (an early perceptual property) was impaired in the patient groups with nfvPPA and svPPA, while processing of phonemic structure and entropy processing were impaired across all three patient groups. These findings substantiate the emerging picture of more generic, extra-linguistic deficits that may contribute to the hallmark neurolinguistic syndromes of PPA.

Due to the lack of statistical power to run robust VBM analyses within individual syndromic groups, I combined the nfvPPA and svPPA groups in order to identify shared neuroanatomical substrates implicated in the processing of these key auditory characteristics. The combined FTD-PPA cohort could necessarily not include the lvPPA participants as this syndrome is typically associated with AD pathology (and indeed at least six of the eight participants included here had CSF profiles consistent with AD pathology; see Section 3.4.1). I focus on this patient group more specifically in Chapter 4.

Across the combined nfvPPA and lvPPA patient cohort, the psychoacoustic deficits identified here had separable structural neuroanatomical substrates within distributed cerebral cortico-subcortical networks that have previously been implicated in the analysis of auditory object and multimodal sensory information (Liberman & Mattingly, 1989; Scott *et al.*, 2000; Griffiths & Warren, 2002; Hickok & Poeppel, 2007; Overath *et al.*, 2007; Rauschecker & Scott, 2009; Ide *et al.*, 2013; Cope *et al.*, 2014; Schaeverbeke *et al.*, 2016).

Impaired processing of auditory rhythm and a neuroanatomical correlate in supplementary motor cortex have been identified previously in nfvPPA (Grube *et al.*, 2016; Schaeverbeke *et al.*, 2016). My findings here confirm work suggesting that this is a structural substrate of auditory rhythm processing that extends to speech signals, and supports a link between impaired perception of production of speech in these patients (see Figure 1.7). In addition to any deficit of motor speech planning, impaired tuning, monitoring and rehearsal of own speech output may contribute to impaired production of lexical stress and prosody in patients with nfvPPA (Ash *et al.*, 2010; Grube *et al.*, 2016; Schaeverbeke *et al.*, 2016). As discussed at more length in the discussion to Chapter 4, the supplementary motor cortex is involved in mediating the tracking and integration of prosodic and syntactical rhythms in the healthy brain (Hertrich *et al.*, 2016), and speech apraxia in nfvPPA may at least in part reflect dysfunctional integration of temporal perceptual and speech output processes (Ash *et al.*, 2010; Grube *et al.*, 2016; Schaeverbeke *et al.*, 2016). An additional correlate of temporal regularity processing was identified here in caudate nucleus, consistent with previous work implicating striatum in tracking of speech and other stimuli with extended temporal structures (Grahn & Rowe, 2013). My findings, therefore, corroborate previous formulations of nfvPPA as an essentially fronto-striatal disorder (Looi *et al.*, 2012; Mandelli *et al.*, 2014).

The phonemic processing deficit exhibited by all three patient groups reflects impaired representation of auditory object features: whereas phonemes constitute a specialised category of auditory objects, an analogous deficit has been demonstrated previously to affect a range of nonverbal sounds across PPA syndromes (Goll *et al.*, 2010a). While linguistic phonological impairment is well recognised as a feature of nfvPPA and lvPPA, my findings here in the context of previous work suggest that phonemic deficits may be underpinned by a generic defect of auditory apperceptive function (Goll *et al.*, 2010a; Hailstone *et al.*, 2012; Grube *et al.*, 2016; Henry *et al.*, 2016).

The neuroanatomical correlate of impaired phoneme detection in my patient cohort was localized to left supramarginal gyrus: this temporo-parietal junctional zone has previously been identified as a phonological processing hub in the healthy brain

(Ravizza *et al.*, 2004) and a seat of apperceptive discrimination of nonlinguistic sound objects such as human voices (Hailstone *et al.*, 2011). Moreover, PPA syndromes show convergent involvement of this region (Rogalski *et al.*, 2011). Although linguistic phonological impairment is not a defining feature of svPPA, this syndromic group has been shown to have deficits extending to the perceptual analysis of sounds (Goll *et al.*, 2010a; Grube *et al.*, 2016): this might be parsimoniously interpreted as evidence for impaired top-down integration of auditory object properties into conceptual representations, in keeping with current computational models of semantic cognition (Lambon Ralph *et al.*, 2016). This interpretation is consistent with previous findings suggesting that semantic and non-semantic systems interact in svPPA to manifest in ostensibly non-semantic deficits (Jefferies *et al.*, 2004; Caine *et al.*, 2009; Adlam *et al.*, 2013; Rogers *et al.*, 2015).

All three syndromic groups here showed impaired analysis of entropy, an index of the fundamental, nonlinguistic information content of speech signals. In the combined nfvPPA and svPPA patient cohort, this deficit had a neuroanatomical correlate in right putamen, corroborating work in the healthy brain implicating striatum in tracking and probabilistic coding of sensory signals (Haruno & Kawato, 2005; Overath *et al.*, 2007; Geiser *et al.*, 2012; Grahn & Rowe, 2013; Nastase *et al.*, 2015). This finding is in line with previous evidence for impaired extraction of global statistical regularities in auditory signals in both nfvPPA and svPPA (Goll *et al.*, 2010a): a core deficit of this kind might potentially disrupt the decoding of syntactic, prosodic and musical patterns in nfvPPA (Rohrer *et al.*, 2012; Golden *et al.*, 2017) and computation of coherent auditory object concepts in svPPA (Lambon Ralph *et al.*, 2010, 2016).

From a clinical perspective, my findings in this Chapter show that generic auditory processing deficits in PPA syndromes extend to the processing of speech signals and suggest that such deficits may correlate with overall disease severity as well as standard indices (here, phonemic discrimination) of linguistic competence in these syndromes. With respect to the nosology of PPA, these findings suggest that certain measures of speech signal analysis (such as temporal coding) may stratify syndromes whereas other measures (such as spectral and statistical coding) may cross

conventional syndrome boundaries. These behavioural measures capture regional atrophy in FTLD-PPA within a distributed fronto-temporal network that overlaps but extends beyond canonical language areas (compare Tables 3.2 and 3.3), involving striatal structures implicated in nonverbal pattern decoding.

The relationship between linguistic and pre-linguistic impairment in PPA will only be fully defined through more comprehensive neuropsychological correlation and functional neuroimaging techniques that address underlying neural mechanisms directly. The work I present in Chapter 4 attempts to do just this, employing functional MRI to delineate the functional mechanisms underpinning the deficits reported in this Chapter.

4. Functional neuroanatomy of speech signal decoding

4.1. Chapter summary

Here, I build on the results presented in Chapter 3, using the paradigm of functional MRI (fMRI) in a cohort of 27 patients with all three of the main syndromic variants of PPA relative to 15 healthy controls. All participants passively listened to sequences of spoken syllables while in the scanner. These sequences were again manipulated for the three auditory speech signal characteristics used in Chapter 3: temporal regularity, phonemic spectral structure, and pitch sequence entropy. Relative to healthy controls, patients with nfvPPA showed reduced activity in medial Heschl's gyrus in response to any auditory stimulation and reduced activation of anterior cingulate and supplementary motor area in response to temporal irregularity. Semantic variant patients had reduced activation of caudate and anterior cingulate in response to increased entropy, while patients with logopenic variant PPA showed reduced activation of posterior superior temporal cortex to phonemic spectral structure. My findings here corroborate those reported in Chapter 3, suggesting that impaired processing of core speech signal attributes may drive particular PPA syndromes.

4.2. Introduction

In this Chapter, I use the same stimuli as outlined in Chapter 3 to further probe the nature of the auditory processing deficits delineated in that Chapter. To do so, I use functional MRI (fMRI) to identify the functional mechanisms subserving the behavioural signatures identified in the previous Chapter. fMRI has been used previously to delineate altered (including compensatory) patterns of cerebral activation in PPA cohorts relative to healthy controls (Vandenbulcke *et al.*, 2005; Wilson *et al.*, 2010a; Nelissen *et al.*, 2011; Goll *et al.*, 2012b). However, this technique has not been used to identify fundamental mechanisms of abnormal auditory information processing in PPA. Here, I used activation fMRI to deconstruct the functional neuroanatomy of speech signal processing in PPA into component neural mechanisms that process core attributes of speech signals. I again studied a cohort of patients representing all major PPA syndromes in relation to healthy older individuals, using the same experimental stimuli

as in the previous experiment. These sequences were again manipulated for three generic auditory speech signal characteristics relevant to previously documented neurolinguistic deficits in PPA syndromes: temporal regularity, phonemic structure, and entropy.

In order to assess the effect of PPA syndromes on these generic mechanisms of speech signal analysis relatively uncontaminated by executive, working memory or other extraneous task demands (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009), I adopted a passive listening paradigm with 'sparse' image acquisition (presentation of auditory stimuli interleaved with scanner noise).

4.3. Key predictions

- PPA syndromes have separable functional neuroanatomical signatures of abnormal speech signal decoding relative to healthy older individuals.
- The functional substrates of isochrony and entropy processing lie within a distributed network including posterior temporal, cingulate and striatal structures that have previously been implicated in the analysis of auditory regularity and predictability (Griffiths & Warren, 2002; Overath *et al.*, 2007; Ide *et al.*, 2013; Cope *et al.*, 2014).
- The substrate of phoneme processing will lie within superior temporal cortex, previously implicated in the analysis of phonemic structure (Liberman & Mattingly, 1989; Scott *et al.*, 2000; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009).

4.4. Materials and methods

4.4.1. Participants

Participants for this study comprised 12 patients with nfvPPA (five female; mean age 70.9 years), nine patients with svPPA (three female; mean age 62.3 years), six patients with lvPPA (two female; mean age 62.7 years), and fifteen healthy older individuals (eight female; mean age 68.8 ± 4.5 years). Participant groups differed slightly to those reported in Chapter 3. Reduced numbers are reported for the healthy control and lvPPA groups due to problems with functional data acquisition. Two extra datasets were available for patients with nfvPPA; their structural scans were not suitable for inclusion in the VBM analysis due to inaccurate tissue segmentation, but their functional scans were of sufficient quality for inclusion in this analysis. Supplementary Table 1 gives an overview of participants involved in the two studies. All participants were recruited in accordance with the general methods outlined in Section 2.1. Cerebrospinal fluid tau/ abeta profiles were available for five of the six patients with lvPPA, all of which were consistent with Alzheimer's pathology based on local reference ranges (total tau: beta-amyloid 1-42 ratio > 1). All participants had a comprehensive general neuropsychological assessment. Demographic, clinical and neuropsychological characteristics of participant groups are summarised in Table 4.1.

4.4.2. Experimental stimuli

Stimuli were created in accordance with the description outlined in Section 3.4.2. The stimulus manipulations are schematised in Figure 3.1, although for the purposes of this Experiment, they were manipulated factorially. Examples of the stimuli are included on the enclosed CD in Audio Files 4.1–4.2 (see Supplementary Table 2). Using these manipulations, eight types of experimental trials were created: i) isochronous - natural speech - high entropy; ii) isochronous - natural speech - low entropy; iii) isochronous - rotated speech - high entropy; iv) isochronous - rotated speech - low entropy; v) anisochronous - natural speech - high entropy; vi) anisochronous - natural speech - low entropy; vii) anisochronous - rotated speech - high entropy; viii) anisochronous - rotated speech - low entropy. Combining these trial types

allowed contrasts between the conditions representing a particular experimental manipulation while balancing for each of the other manipulations.

4.4.3. Post-scan behavioural testing

Post-scan behavioural testing was carried out in accordance with the description given in Section 3.4.3. Please note that these behavioural data have been partially presented in Chapter 3, albeit for slightly altered participant groups as outlined in Section 4.4.1. These are reprised here as an adjunct to the main results of interest: the functional neuroanatomical signatures.

4.4.4. Functional MRI protocol

4.4.4.1. Stimulus delivery

During fMRI scanning, stimuli were presented in randomised order via a notebook computer running the Cogent v1.32 extension of MATLAB (www.vislab.ucl.ac.uk/cogent_2000.php). Each stimulus trial was triggered by the MR scanner on completion of the previous MR image acquisition in a sparse acquisition protocol. Stimuli were played binaurally via electrodynamic headphones (www.mr-confon.de) at a comfortable listening level (at least 70dB). Twenty stimulus trials were administered for each of eight trial types (Figure 1): across trial types, the contrasts of interest were constructed by comparing conditions that differed in the speech signal parameter of interest (temporal regularity, 80 isochronous vs 80 anisochronous trials; phonemic structure, 80 natural vs 80 spectrally rotated trials; information content, 40 high vs 40 low entropy trials, assessed separately for natural and spectrally rotated speech stimuli). In addition, there were 20 silent 'rest' trials, yielding a total of 180 trials for the experiment for each participant. Participants were instructed to lie quietly and listen to the sounds with eyes lightly closed; there was no in-scanner output task.

4.4.4.2. Brain image acquisition

Functional MRI scans were acquired using a 12-channel RF receive head coil on a 3T Siemens Tim Trio MRI scanner. The EPI sequence comprised 48 oblique transverse slices covering the whole brain (slice thickness 2mm, inter-slice gap 1mm, 3mm in-plane resolution, slice TR/TE 70/30ms, echo spacing 0.5ms, matrix size

64 x 64 pixels, FoV 192 x 192mm, phase encoding (PE) direction anterior-posterior) with slice tilt -30^{o} (T>C). Sparse-sampling EPI acquisition with repetition time 11.36 seconds (corresponding to an inter-scan interval of eight seconds) was used to reduce any interaction between scanner acoustic noise and auditory stimulus presentations. One initial brain volume was acquired to allow equilibration of longitudinal T1 magnetisation and discarded from further analysis. A B0 field-map was also acquired (TR = 688ms; TE1 = 4.92ms, TE2 = 7.38ms, 3 x 3 x 3mm resolution, no interslice gap; matrix size = 80 x 80 pixels; FoV = 240 x 240mm; phase encoding direction = A-P) to allow post-processing geometric correction of EPI data for B0 field inhomogeneity distortions.

To enable structural coregistration and comparison with activation data, volumetric brain MRI scans were also acquired for each participant using the procedures described in General Methods Section 2.7.

4.4.5. Data analyses

4.4.5.1. Analysis of clinical and background neuropsychological data

All clinical and background neuropsychological data were analysed in accordance with the procedures outlined in Section 2.10.1.

4.4.5.2. Analysis of fMRI data

Functional MRI data were analysed using statistical parametric mapping software (SPM12; www.fil.ion.ucl.ac.uk/spm). During initial image preprocessing, the EPI functional series for each participant was realigned to the first image. Images were unwarped incorporating field-map distortion information (Hutton et al., 2002). All individual functional images were spatially registered to a group mean template image using the DARTEL toolbox (Ashburner, 2007) and then normalised to Montreal Neurological Institute (MNI) standard stereotactic space. To construct the group brain template, each individual T1 weighted MR brain image was first coregistered to the corresponding EPI series and segmented into grey matter, white matter and cerebrospinal fluid. Functional images were smoothed using a 6mm full-width-at-half-maximum Gaussian kernel, with voxel volume 3x3x3mm. For visualisation of results, a study-specific mean structural brain image template was created using the strategy

outlined in Section 2.8. An explicit mask was created using the procedure depicted in Section 2.8.

Preprocessed functional images were entered into a first-level design matrix incorporating the experimental conditions modelled as separate regressors convolved with the standard haemodynamic response function and also including six head movement regressors generated from the realignment process. For each participant, first-level t-test contrast images were generated for the main effects of auditory stimulation (any sound versus silence); temporal regularity (isochronous > anisochronous sequences); phonemic structure (natural speech > spectrally rotated speech); and fundamental signal information content (high entropy > low entropy sequences), separately for natural and spectrally rotated speech conditions (since the decoding of pitch pattern is likely a priori to differ for speech signals with dissimilar spectral structure). Both 'forward' and 'reverse' contrasts were assessed in each case. Contrast images for each participant were entered into a second-level full factorial model in which effects within each participant group and differences between patient and healthy control groups were explored using t-test contrasts.

Contrasts were assessed after a cluster-defining threshold of $p<0.001$ uncorrected, then at a cluster-level significance threshold of $p<0.05$ after family-wise error (FWE) correction for multiple comparisons over the whole-brain and at a peak-level significance threshold of $p<0.05_{FWE}$ within two pre-specified neuroanatomical regions of interest in each cerebral hemisphere, in line with neuroanatomical evidence from previous studies. Correlates of speech temporal regularity and sequence information content (entropy) processing were assessed within a region comprising posterior superior temporal gyrus and sulcus, planum temporale, dorsal striatum and anterior cingulate cortex (Griffiths & Warren, 2002; Overath *et al.*, 2007; Ide *et al.*, 2013; Cope *et al.*, 2014); while correlates of phonemic processing were assessed within a more restricted subregion comprising planum temporale and posterior to mid superior temporal gyrus and sulcus (Liberman & Mattingly, 1989; Scott *et al.*, 2000; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009). Anatomical regions were obtained and edited to conform to the study-specific template brain image using the procedures

described in General Methods Section 2.9. Regions of interest are presented in Figure 4.1.

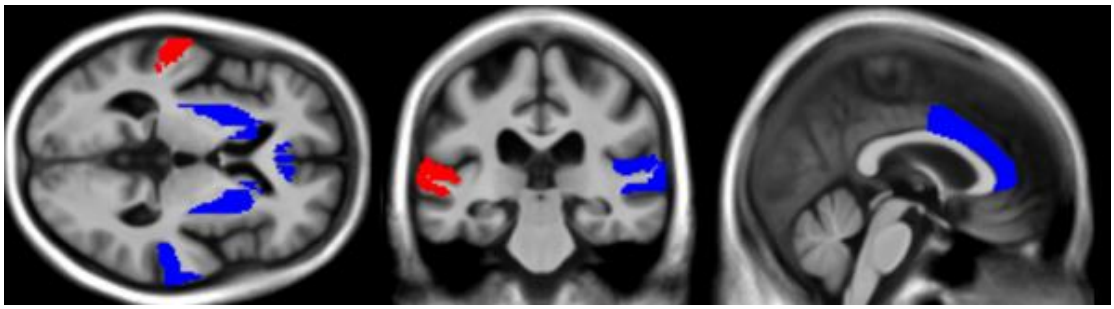

Figure 4.1. Anatomical regions of interest. The Figure shows representative sections of anatomical regions used for multiple voxel-wise comparisons corrections in region-of-interest analyses based on prior anatomical hypotheses (see text). Bi-hemispheric regions of interest are rendered on sections of the average normalized brain template for the combined patient cohort. The left cerebral hemisphere is shown on the left on the coronal section and above in the axial section. For the contrast assessing phonemic processing, the anatomical region for small volume correction comprised left posterior superior temporal gyrus/sulcus and planum temporale (red areas). For the contrasts assessing temporal processing and sequence information (entropy) processing, the anatomical region of interest comprised this left superior temporal lobe region plus additional regions in right superior temporal lobe, striatum (caudate and putamen), and anterior cingulate cortex (red plus blue areas).

For experimental contrasts of interest in analyses directly comparing the healthy control group with each patient group, linear regression models were used to assess any correlation of effect size (beta parameter) with performance on the corresponding post-scan behavioural task across the two groups.

4.5. Results

4.5.1. General participant characteristics

Participant groups did not differ in terms of gender, handedness or educational attainment (all $p>0.05$; Table 4.1); the svPPA and lvPPA groups were on average significantly younger than the healthy control and nfvPPA groups ($p<0.05$). Patient groups did not differ for mean symptom duration and showed profiles of neuropsychological impairment in keeping with the respective syndromic diagnoses (Table 4.1). There were no significant differences in peripheral hearing function between participant groups (Table 4.1).

Table 4.1. Demographic, clinical and neuropsychological characteristics of participant groups

Characteristic	Controls	nfvPPA	svPPA	lvPPA
Demographic and clinical				
No. (m:f)	7:8	7:5	6:3	4:2
Age (yrs)	68.8 (4.5)	70.9 (8.6)	**62.3 (5.7)†**	**62.7 (5.8)†**
Handedness (R:L)	14:1	10:2	8:1	5:1
Education (yrs)	16.4 (2.6)	14.8 (2.9)	14.9 (2.9)	14.3 (3.1)
MMSE (/30)	29.8 (0.4)	**24.4 (5.2)**	**19.8 (9.3)**	**16.0 (8.8)†**
Symptom duration (yrs)	-	4.9 (2.6)	5.0 (2.7)	4.7 (1.6)
PTA best ear (N:Mild:Mod)	8:7:0	3:6:2[a]	5:3:0[a]	3:3:0
General intellect: IQ				
PIQ	126.7 (7.3)	**84.5 (23.6)[a]**	**70.9 (7.3)**	**68.8 (20.9)**
VIQ	126.1 (9.8)	**97.0 (22.2)**	**101.4 (25.2)**	**86.0 (15.4)**
Episodic memory				
RMT words (/50)	49.5 (0.9)	**42.5 (6.8)[a]**	**35.3 (8.5)[b]**	**34.0 (11.9)[b]**
RMT faces (/50)	45.5 (2.9)	**38.8 (5.8)**	**32.0 (5.9)[b†]**	**34.8 (7.4)**
Working memory				
Digit span forward (max)	7.3 (1.0)	**4.9 (1.1)[c]**	6.2 (2.0)	**3.0 (0.6) †‡**
Spatial span forward (max)	5.5 (1.0)[b]	**4.3 (1.0)[d]**	5.4 (0.9)	**3.5 (0.8)†‡**
Executive skills				
WASI Block Design (/71)	45.8 (12.4)	**21.3 (18.5)**	33.6 (23.3)	**15.7 (16.4)**
WASI Matrices (/32)	27.3 (2.3)	**15.9 (8.7)**	**19.3 (10.5)**	**14.0 (6.7)**
Digit span reverse (max)	5.7 (1.2)	**3.0 (1.4)[c] ‡**	4.4 (2.1)	**1.8 (1.5)‡**
Spatial span reverse (max)	5.6 (0.9)[b]	**4.1 (1.6)[d]**	4.7 (1.9)	**3.0 (1.3)‡**
Letter fluency (total)	17.4 (4.6)	**5.5 (5.8)†**	**7.3 (6.3)[a]**	**2.2 (1.8)[a]**
Category fluency (total)	25.3 (5.1)	**10.7 (4.3)[e]**	**5.2 (5.7)**	**5.0 (3.5)[a†]**
Trails A (s)	34.2 (5.3)	**90.7 (49.4)[b] ‡**	46.9 (19.3)[a]	**126.2 (96.2)‡**
Posterior cortical skills				
GDA calculation (/24)	14.7 (5.9)	**5.0 (3.9)[d]**	9.8 (8.8)	**1.7 (5.9)‡**
VOSP object decision (/20)	18.9 (1.4)	**15.2 (4.1)[a]**	**16.3 (3.2)[a]**	**16.7 (2.3)**
Neurolinguistic skills				
Auditory input processing				
PALPA-3 (/36)	35.8 (0.6)[b]	**33.3 (3.2)[d]**	**32.0 (6.5)**	**31.2 (3.9)**
Word retrieval				
GNT (/30)	26.3 (2.7)	**15.6 (7.8)[a]**	**1.9 (4.6)†**	**4.7 (7.2)†**
BNT (/30)	29.7 (0.7)[c]	**20.6 (8.9)[e]**	**5.3 (7.1)†**	**9.3 (7.7)†**
Comprehension				
BPVS (/51)	49.5 (1.4)	**42.1 (8.0)**	**9.6 (15.8)[a†]***	**34.2 (14.7)**
Concrete synonyms (/25)	24.3 (0.9)[b]	21.1 (4.7)[c]	**14.2 (3.2)*†**	**17.8 (3.1)[a]**
Abstract synonyms (/25)	24.4 (1.0)[b]	**20.8 (5.0)[c]**	**15.5 (3.5)[a†]**	**15.8 (4.5)[a]**
PALPA-55 sentences (/24)	23.7 (0.6)[d]	**21.1 (4.2)[d]**	**19.4 (6.7)**	**13.7 (5.1)†**
Speech repetition				
Polysyllabic words (/45)	44.5 (0.9)[b]	**27.7 (17.3)†‡**	43.8 (1.6)	**32.2 (7.0)‡**
Short sentences (/10)	10.0 (0.0)[c]	**5.0 (4.7)†‡**	**9.6 (0.7)[a]**	**3.5 (3.1)[a]‡**
Spelling				
BST (/30)	26.8 (1.7)[b]	**16.1 (9.3)[e]**	**11.5 (9.8)[a]**	**8.6 (5.7)[a]**

Significant differences ($p<0.05$) from healthy control values are in **bold**; *significantly different from lvPPA group; †significantly different ($p<0.05$) from nfvPPA group ‡significantly different from svPPA group. Reduced numbers of participants are indicated: [a]n–1; [b]n–2; [c]n–3; [d]n–4; [e]n–5; [f]n–6.

4.5.2. Functional MRI data

Significant neuroanatomical findings from the fMRI analysis are summarised in Table 4.2; Figure 4.2 shows statistical parametric maps and beta parameter estimates for key contrasts and conditions.

Table 4.2. Summary of fMRI associations of speech signal processing across participant groups

Group	**Domain**	**Contrast**	**Region**	**Side**	**Cluster**	**Peak** (mm)			**t-score**	**p-value**
					(voxels)	x	y	z		
Within groups										
Healthy controls	Auditory stimulation	All sound > silence	HG/ STG	R	1352	54	-12	0	**14.80**	**<0.001**
			HG/ PT	L	1424	-42	-24	6	**14.54**	**<0.001**
			IFG	R	45	54	27	18	**4.73**	**0.049**
			IFG	L	102	-45	30	12	**4.70**	**0.001**
		Silence > all sound	PCu	R	58	21	-63	27	**5.59**	**0.018**
	Temporal regularity	Anisochronous > isochronous	Post STG	R	7	69	-30	9	4.25	0.049
	Phonemic structure	Natural > rotated speech	Post STG/ STS	L	739	-60	-12	-3	**10.38**	**<0.001**
			Post STS/ Mid STG	R	593	54	-30	3	**8.01**	**<0.001**
			M1	L	69	-51	-6	48	**7.97**	**0.006**
			M1	R	44	45	6	51	**5.80**	**0.045**
	Entropy	High > low entropy	Caud[†]	R	54	18	12	3	**4.35**	**0.015**
nfvPPA	Auditory stimulation	All sound > silence	HG/ PT	L	938	-60	-18	3	**11.2**	**<0.001**
			HG/ PT/ post STG/S	R	936	63	-18	9	**10.4**	**<0.001**
		Silence > all sound	TPO	R	50	42	-60	9	**4.35**	**0.033**
	Temporal regularity	Isochronous > anisochronous	ACC/ SMA	R	56	6	3	42	**5.43**	**0.018**
	Phonemic structure	Natural > rotated speech	Post STS/ Mid STG	L	275	-54	3	-12	**6.26**	**<0.001**
			Post /Mid STS	R	257	69	-18	-6	**5.53**	**<0.001**
			IFG	L	108	-57	18	12	**4.95**	**<0.001**
			M1	R	52	51	0	48	**4.93**	**0.023**
svPPA	Auditory stimulation	All sound > silence	HG/ PT	L	877	-45	-36	12	**11.08**	**<0.001**
			HG/PT/Post STG/S	R	867	63	-30	3	**7.25**	**<0.001**

		Silence > all sound	Post ITS*	R	62	54	-18	-21	**4.40**	**0.013**
	Phonemic structure	Natural > rotated speech	M1	L	48	-51	3	48	**6.53**	**0.032**
			Post STS	R	132	57	-30	3	**5.82**	**<0.001**
			Post STS/ Mid STG/S	L	104	-63	-30	-3	**5.68**	**0.001**
			SMA	R	49	6	12	63	**5.20**	**0.030**
			M1	R	67	48	0	45	**4.97**	**0.007**
	Entropy	High > low entropy	OFC/IFG‡	R	83	39	57	-15	**4.33**	**0.003**
		Low > high entropy	DLPFC‡	R	64	18	39	39	**4.81**	**0.012**
			ACC‡	L	13	-9	21	30	4.41	0.002
			Caud‡	L	11	-21	-3	21	4.85	0.009
lvPPA	Auditory stimulation	All sound > silence	HG	L	296	-39	-27	6	**7.95**	**<0.001**
			HG/ PT/ Post STG/S*	R	641	63	-24	0	**6.90**	**<0.001**
	Phonemic structure	Rotated > natural speech	DLPFC*	L	76	-33	42	30	**4.90**	**0.004**
Between groups										
Controls > nfvPPA	Auditory stimulation	All sound > silence	Medial HG	R	48	39	-21	12	**5.59**	**0.038**
	Temporal regularity	Anisochronous > isochronous	ACC	R	16	6	3	42	4.65	0.014
Controls > svPPA	Entropy	High > low entropy	Caud‡	L	12	-21	-3	21	4.32	0.006
			ACC‡	L	12	-9	21	30	5.08	0.004
Controls > lvPPA	Phonemic structure	Natural > rotated speech	Post STG/ STS*	L	12	-60	-24	0	4.12	0.025

Regional cerebral activations for contrasts of interest in each participant group and between control and patient groups are summarised (see text for details of contrasts). †indicates that signal was driven by natural speech condition, or ‡by spectrally rotated speech condition; *indicates region also the site of a local maximum in the VBM analysis of grey matter atrophy (see Table 3.3). Local maxima significant at $p<0.05_{FWE}$ cluster-level, corrected for multiple voxel-wise comparisons over the whole brain are in bold; other maxima are significant at $p<0.05_{FWE}$ peak-level corrected for multiple comparisons over prespecified anatomical regions of interest (see text and Figure 4.1).

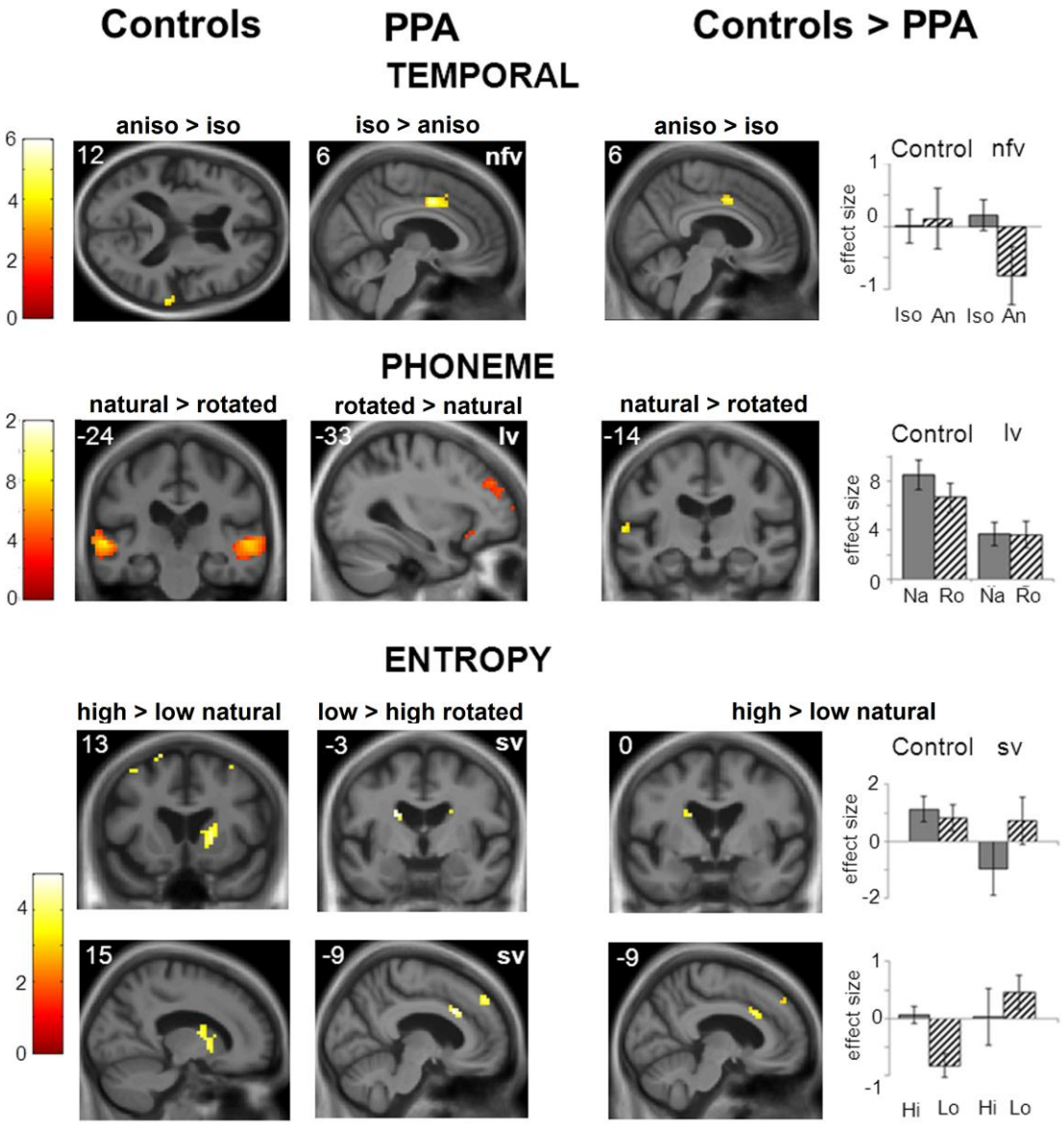

Figure 4.2. Statistical parametric maps showing fMRI associations of speech signal processing across participant groups. Significant regional brain activations for contrast of interest are shown within healthy control and patient groups (left and middle image panels; T scores for relevant contrasts coded in colour bars) and between groups (significantly greater activation in healthy controls than the corresponding patient group; right image panels). Contrasts are coded as follows (see text for details): **Temporal**, anisochronous > isochronous conditions (within-controls; controls > nfvPPA), isochronous > anisochronous conditions (within-nfvPPA); **Phoneme**, natural > spectrally rotated speech conditions (within-controls; controls > lvPPA), spectrally rotated > natural speech conditions (within-lvPPA); **Entropy**, high > low sequence entropy conditions (for natural speech conditions, within-controls; controls > svPPA), low > high sequence entropy conditions (for spectrally rotated speech conditions, within-svPPA). Plots of condition effect size (mean beta parameter estimate ± standard error) are shown (right) for the group comparisons, based on data for peak voxels from the between-group contrasts (see Table 4.2) in anterior cingulate (temporal contrast), posterior superior temporal gyrus (phoneme contrast), caudate nucleus (entropy contrast, top) and anterior cingulate (entropy contrast, bottom).

4.5.2.1. Auditory stimulation

Auditory stimulation (all sound conditions versus silence) produced extensive bilateral activation of Heschl's gyrus and superior temporal gyrus in all participant groups (all $p<0.05_{FWE}$ over the whole brain). Certain participant groups showed a significantly greater effect of silence than auditory stimulation in posterior temporo-parietal cortices: the healthy control group showed this effect in precuneus, the nfvPPA group in right temporo-parieto-occipital junction and the svPPA group in posterior inferior temporal sulcus (all $p<0.05_{FWE}$ over the whole brain). Auditory stimulation produced significantly greater activation of medial Heschl's gyrus in the healthy control group than the nfvPPA group but no other significant group differences at the prescribed threshold ($p<0.05_{FWE}$ over the whole brain).

4.5.2.2. Temporal irregularity

Processing of temporal irregularity in speech signals (anisochronous versus isochronous conditions) was associated in the healthy control group with significant activation of right posterior superior temporal gyrus ($p<0.05_{FWE}$ within the pre-specified anatomical region of interest); while temporal regularity (isochronous versus anisochronous conditions) was associated in the nfvPPA group with significant activation of right anterior cingulate and supplementary motor cortices ($p<0.05_{FWE}$ over the whole brain; Figure 4.2). The effect of temporal irregularity was significantly greater for the healthy control group than the nfvPPA group in anterior cingulate cortex ($p<0.05_{FWE}$ within the pre-specified anatomical region of interest; Figure 4.2). Plotting parameter estimates for the temporal regularity contrast (Figure 4.2) revealed a relative deactivation to anisochronous syllable sequences in the nfvPPA group that was not present in the healthy control group. No other significant group correlates of temporal processing were identified.

4.5.2.3. Phonemic structure

The presence of phonemic structure (natural versus spectrally rotated phonemes) was associated with significant bilateral activation of lateral posterior to mid superior temporal gyrus and sulcus and more dorsal motor areas in the healthy control group, the nfvPPA group and the svPPA group (all $p<0.05_{FWE}$ over the whole brain; Figure 4.2). Conversely, the lvPPA group showed no activation in response to phonemic structure at the

prescribed threshold but rather significant activation of left dorsolateral prefrontal cortex in response to spectrally rotated speech ($p<0.05_{FWE}$ over the whole brain). The effect of phonemic structure in left posterior superior temporal cortex was significantly greater for the healthy control group than the lvPPA group ($p<0.05_{FWE}$ within the pre-specified anatomical region of interest), driven by increased activation in response to natural speech in healthy controls that was not present in patients with lvPPA (Figure 4.2).

4.5.2.4. Entropy

Increasing signal information content (high versus low sequence entropy) in natural speech sequences was associated with significant activation of right caudate nucleus in the healthy control group ($p<0.05_{FWE}$ over the whole brain; Figure 4.2); none of the patient groups showed a significant effect for this contrast while healthy controls showed no significant effect for spectrally rotated speech conditions at the prescribed threshold. However, for spectrally rotated speech conditions the svPPA group showed significant activation of right orbitofrontal cortex and inferior frontal gyrus in response to increasing signal information content ($p<0.05_{FWE}$ over the whole brain) and significant activation of right dorsolateral prefrontal cortex, left anterior cingulate and left caudate in response to reduced signal information content (low vs high sequence entropy; $p<0.05_{FWE}$ within the pre-specified anatomical region of interest, Figure 4.2). The effect of increasing signal information was significantly greater in the healthy control group than the svPPA group ($p<0.05_{FWE}$ within the pre-specified anatomical region of interest), driven by relative deactivation of left caudate in the high entropy condition and activation of anterior cingulate cortex in the low entropy condition in the patients with svPPA (Figure 4.2).

4.5.3. Correlations of functional neuroanatomical with post-scan behavioural data

Using the behavioural data reported in Chapter 3, performance on the test of phoneme processing was significantly positively correlated with peak activation of left superior temporal gyrus across the lvPPA and healthy control groups ($t(19) = 4.08$, $p = .001$, $R^2 = 0.47$), though this was not significant within the lvPPA group ($t(4) = 0.68$, $p = 0.53$, $R^2 = 0.10$). Performance on the test of entropy processing was significantly inversely correlated with peak activation of left caudate ($t(21) = 3.38$, $p = 0.003$, $R^2 = 0.35$) and left anterior

cingulate ($t(21) = 3.42$, $p = 0.003$, $R^2 = 0.35$) across the svPPA and healthy control groups, though not significant within the svPPA group ($t(6) = 1.62$, $p = 0.16$, $R^2 = 0.30$ in left caudate and $t(6) = 0.94$, $p = 0.38$, $R^2 = 0.13$ in left anterior cingulate). There were no significant functional neuroanatomical correlations with performance on the temporal regularity processing test.

4.6. Discussion

In this study, I have corroborated and built upon the behavioural and structural neuroanatomical data presented in Chapter 3, here showing that the three major PPA syndromes are associated with distinctive functional neuroanatomical profiles of abnormal speech signal decoding relative to healthy older individuals. Compared directly with the healthy control group, patients with nfvPPA showed reduced activation of medial Heschl's gyrus in response to auditory stimulation (across all sound conditions) and reduced activation of anterior cingulate cortex in response to temporal irregularity in speech signals. The svPPA group showed reduced activation of caudate and anterior cingulate in response to increased entropy (information content) in spectrally rotated speech. The lvPPA group showed reduced activation of posterior superior temporal cortex in response to phonemic spectral structure. These syndromic signatures are consistent with prior predictions concerning the informational components of speech signals that are most likely to be vulnerable in each PPA syndrome (Holland & Lambon Ralph, 2010; Rohrer *et al.*, 2010b; Hsieh *et al.*, 2011; Hailstone *et al.*, 2012; Golden *et al.*, 2015b; Hardy *et al.*, 2015; Grube *et al.*, 2016; Henry *et al.*, 2016).

Whilst not the key focus of the work presented in this Chapter, it is worth noting that performance on out-of-scanner tasks correlated with regional neural activation for the processing of phonemic structure and signal information content for the relevant syndromic (lvPPA and svPPA) groups relative to healthy controls: functional neuroanatomical profiles may therefore underpin behavioural speech processing deficits in these syndromes, though the lack of correlation within the respective patient groups suggests that additional factors may drive individual performance variation.

In the contrast assessing all auditory stimulation, all participant groups showed the anticipated extensive activation of primary and association auditory cortices (Binder *et al.*,

2000; Scott *et al.*, 2000; Griffiths & Warren, 2002; Dhamala *et al.*, 2003; Greicius *et al.*, 2003; Dehaene-Lambertz *et al.*, 2005; Liebenthal *et al.*, 2005; Goll *et al.*, 2012b). Only the nfvPPA group showed a profile of activation in response to any auditory stimulation that differed significantly from the healthy controls, in line with emerging evidence for deficits of early auditory perceptual processing in nfvPPA that may distinguish it from other PPA syndromes (Goll *et al.*, 2010a; Maruta *et al.*, 2014; Grube *et al.*, 2016).

For the processing of temporal irregularity in speech signals, more selective alterations emerged at group levels. The healthy control participants showed an activation profile in line with previous work in healthy individuals showing that auditory rhythmic variation engaged posterior superior temporal cortices (Griffiths *et al.*, 1999; Rauschecker & Scott, 2009). None of the patient groups showed increased activation in response to syllable anisochrony, while patients with nfvPPA actually showed reduced activation to anisochronous relative to isochronous sequences in anterior cingulate and supplementary motor cortices. In the healthy brain, this medial prefrontal cortical region is engaged in speech syntax and prosody (Hertrich *et al.*, 2016), while in nfvPPA a similar region has been implicated in the pathophysiology of both speech production and rhythm processing deficits, participating in a network including inferior frontal gyrus (Catani *et al.*, 2013; Ballard *et al.*, 2014; Schaeverbeke *et al.*, 2016; see Chapter 3). In light of emerging formulations linking temporal perceptual with output processes in the healthy brain (Warren *et al.*, 2005) and in nfvPPA (Grube *et al.*, 2016; Schaeverbeke *et al.*, 2016), my finding here could signify a dysfunctional mechanism mediating the sensorimotor transformation of speech signals.

For the detection of phonemic spectral structure, the healthy control group showed preferential activation of lateral posterior and mid superior temporal cortex for natural versus spectrally rotated speech. This region of association auditory cortex has been previously identified as an area critical to phoneme processing in the healthy brain (Liberman & Mattingly, 1989; Scott *et al.*, 2000, 2009; Hickok & Poeppel, 2007; Rauschecker & Scott, 2009; Leaver & Rauschecker, 2010; Obleser *et al.*, 2010; Zhang *et al.*, 2016). Neural processes in this region are likely to be essential for the disambiguation of speech from complex nonspeech sounds at the level of auditory object (i.e. phonemic) representation. These mechanisms are bihemispheric and left hemisphere specialization may be in part

directed by connectivity changes under linguistic tasks (Leaver & Rauschecker, 2010; Obleser *et al.*, 2010; Markiewicz & Bohland, 2016; Zhang *et al.*, 2016). This interpretation is consistent with the differential activation profiles shown by patient groups here: compared with healthy controls, the nfvPPA and svPPA groups showed relatively normal activation profiles, whereas the lvPPA group showed a significantly attenuated response to natural phonemes in the key superior temporal region, in accordance with the clinical deficits of phonological processing (Gorno-Tempini *et al.*, 2008; Rohrer *et al.*, 2010b; Hailstone *et al.*, 2012; Hardy *et al.*, 2015; Grube *et al.*, 2016; Henry *et al.*, 2016) and related deficits of paralinguistic analysis (Rohrer *et al.*, 2012) previously documented in lvPPA.

Although I did not directly assess phonological working memory in this experiment, posterior superior temporal cortex plays an integral role in auditory working memory for phonemes and other auditory objects (Kumar *et al.*, 2016), suggesting that the profile seen here is relevant to the phonological working memory impairment that is a defining feature of lvPPA (Gorno-Tempini *et al.*, 2008, 2011). Clinically, phonological working memory deficits are a feature of nfvPPA as well as lvPPA (Rohrer *et al.*, 2010b; Hailstone *et al.*, 2012; Hardy *et al.*, 2015; Henry *et al.*, 2016). My findings suggest that these deficits may be underpinned by different mechanisms across the two syndromes, as the relevant experimental contrast isolated a stage of phonological object representation that is likely to be core to lvPPA, and not nfvPPA (Rohrer *et al.*, 2010b). Importantly, this posterior superior temporal cortical region is contiguous with typical patterns of atrophy in lvPPA cohort studies (Gorno-Tempini *et al.*, 2004, 2008; Rohrer *et al.*, 2010b). Although care is needed when interpreting functional changes in the setting of regional structural atrophy, it is worth nothing that this differential activation pattern was driven by an attenuated response to natural (but not spectrally rotated) speech. This implies that the group-wise activation difference between controls and lvPPA patients was at least partly attributable to a functionally selective mechanism, rather than simply a nonspecific consequence of grey matter loss.

In the healthy control, nfvPPA and svPPA groups, processing of natural speech was also associated with prefrontal and motor activation, consistent with obligatory engagement of the dorsal language processing network previously implicated in phonological processing (Warren *et al.*, 2005; Hickok & Poeppel, 2007); see Figure 1.7. In

contrast, the lvPPA group showed a paradoxically enhanced response to spectrally rotated speech in dorsal prefrontal cortex. Reduced capacity to integrate spectrotemporal information into auditory object-level representations could potentially underpin both phonological and nonverbal auditory deficits in lvPPA (Goll *et al.*, 2011; Rohrer *et al.*, 2012; Golden *et al.*, 2017), and may in fact be relatively specific to this syndrome, perhaps aligning lvPPA with the auditory apperceptive deficit seen in typical Alzheimer's disease (Goll *et al.*, 2011; Golden *et al.*, 2017).

The healthy control and patient groups were further stratified by activation profiles in response to signal information content (entropy) in syllable sequences. In healthy control participants, increased entropy in natural speech signals engaged right caudate nucleus, corroborating previous work in the healthy brain implicating the striatum in the obligatory tracking of sequence entropy (Overath *et al.*, 2007; Nastase *et al.*, 2015) and more broadly, in the predictive and probabilistic encoding of speech and other stimuli (Haruno & Kawato, 2005; Kotz *et al.*, 2009; Geiser *et al.*, 2012; Grahn & Rowe, 2013). The nfvPPA and lvPPA groups did not show any significant activation patterns in response to the entropy manipulation. While this null result should be interpreted with caution (given that no significant differences were identified in these syndromic groups relative to the healthy control group), sensitivity to the long-range structure of speech signals might plausibly be reduced in PPA syndromes characterized by impaired integration of auditory features unfolding over time (Hailstone *et al.*, 2012; Rohrer *et al.*, 2012; Golden *et al.*, 2017).

As predicted, a clearer profile of abnormal entropy processing was evident in the svPPA group, implicating a fronto-cingulo-striatal network that is associated with the processing of signal statistics in the healthy brain (Fan, 2014). Patients showed responses preferentially for the high entropy condition in inferior frontal cortex, which has shown to be sensitive to increasing uncertainty in speech signals (Nastase *et al.*, 2014); and preferentially in the low entropy condition in caudate, dorsolateral prefrontal cortex: regions that have previously shown more complex responses to varying signal predictability (Nastase *et al.*, 2014, 2015). In healthy participants, the anterior cingulate cortex has been implicated in the predictive coding and analysis of deviance in auditory and other stimuli (Kiehl *et al.*, 2000; Magno, 2006; Lee *et al.*, 2011; Ide *et al.*, 2013). Importantly, however, the

response profile of the svPPA group differed from the healthy control group. Qualitatively, patients with svPPA showed sensitivity to entropy variation in spectrally rotated but not natural speech. Quantitatively, these patients showed lower overall sensitivity to increasing signal entropy due to a bidirectional profile of altered activation within the cingulo-striatal network. Damage to this network has previously been demonstrated in svPPA (Rohrer *et al.*, 2009c). The anterior cingulate cortex mediates widespread shifts in connectivity between distributed brain regions in the healthy brain (Crottaz-Herbette & Menon, 2006; Nastase *et al.*, 2014, 2015), and my findings leave open the possibility that altered connectivity to the temporal lobe and other structures may have contributed to the behavioural correlate seen here.

In terms of information processing, my results point to an essential operation in sensory signal analysis that is critically vulnerable in svPPA: the computation of coherent object concepts, here demonstrated in the auditory domain but likely to extrapolate to other modalities as well (Lambon Ralph *et al.*, 2010). This goes beyond the moment-to-moment perceptual coding of sensory data and detection of 'patterns' to extract global statistical regularities in the signal. This signal information might then be used to determine membership of a sensory object category and to identify and predict correspondences between signals in different sensory modalities: a basic requirement for semantic concept formation and evaluation. Current models of semantic cognition emphasise the graded and predictive nature of object concepts, and the problem of integrating object information cross-modally into coherent multi-modal concepts (Lambon Ralph *et al.*, 2016). Based on my findings in svPPA here, I suggest that signal entropy may access a generic neural algorithm that computes and predicts sensory object attributes for further semantic analysis. In these terms, the lack of a differential effect of entropy conditions in the nonfluent nfvPPA and lvPPA syndromes would be consistent with a more fundamental impairment of pitch pattern analysis, while the differential entropy effect seen in svPPA could reflect a disproportionate deficit in computing object-level statistics in svPPA (Lambon Ralph *et al.*, 2010; Hsieh *et al.*, 2011; Rohrer *et al.*, 2012; Golden *et al.*, 2015b, 2017).

From a clinical perspective, the identification of pathophysiological mechanisms using fMRI has several implications. Functional MRI can identify aberrant increases as well

as reductions in cerebral activity (see Fig. 4.3) and functional alterations remote from the foci of atrophy (see Table 4.2): in the context of a clinical trial, incorporation of an activation fMRI limb might allow detection of dynamic therapeutic effects on working brain function that are not captured by conventional structural or even resting-state fMRI techniques. More broadly, fMRI provides a neuroanatomical grounding for behavioural measures (such as phonemic processing in lvPPA and entropy processing in svPPA) that correlate with brain network changes in particular syndromes: such surrogate behavioural measures could yield new, translatable biomarkers that both capture core pathophysiology and do not depend on conventional neurolinguistic tests.

From a neurobiological perspective, this study has uncovered defective brain mechanisms for decoding auditory speech signal attributes (temporal structure, spectral structure, and information content) that are likely to underpin particular PPA syndromes (nfvPPA, lvPPA, and svPPA, respectively). Considered collectively, the findings suggest a common pathophysiological theme in these syndromes. Efficient decoding mechanisms in the healthy brain use fewer computational (physiological) resources in decoding less complex sensory signals (Overath *et al.*, 2007): it is noteworthy that each of the PPA syndromes here (in the key contrast signifying that syndrome) reversed this normal pattern. This was most clearly the case for svPPA (in which “low information” [entropy] stimulus conditions evoked more activity in relevant brain regions), but analogous inefficiency may also account for the greater response to isochronous than anisochronous stimuli in nfvPPA and the loss of the processing advantage for natural speech in lvPPA.

Reduced computational efficiency of cortical information processing may be pathophysiologically relevant to many neurodegenerative proteinopathies (Warren *et al.*, 2013): increased metabolic demands related to reduced efficiency may be a mechanism of neural network vulnerability in these diseases. Bayesian accounts of the brain as an engine for minimizing prediction errors about the world at large and disease effects on this predictive coding are gaining wide currency (Adams *et al.*, 2013; O’Reilly *et al.*, 2013; Barascud *et al.*, 2016). In Bayesian terms, loss of computational efficiency in PPA syndromes might plausibly be associated with imprecise coding of speech and other auditory patterns and therefore less reliable detection of unexpected, deviant, or irregular

auditory events. It is noteworthy that the auditory cortical and prefrontal areas identified as differentially active in our patient groups participate in predictive sensory coding in the healthy brain (O'Reilly *et al.*, 2013; Barascud *et al.*, 2016).

The work described in this Chapter has several limitations that suggest opportunities for future work. Combining neuroanatomical modalities might yield further perspectives on these issues: it is likely, for example, that the temporal signature of signal processing will be sensitive to the effects of PPA pathologies, and this could be captured using a technique such as magnetoencephalography (Wibral *et al.*, 2011). My fMRI paradigm was based on passive listening: in future studies, it will be important to determine the extent to which the functional neuroanatomical profiles demonstrated here are modulated in the context of an output task. This speaks to the relevance of such profiles to the symptoms and capacities that patients exhibit in their everyday lives: further work is required to determine how functional neuroanatomy relates to neurolinguistic deficits and to measures of daily-life disease burden.

5. Delayed auditory feedback

5.1. Chapter summary

Chapters 3 and 4 focussed exclusively on speech perception, largely ignoring the interaction between speech perception and speech production. In this Chapter, I report on an experiment that manipulated the auditory feedback via which participants heard their own voices during spontaneous speech and reading aloud. I studied 41 patients (seven nfvPPA; eight svPPA; seven lvPPA; 11 tAD; eight bvFTD) and 13 healthy controls, and assessed the impact of delayed auditory feedback (DAF) relative to natural auditory feedback (NAF) on a number of speech production metrics. Healthy control participants and patients with svPPA, tAD and bvFTD were significantly affected by the DAF condition, speaking less fluently and with more errors, but those with nfvPPA and lvPPA were affected significantly less than healthy control participants. Sensitivity to DAF correlated with auditory phonemic discrimination ability in the healthy control participants, but not in a combined nfvPPA and lvPPA cohort. Results here must be interpreted with caution, as I had predicted *a priori* that the nonfluent patient groups would actually show sustained improvement under DAF. However, I suggest that these findings are consistent with previous research indicating that the two nonfluent PPA syndromes are associated with significant damage to the dorsal language pathway that is used to process and fine-tune auditory feedback for sensori-motor integration in the healthy brain.

5.2. Introduction

My thesis until this point has focussed almost exclusively on speech *perception*, neglecting *production*. However, the two are inextricably linked; see Figure 1.4 and the discussion in Section 1.2.1. During speech production in healthy individuals, auditory feedback provides sensory information that is consequently used to fine-tune vocal motor output, thought to involve a mechanism in posterior STG that links auditory vocal representations with articulation via the dorsal language pathway (Warren *et al.*, 2005).

Altering this auditory feedback dramatically affects speech production. In healthy volunteers subjected to a procedure known as delayed auditory feedback (DAF), whereby

the participant is asked to speak aloud while their own speech is played back to them with a slight delay (typically between 100-200ms), speech rate slows and errors increase (Stuart *et al.*, 2002; Chon *et al.*, 2013; Maruta *et al.*, 2014; Yamamoto & Kawabata, 2014; Chesters *et al.*, 2015; Cler *et al.*, 2017). DAF has even been shown to alter birdsong in zebra finches (Fukushima & Margoliash, 2015) and to have an effect on auditory production beyond the domain of speech, such as in keyboard playing (Pfordresher *et al.*, 2014).

From a neurobiological perspective, altered auditory feedback (AAF, of which DAF is an example) has been associated with activity in bilateral STG (McGuire *et al.*, 1996; Hirano *et al.*, 1997) in healthy control participants. One study directly comparing delayed with natural auditory feedback when participants were asked to read a series of sentences found bilateral activation in STG and supramarginal gyrus, with additional left postcentral gyrus activation (Hashimoto & Sakai, 2003). Zheng and colleagues identified three functional networks that were differentially sensitive to AAF: the first encoding an error signal comprising right SMA, angular gyrus and bilateral cerebellum; the second a frontotemporal network sensitive to speech features of auditory stimulation; and the third a distinct functional pattern from the other two appearing to capture aspects of both (Zheng *et al.*, 2013). Broadly speaking, converging neuroanatomical evidence suggests that the dorsal language pathway underpins processing of auditory feedback, which allows for fine sensori-motor retuning of subsequent speech production. (McGuire *et al.*, 1996; Hirano *et al.*, 1997; Hashimoto & Sakai, 2003; Warren *et al.*, 2005; Zheng *et al.*, 2013; Huang *et al.*, 2016).

Crucially, the speech errors (speech slowing and speech sound distortions) produced by healthy individuals under the influence of DAF have been equated to those observed in nfvPPA (Maruta *et al.*, 2014), suggesting that nfvPPA may itself be associated with distorted speech input signal processing. In Section 1.1, I have also discussed at length the structural neuroanatomical profiles associated with nfvPPA and lvPPA, which are both characterised by damage to the dorsal language pathway, although more so in nfvPPA (Henry *et al.*, 2016), and it is therefore possible that the language production problems associated with neurodegeneration to this pathway in nfvPPA/ lvPPA and DAF in healthy individuals are subserved by pathophysiological mechanisms that are not mutually exclusive.

In contradiction to the work showing that DAF negatively affects speech production in healthy individuals, DAF can actually improve speech output in stutterers (Andrews *et al.*, 1982; Lincoln *et al.*, 2006; Foundas *et al.*, 2013). DAF paradigms have previously been used in the context of stroke aphasia (Boller *et al.*, 1978; Chapin *et al.*, 1981), autism spectrum disorder (Lin *et al.*, 2015), progressive supranuclear palsy (Hanson & Metter, 1980), and Parkinson's disease (Downie *et al.*, 1981; Huang *et al.*, 2016), but to my knowledge, never in the context of nfvPPA. The mechanism by which DAF is purported to improve speech output is unknown, though it seems likely that the delay must allow for damaged cortex along the dorsal language pathway to process and benefit from the auditory feedback that is for some reason not possible under natural (i.e. instant) conditions.

The speech output of patients with rapid, festinating speech phenotypes has been shown to benefit from short delays in the range of 50-100ms (Hanson & Metter, 1980; Downie *et al.*, 1981). Here, given that nfvPPA is typically associated with a much slower rate of speech, I used a delay of 200ms, corresponding approximately to the duration of a syllable in conversational spoken English and shown to be associated with maximal fluency disruption in healthy individuals (Stuart *et al.*, 2002; Maruta *et al.*, 2014; Max & Maffett, 2015; Mitsuya *et al.*, 2017). Asking participants to read aloud and produce spontaneous speech offer two alternative ways in which to assess their speech production. This is beneficial when considering that the PPA syndromes are differentially associated with reading impairments (Cipolotti & Warrington, 1995; Wilson *et al.*, 2009; Gorno-Tempini *et al.*, 2011; Snowden *et al.*, 2012), and 'verbal adynamia' – meaning lack of spontaneity of propositional speech – has been described in the context of bvFTD previously (Warren *et al.*, 2003). Here, I compared reading aloud and producing spontaneous speech under conditions of DAF and natural auditory feedback (NAF) in patients with all major FTD and PPA syndromes, with reference to a group of healthy control participants and patients with typical Alzheimer's disease. The key outcome measurements, defined on the basis of previous literature, were speech rate and error rate (Wilson *et al.*, 2010b; Maruta *et al.*, 2014).

5.3. Key predictions

- Healthy control participants will show significant impairment on reading and spontaneous speech tasks under DAF (Stuart et al., 2002; Maruta et al., 2014; Max & Maffett, 2015; Mitsuya et al., 2017).
- Patients with nfvPPA and lvPPA will show the opposite result, speaking faster and with fewer speech errors under DAF than NAF (Wilson *et al.*, 2010b; Maruta *et al.*, 2014; Henry *et al.*, 2016).
- Patients with svPPA, bvFTD, and tAD will show response profiles across conditions similar to that seen in the healthy control group (Stuart et al., 2002; Maruta et al., 2014; Max & Maffett, 2015; Mitsuya et al., 2017).

5.4. Materials and methods

5.4.1. Participants

Seven patients with nfvPPA (four female; mean age 70.7 ± 10.4 (SD) years),eight patients with svPPA (three female; mean age 68.1 ± 7.0 years); and seven patients with lvPPA (one female; mean age 70.9 ± 8.6 years) were recruited in line with the procedures outlined in Section 2.1. A group of 11 patients with tAD (seven female; mean age 70.0 ± 8.8 years), and a group of eight patients meeting consensus criteria (Rascovsky *et al.*, 2007) for bvFTD (one female, mean age 65.6 ± 8.7 years) also participated in the study as disease control groups. Cerebrospinal fluid tau/ abeta profiles were available for four of the seven patients with lvPPA, all of which were consistent with Alzheimer's pathology based on local reference ranges (total tau: beta-amyloid 1-42 ratio > 1). Thirteen healthy elderly individuals (seven female; mean age 68.4 ± 5.4 years) also participated in the study as a healthy control group. Demographic, clinical and basic neuropsychological data for all participants are summarized in Table 5.1.

5.4.2. Experimental procedures

All participants were asked to read a slightly reduced version of the "Rainbow passage" (Fairbanks, 1960) (see Figure 5.1) under conditions of DAF and NAF. The order in which they did this was counterbalanced across participants. Next, all participants were asked to describe the "Beach scene" (Warrington, 2010) (see Figure 5.1), again under conditions of DAF and NAF. The order here was again counterbalanced across participants.

The DAF paradigm was created using MATLAB v 2014b with the Psychtoolbox extension (http://psychtoolbox.org/). I used a modified version of a master script (found at http://docs.psychtoolbox.org/BasicSoundFeedbackDemo), which records sound from the boom mic attached to the Sennheiser PC 350 SE headphones worn by all participants (48kHZ sampling rate), and plays this sound back via the headphones. Two versions of this script were used to create NAF and DAF conditions. For NAF, the audio recorded was played back to the participant with the shortest possible delay that was supported by the 2015 MacBook Pro used to run the experiment (delay typically ~18ms, range 16-24ms); while for DAF, the audio recorded was played back with a 190ms delay added to the

minimum latency possible with the hardware set-up, resulting in total delay of ~200ms (range 190-210ms). Two experimenters collected the data for this study: I collected 65% of all speech samples, and another researcher collected the remaining 35%. All testing was performed in a quiet room, and all speech samples were recorded for offline analysis.

5.4.3. Scoring of speech samples

Speech samples were edited manually by myself (56% of samples) and another researcher (44% of samples) in Audacity to remove experimenter interruption, extraneous noises or pauses at the beginning or end of the recording (word-finding pauses were not removed). We then listened carefully to each recording several times, assigning speech errors to several categories. An 'omission' was scored for the omission of a phoneme, e.g "rainbow" instead of "rainbows". 'Substitutions or misarticulations' were scored if a phoneme was incorrectly articulated and/or replaced with a different phoneme, e.g. "retraction" instead of "refraction". 'Duplications or additions' were scored if a phoneme was duplicated or added unnecessarily e.g. "sunlight-t" instead of "sunlight". 'Elongations' were scored if a phoneme was judged to have been elongated beyond normal limits for the speaker, e.g. "horiiizon" for "horizon". I included an additional category for dysfluencies, scored when a participant said "um" or "er" or an equivalent, and also scored grammatical errors in the spontaneous speech condition. The total number of words produced in each condition was manually counted, and the speech rate for each condition was calculated as the total number of words produced divided by the recording length in seconds. Error rates were calculated per hundred words (phw) by dividing the number of errors made by the number of words produced and then multiplying by a hundred, consistent with previous approaches (Wilson *et al.*, 2010b).

Of these many variables, I identified two on the basis of previous literature that would be of critical interest to examine here (Wilson *et al.*, 2010b; Maruta *et al.*, 2014): speech rate, defined by words per minute (wpm), and error rate, defined by number of speech errors of any kind per hundred words (phw).

A When the sunlight strikes raindrops in the air, they act as a prism and form a rainbow. The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is , according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow. Throughout the centuries people have explained the rainbow in various ways. Some have accepted it as a miracle without physical explanation. To the Hebrews it was a token that there would be no more universal floods. The Greeks used to imagine that it was a sign from the gods to foretell war or heavy rain. The Norsemen considered the rainbow as a bridge over which the gods passed from earth to their home in the sky. Others have tried to explain the phenomenon physically. Aristotle thought that the rainbow was caused by reflection of the sun's rays by the rain. Since then physicists have found that it is not reflection, but refraction by the raindrops which causes the rainbows.

B

Figure 5.1. Stimuli used in the DAF experiment. A) A reduced version of the Rainbow passage (Fairbanks, 1960) used in the reading conditions; **B)** The beach scene (Warrington, 2010) used to generate spontaneous speech.

5.4.4. Analysis of clinical and background neuropsychological data

All analyses were carried out in accordance with details given in Section 2.9.1.

5.4.5. Analysis of DAF and NAF data

First, each patient group was assessed for within-group change from NAF to DAF for all possible variables, including speech rate and error rate, using one-tailed dependent-samples t-tests.

Second, I focused specifically on my two dependent variables of critical interest: speech rate (wpm) and error rate (phw). Here, I ran a mixed ANOVA for each dependent variable, using two within-subject factors (feedback: natural vs delay; and task: reading vs spontaneous) and one between-subjects factor (diagnosis).

Third, I created change variables for error rate and speech rate by taking total on the NAF condition away from total on the DAF condition, and compared each patient group to the control group using these new change scores as dependent variables in one-tailed independent-samples t-tests. For this set of analyses, I also used a combined nonfluent (nfvPPA plus lvPPA) cohort to account for the small *n* in both groups, and because as outlined in Section 6.1, there are theoretical reasons for aligning the two in terms of their speech phenotypes.

Finally, I correlated change in speech rate and error rate from NAF to DAF with score on the PALPA-3 test of auditory input processing in the healthy control and combined nonfluent cohorts separately. All analyses were run for the reading and spontaneous speech conditions separately.

5.5. Results

5.5.1. Demographic and neuropsychological comparisons

Groups did not differ overall in terms of age ($F(1,53) = 0.05$, $p = 0.828$), handedness ($\chi2 = 4.13$, $p = 0.659$), gender ($\chi2 = 9.38$, $p = 0.153$), peripheral hearing ability ($\chi2 = 10.30$, $p = 0.590$) or education ($F(1,53) = 1.11$, $p = 0.298$). Patient groups did not differ in terms of symptom duration ($F(1,40) = 3.42$, $p = 0.072$) or MMSE score ($F(1,40) = 0.40$, $p = 0.529$). Core demographic and neuropsychological characteristics for all patient groups are presented in Table 5.1.

Table 5.1. Demographic, clinical and neuropsychological characteristics of participant groups.

Characteristic	Controls	nfvPPA	svPPA	lvPPA	AD	bvFTD
Demographic and clinical						
No. (m:f)	6:7	3:4	5:3	6:1	4:7	7:1
Age (yrs)	68.4 (5.4)	70.7 (10.4)	68.1 (7.0)	70.9 (8.6)	70.0 (8.0)	65.6 (8.7)
Handedness (R:L)	13:0	6:1	8:0	6:1	10:1	8:0
Education (yrs)	17.2 (1.7)	**14.0 (2.4)**	15.1 (2.9)	15.4 (2.5)	**14.6 (1.7)**	16.0 (3.1)
MMSE (/30)	29.8 (0.4)	**23.4 (5.3)**	**24.4 (5.5)**	**18.7 (7.6)**	**17.1 (4.8)**	**17.1 (4.8)**
Symptom duration (yrs)	NA	3.3 (1.4)	5.6 (2.2)	3.9 (2.2)	5.5 (3.0)	6.5 (3.3)
PTA best ear (N:Mild:Mod)	3:8:0	1:4:1[a]	2:4:0[b]	2:2:2[a]	2:7:0[b]	1:5:2
General intellect: IQ						
VIQ	127.1 (6.0)	**74.9 (18.8)**	**78.3 (14.1)**	**69.6 (15.5)**	**87.1 (14.9)[a]**	**96.8 (24.2)**
PIQ	127.0 (13.8)	**90.3 (21.5)**	121.5 (15.0)	**85.0 (14.0)**	**81.9 (18.4)[a]**	**106.3 (18.5)**
Episodic memory						
RMT words (/50)	45.1 (11.0)	37.0 (6.2)[a]	**32.3 (7.4)[a]**	37.2 (10.0)[b]	**15.3 (2.8)[a,*]**	38.4 (10.5)[a]
RMT faces (/50)	43.7 (4.6)	**37.0 (4.0)[a]**	**35.6 (5.4)[a]**	**34.7 (9.0)[a]**	**17.7 (2.7)[a,*]**	**33.1 (10.1)[a]**
Working memory						
Digit span forward (max)	7.1 (1.0)	**4.9 (1.5)**	6.6 (1.4)	**4.3 (1.2)[a]**	**5.6 (1.4)**	6.7 (1.5)
Spatial span forward (max)	5.6 (0.9)[a]	4.7 (1.3)	4.9 (0.9)[a]	**3.3 (0.8)**	NA	NA
Executive skills						
Digit span reverse (max)	4.8 (1.3)	**2.5 (0.8)[a]**	5.0 (1.9)	**2.7 (0.8)[a]**	**3.6 (0.7)[a]**	4.4 (1.2)
Spatial span reverse (max)	5.6 (0.9)[a]	**3.6 (1.4)**	5.0 (1.0)[a]	**3.2 (1.0)[a]**	NA	NA
Letter fluency (total)	20.5 (5.5)	**5.0 (5.2)[a]**	**10.3 (4.3)**	**5.3 (5.9)[c]**	**8.4 (4.2)**	**10.5 (4.8)**
Category fluency (total)	24.8 (5.6)	**9.4 (5.1)**	21.1 (41.3)	**5.5 (8.1)[a]**	**5.3 (3.0)**	13.3 (8.5)
Trails A (s)	30.7 (8.2)	**84.3 (38.1)**	41.0 (21.9)	**99.4 (38.2)**	**95.8 (37.0)[b]**	38.3 (25.5)
Posterior cortical skills						
GDA calculation (/24)	15.8 (4.1)	**5.8 (6.6)[b]**	12.7 (7.4)[a]	**1.8 (2.1)[c]**	**1.9 (1.0)[c]**	**10.9 (7.4)**

VOSP object decision (/20)	19.2 (1.0)	17.3 (1.8)	17.5 (1.6)	**15.0 (2.9)**	**15.5 (2.3)**	17.3 (3.6)[a]
Neurolinguistic skills						
Auditory input processing						
PALPA-3 (/36)	35.4 (0.3)	34.4 (1.0)	35.1 (0.3)[a]	**33.0 (0.8)[a]**	NA	NA
Word retrieval						
GNT (/30)	26.9 (2.7)	**15.0 (4.6)**	**1.0 (2.2)**	**6.2 (7.9)[b]**	**10.1 (8.4)[a]**	**15.3 (11.9)**
BNT (/30)	29.3 (0.2)	**22.3 (2.1)**	**7.4 (2.1)[a]**	**9.6 (3.3)**	NA	NA
Comprehension						
BPVS (/51)	47.8 (6.3)	**35.7 (8.4)**	**13.0 (15.6)**	**28.7 (16.2)[a]**	**38.3 (5.9)[a]**	40.6 (10.0)
Concrete synonyms (/25)	24.7 (0.1)	**18.0 (1.8)[a]**	**17.3 (1.5)[b]**	**18.3 (1.0)[a]**	NA	NA
Abstract synonyms (/25)	24.6 (0.3)	**18.7 (2.1)[a]**	**16.7 (1.5)[b]**	**18.8 (1.6)[b]**	NA	NA
PALPA-55 sentences (/24)	23.9 (0.1)	**17.9 (1.7)**	**22.3 (0.9)[a]**	**16.3 (2.0)[a]**	NA	NA
Speech repetition						
Polysyllabic words (/45)	44.8 (0.1)	**36.3 (3.4)**	44.0 (0.6)[a]	**32.7 (3.1)**	NA	NA
Graded sentences	9.6 (0.2)	**4.0 (1.1)**	**8.3 (0.4)[a]**	**4.4 (0.9)**	NA	NA
Spelling						
BST (/30)	26.3 (0.4)	**15.6 (3.1)**	**15.9 (2.8)[a]**	**13.0 (3.0)[a]**	NA	NA

Values in **bold** are significantly different from the control group. Reduced numbers of participants are indicated: [a]n-1; [b]n-2; [c]n-3; [d]n-4; [e]n-6.

Table 5.2. Quantitative analysis of reading and spontaneous speech production across participant groups with natural and delayed auditory feedback

	Control		nfvPPA		svPPA		lvPPA		tAD		bvFTD	
Reading	Natural	Delayed	Natural	Delayed	Natural	Delayed	Natural	Delayed	Natural	Delayed	Natural	Delayed
Time (s)	79.2 (3.2)	**98.1 (6.6)**	129 (29.5)	130 (39.1)	110 (12.9)	**133 (11.5)**	152 (18.5)	181 (21.4)	107 (10.0)	114 (8.6)	87.9 (7.7)	**120 (18.5)**
Total words	216 (0.5)	216 (0.9)	140 (38.2)	114 (38.5)	201 (14.7)	200 (16.9)	223 (2.0)	220 (6.0)	213 (14.6)	208 (14.9)	215 (0.8)	213 (1.3)
Speech rate	166 (6.5)	**139 (8.2)**	59.7 (6.6)	**48.6 (6.6)**	116 (12.6)	**96.2 (12.3)**	93.7 (8.1)	**78.7 (8.3)**	123 (10.2)	110 (8.2)	154 (13.0)	**124 (18.3)**
Error rate	1.3 (0.3)	**6.6 (1.6)**	58.0 (17.3)	**74.3 (21.7)**	5.8 (1.8)	**21.0 (8.6)**	15.4 (5.1)	32.0 (15.1)	15.6 (4.5)	**23.2 (7.4)**	2.6 (0.8)	12.0 (5.8)
Omissions	0.4 (0.1)	0.5 (0.2)	20.1 (6.5)	**32.8 (12.3)**	0.7 (0.3)	3.3 (2.7)	2.0 (0.7)	6.8 (4.3)	2.9 (1.3)	**4.7 (1.5)**	0.6 (0.2)	**2.0 (0.8)**
Distortions	0.4 (0.1)	**1.6 (0.4)**	23.6 (11.1)	24.7 (7.9)	3.3 (1.6)	**5.4 (2.3)**	8.5 (4.1)	11.1 (5.1)	5.7 (1.6)	6.6 (1.8)	0.7 (0.3)	**1.3 (0.5)**
Additions	0.4 (0.1)	**2.0 (0.7)**	14.8 (4.4)	14.8 (7.7)	1.1 (0.3)	2.3 (0.7)	4.4 (1.6)	**7.1 (1.7)**	5.9 (1.6)	10.1 (4.8)	1.0 (0.3)	1.2 (0.6)
Elongations	0.1 (0.0)	**2.5 (0.8)**	0.5 (0.3)	2.5 (1.3)	0.7 (0.3)	**10.1 (4.6)**	0.4 (0.1)	7.1 (5.5)	1.2 (0.6)	1.8 (0.8)	0.3 (0.1)	7.5 (4.5)
Dysfluencies	0.0 (0.0)	0.0 (0.0)	3.0 (1.4)	3.0 (2.3)	0.1 (0.1)	0.1 (0.1)	0.4 (0.4)	1.1 (1.1)	0.4 (0.2)	0.2 (0.2)	0.0 (0.0)	0.0 (0.0)
Spontaneous												
Time (s)	45.4 (5.6)	47.4 (6.7)	54.5 (14.9)	57.7 (11.7)	68.4 (15.5)	69.3 (13.5)	76.8 (18.5)	82.0 (17.7)	62.2 (7.1)	67.3 (8.0)	51.1 (8.0)	50.9 (9.4)
Total words	104 (9.8)	101 (13.1)	40.5 (16.4)	41.2 (11.3)	129 (32.2)	113 (24.6)	102 (22.7)	114 (29.4)	118 (17.0)	107 (15.3)	105 (22.5)	95.9 (24.9)
Speech rate	142 (6.2)	**129 (5.5)**	42.9 (7.0)	41.2 (4.0)	122 (14.9)	**101 (9.5)**	81.1 (6.8)	81.3 (6.0)	112 (7.0)	**95.8 (7.1)**	123 (18.5)	104 (15.5)
Error rate	3.0 (0.8)	**9.6 (1.7)**	49.4 (20.7)	53.9 (18.2)	3.0 (1.5)	9.6 (5.4)	8.6 (1.8)	14.0 (3.9)	5.2 (1.4)	**15.4 (4.1)**	3.0 (1.1)	**8.4 (2.9)**
Omissions	0.1 (0.1)	0.0 (0.0)	4.7 (2.6)	8.6 (4.2)	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	1.2 (1.2)	0.3 (0.3)	0.8 (0.6)	0.1 (0.1)	0.4 (0.4)
Distortions	0.4 (0.2)	**1.3 (0.4)**	16.7 (6.6)	19.3 (8.2)	0.5 (0.3)	1.1 (0.3)	3.8 (1.9)	5.9 (2.6)	1.1 (0.4)	**4.0 (1.0)**	0.5 (0.3)	2.5 (1.6)
Additions	0.8 (0.3)	**1.9 (0.6)**	22.6 (17.9)	20.8 (11.8)	1.6 (1.1)	**3.0 (1.7)**	4.3 (1.7)	**5.4 (1.4)**	3.5 (1.1)	**8.2 (3.0)**	2.1 (1.2)	2.4 (1.1)
Elongations	1.8 (0.5)	**6.3 (1.1)**	5.3 (5.3)	5.2 (3.6)	0.6 (0.3)	5.0 (3.8)	0.0 (0.0)	1.5 (1.0)	0.2 (0.1)	**2.5 (1.1)**	0.3 (0.2)	3.2 (1.5)
Dysfluencies	3.0 (0.7)	1.9 (0.6)	14.3 (8.1)	8.6 (4.8)	4.1 (1.1)	4.1 (1.3)	7.0 (1.3)	6.9 (1.2)	4.6 (0.8)	7.0 (1.8)	5.9 (1.9)	5.0 (2.0)
Grammatical	0.3 (0.2)	**1.0 (0.4)**	5.3 (2.9)	8.1 (6.3)	1.0 (0.5)	**2.3 (0.8)**	3.7 (1.1)	4.0 (1.5)	1.5 (0.3)	**2.6 (0.5)**	1.3 (0.4)	1.0 (0.4)

The table shows performance of each participant group across reading and spontaneous speech conditions under natural and delayed auditory feedback. Speech rate is defined as words per minute; error rate is defined as errors per hundred words. **Bold** = significant within-group difference ($p < 0.05$). Note that numbers over 100 are reported without decimal places to aid visual interpretation. Cells highlighted green indicate the key metrics of interest.

5.5.2. Mixed within and between subject modelling of results

Taking error rate as dependent variable, an ANOVA incorporating feedback (natural vs delayed) and task (reading vs spontaneous) as within-subject factors and diagnosis as a between-subject factor resulted in a significant main effect of feedback, $F(1,45) = 19.51$, $p < 0.001$, driven by more errors being made in the delayed condition. There was also a significant main effect of task, $F(1,45) = 8.89$, $p = 0.005$, with more errors being made in the reading condition than the spontaneous speech. There was also a marginally significant interaction between feedback and task, $F(1,45) = 4.09$, $p = 0.049$, driven by more errors being made under delayed feedback on the reading task. There was no interaction between task and diagnosis, $F(5,45) = 1.43$, $p = 0.231$, feedback and diagnosis, $F(5,45) = 0.344$, $p = 0.883$, or feedback, task and diagnosis, $F(5,45) = 70.89$, $p = 0.388$. Here, there was a between-subjects main effect of diagnosis, $F(5,45) = 7.3$, $p < 0.001$.

Running the same model with speech rate as dependent variable, there was a significant main effect of feedback, $F(1,45) = 36.12$, $p < 0.001$, this time driven by faster speech in the natural feedback condition. There was a significant main effect of task, $F(1,45) = 6.53$, $p = 0.014$, driven by faster speech for reading rather than spontaneous speech. There was a significant interaction between feedback and task, $F(1,45) = 4.81$, $p = 0.034$, here driven by a greater reduction in speech rate for reading relative to spontaneous speech under delayed relative to natural feedback. There were no interactions between feedback and diagnosis, $F(5,45) = 1.39$, $p = 0.211$, diagnosis and task, $F(5,45) = 1.16$, $p = 0.342$, or diagnosis, task and feedback, $F(5,45) = 1.09$, $p = 0.393$. There was a between-subjects main effect of diagnosis, $F(5,45 = 13.54$, $p < 0.001$).

5.5.3. Within-group differences under DAF relative to NAF

Table 5.2 shows data on speech rates and errors for all participant groups. For reading, all groups spoke significantly slower under DAF relative to NAF (all $p < 0.05$), with the exception of the patient group with typical Alzheimer's disease, which trended toward significance, $t(10) = 1.57$, $p = 0.073$. A different pattern was observed for spontaneous

speech: only control participants and patients with svPPA and tAD spoke slower under DAF. The difference in the bvFTD group bordered on significance, t(7) = 1.83, p = 0.055, whereas in the nfvPPA and lvPPA groups the differences did not approach statistical significance (t = 0.28/ -0.03; p = 0.396/ 0.512, respectively). For error rate per hundred words (phw), all groups made significantly more errors under DAF in the reading condition, with the exception of those with lvPPA and bvFTD. Here, both differences trended toward significance (lvPPA: t(6) = -1.59, p =0.081; bvFTD: t(7) = -1.76, p = 0.061). In the spontaneous speech condition, only the healthy control, tAD and bvFTD groups made significantly more errors under DAF than NAF, although two of the three other groups all trended toward a significant difference (svPPA: t(7) = -1.67, p = 0.069; lvPPA: t(5) = -1.54, p = 0.092). In nfvPPA here, this difference was non-significant, t(5) = -0.34, p = 0.373.

5.5.4. Between-group differences in sensitivity to DAF relative to NAF

To account for the low *n* in the lvPPA and nfvPPA groups here, I ran analyses as planned comparing each patient group to controls separately, but also created a pooled nonfluent group comprising just the nfvPPA and lvPPA patients. This group was also compared directly with controls.

Table 5.3 shows change in terms of words per minute and error rate between the NAF and DAF conditions, by participant group for spontaneous speech and reading separately. In the reading condition, nfvPPA patients showed change in terms of words per minute that was significantly less reduced relative to healthy controls, t(17) = -1.94, p = 0.034. Conversely, however, these same patients also had a significantly higher change in error rate relative to healthy control participants, t(17) = -1.90, p = 0.037. There were no direct differences between the lvPPA and control groups (WPM: t(18) = -1.42, p = 0.087; error rate: t(18) = -1.45, p = 0.082), but the combined nonfluent patient cohort again showed significantly less change in words per minute in the reading condition relative to control participants, t(24) = -2.16, p = 0.02, and a marginally significant difference in error rate, t(24) = -1.68, p = 0.053.

In terms of spontaneous speech, there were no differences between any patient group and control participants for change in error rate (all p > 0.05). Change in words per minute was significantly reduced in lvPPA compared to healthy controls, t(17) = -1.80, p =

0.045, and this was reflected in the combined patient cohort too, t(23) = -2.07, p = 0.025, though did not quite reach significance in the nfvPPA cohort alone, t(17) = -1.62, p = 0.062. Figure 5.2 shows change in words per minute from NAF to DAF for reading and spontaneous speech in the healthy control and combined nonfluent cohorts. Figure 5.3 plots change in error rates from NAF to DAF in the same groups.

Table 5.3. Change on critical measures of speech production from NAF to DAF across participant groups.

	Control	nfvPPA	svPPA	lvPPA	tAD	bvFTD	Pooled nonfluents
Reading							
Speech rate	-27.6 (5.4)	**-11.2 (3.5)**	-19.9 (7.0)	-15.0 (6.7)	-12.3 (7.8)	29.8 (10.3)	**-13.2 (3.8)**
Error rate	5.3 (1.6)	**16.3 (8.0)**	15.3 (7.5)	16.6 (10.4)	7.6 (4.2)	9.4 (5.4)	16.5 (6.5)
Spontaneous							
Speech rate	-12.6 (3.6)	-1.7 (6.2)	-21.0 (9.7)	**0.2 (7.2)**	-16.3 (4.8)	-18.2 (9.9)	**-0.7 (4.5)**
Error rate	6.5 (2.1)	4.5 (13.2)	6.6 (3.9)	5.3 (3.5)	10.2 (3.2)	5.4 (2.7)	4.9 (6.5)

The Table shows change in speech and error rates across participant groups under DAF relative to NAF, for reading and spontaneous speech separately. **Bold** = significantly different from healthy controls at $p < 0.05$.

5.5.5. Correlation with auditory input processing

In the healthy control group, change on each of the key measures outlined in Table 5.3 was significantly correlated with score on the PALPA-3 task of auditory input processing: reading WPM, t(11) = 3.2, p = 0.10; spontaneous WPM, t(11) = 2.37, p =0.039; reading error rate, t(11) = -2.37, p = 0.039; spontaneous error rate, t(11) = -2.43, p = 0.036. In the combined nonfluent cohort, none of these same metrics correlated with auditory input processing: reading WPM, t(11) = -0.05, p = 0.962; spontaneous WPM, t(10) = -1.82, p = 0.103; reading error rate, t(11) = -1.56, p = 0.150; spontaneous error rate, t(10) = 2.08, p = 0.068.

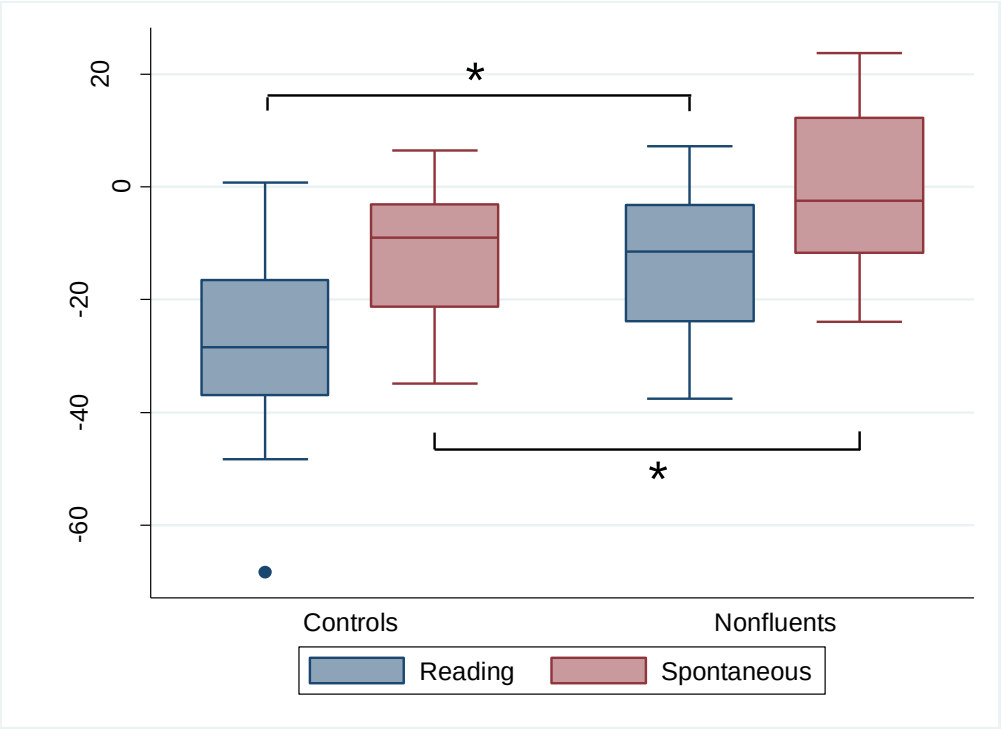

Figure 5.2. Box plots showing change in words per minute (WPM) from DAF relative to NAF in healthy control and combined nonfluent cohorts. The boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. Values falling outside these ranges are indicated. *significantly different at $p < 0.05$.

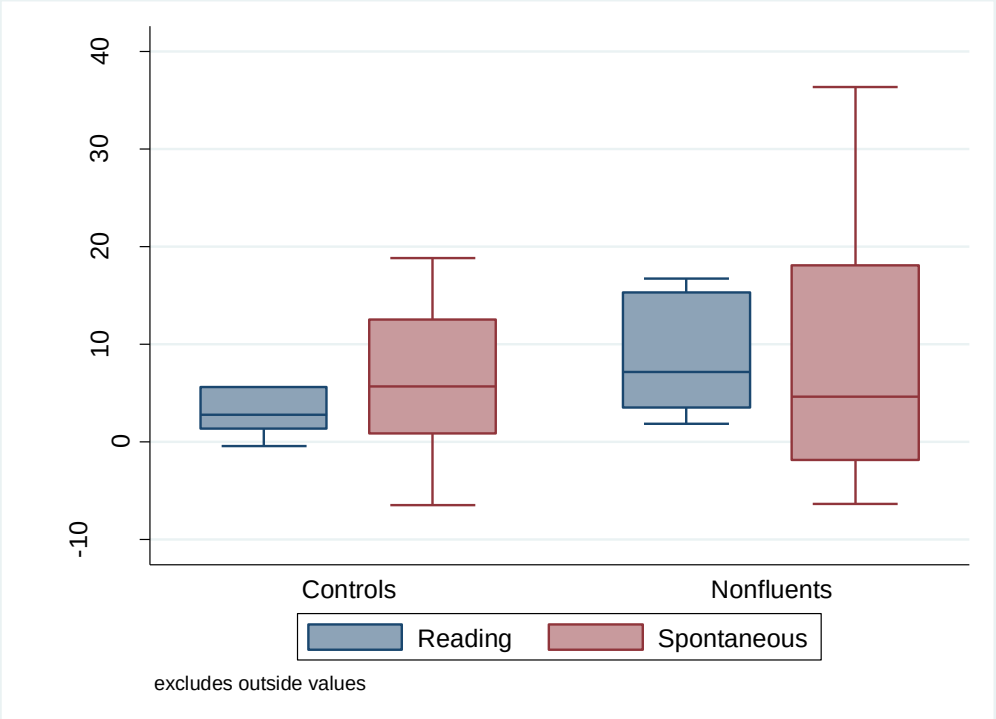

Figure 5.3. Box plots showing change in total error rate per hundred words from DAF relative to NAF in healthy control and combined nonfluent cohorts. The boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line

in each box represents the median. Values falling outside these ranges have been suppressed to aid visual interpretation.

5.6. Discussion

Here I have shown that DAF of 200ms is associated with significant deterioration of speech output (characterized by slower speech rate and higher error rate) in healthy control participants for reading and spontaneous speech. Different profiles emerged in the patient groups studied here, but crucially the two groups of cardinal interest, nfvPPA and lvPPA, did not improve on either of these metrics under DAF, contrary to the hypotheses I set out in section 5.3.

The mixed ANOVA models incorporating diagnostic group as between-subject factor and feedback and task as within-subject factors suggested that performance across all diagnostic groups was negatively affected by delayed feedback, in terms of error rate and speech rate. However, this approach lacked sensitivity to detect changes across task (reading vs spontaneous) or feedback (delayed vs natural) within or between diagnostic groups. This represented the most principled way of analysing these data, and it is likely to have been ineffective due to small individual group numbers and huge variance within groups.

There was, however, some suggestion that the lvPPA and nfvPPA patient groups may in fact show reduced sensitivity to the effects of DAF, especially in the spontaneous speech condition. Using t-tests as an alternative, it is worth noting that in comparing each patient group to the healthy control participants, only the lvPPA and nfvPPA (and pooled nonfluent cohort) groups emerged as statistically different in terms of change in the DAF condition relative to NAF. Here, the pooled nonfluent cohort of lvPPA and nfvPPA patients spoke at essentially exactly the same speech rate (<1 word per minute difference under DAF relative to NAF), while the control group spoke on average at 12.6 words per minute slower with DAF. The same pattern was observed in the reading condition: the pooled nonfluent cohort here spoke roughly 13 wpm slower under DAF, compared to the controls' average speech rate reduction of 27.6 words per minute. Both of these differences were statistically significant (see Table 5.3; Figure 5.2). They should, however, be regarded with caution: error rates in the nonfluent groups increased for both reading and spontaneous

speech under DAF, though neither of these was significantly different to the change seen in the healthy control group.

Nevertheless, Figure 5.2 suggests that individual participants in the nonfluent group might in fact show improved speech rate under DAF relative to NAF in the spontaneous speech condition. Examining individual change trajectories here, one patient with nfvPPA spoke ~24 words per minute faster under DAF than NAF, and two patients with lvPPA spoke more than 10 wpm faster with the delay. It would not be apposite to interpret change data from individual participants as anything more than qualitative, though I do note that the majority of 'successes' with DAF in previous studies have emerged in the context of single case work (Hanson & Metter, 1980; Downie *et al.*, 1981). The nature of this improvement will need to be investigated, but there would be considerable interest in identifying factors that may predict patients with nfvPPA and lvPPA who show a benefit under DAF.

The findings reported here corroborate previous research in healthy control participants (Stuart *et al.*, 2002; Maruta *et al.*, 2014; Max & Maffett, 2015; Mitsuya *et al.*, 2017), and suggest that dementia syndromes not underpinned by damage to the dorsal language network are affected similarly to healthy control participants (see the svPPA, bvFTD and tAD groups in Table 5.3). However, based on previous literature implicating dorsal language structures in using sensory information from auditory feedback to fine-tune vocal motor output (McGuire *et al.*, 1996; Hirano *et al.*, 1997; Hashimoto & Sakai, 2003; Zheng *et al.*, 2013), and previous work showing that DAF can actually improve motor speech output (Hanson & Metter, 1980; Downie *et al.*, 1981; Andrews *et al.*, 1982; Lincoln *et al.*, 2006; Foundas *et al.*, 2013) I had predicted that lvPPA and nfvPPA would show improvement under the influence of DAF.

This hypothesis was not supported by the results presented in this Chapter, and one possible explanation is that developmental stammerers, late onset acquired focal vascular lesions, and late onset degenerative (i.e. nfvPPA/ lvPPA) cases represent very different dysfluency disorders of the language system, and consequently show different profiles of DAF sensitivity. In developmental cases, this could reflect longstanding compensatory structural reorganisation, and the focal lesion of a stroke is likely to represent

a very different proposition to the network-based dysfunction seen in the nonfluent PPA syndromes (see section 1.1.4 for more discussion of this point). As considered in the Introduction section of this Chapter, patients with rapid, festinating speech phenotypes in the context of progressive supranuclear palsy (Hanson & Metter, 1980) and Parkinson's disease (Downie *et al.*, 1981) have been shown to benefit from short delays in the range of 50-100ms, but it is perhaps not surprising that the sensitivity seen in the nonfluent participants here is intrinsically different to that seen in other conditions.

Although the finding that nfvPPA and lvPPA patients show reduced sensitivity to DAF should be regarded with some caution, it is still consistent with previous work suggesting that DAF impacts on motor speech output via the dorsal language pathway (Maruta *et al.*, 2015), which is damaged insidiously in nfvPPA and lvPPA (Wilson *et al.*, 2010b; Henry *et al.*, 2016). One possibility is that these syndromes are associated with net reductions of processing speed in damaged cortex along the dorsal language pathway, which disrupt sensori-motor integration here, which in turn means that the normal controls on speech output gained via normal auditory feedback are negated (Warren *et al.*, 2005; Maruta *et al.*, 2014). In the patient groups with svPPA, tAD and bvFTD, as well as the healthy control participants, DAF had a dramatic effect on speech production. In these groups, I suggest that the normal sensori-motor integration of auditory feedback into fine-motor tuning of speech output was disrupted by DAF, consistent with previous reports in individuals with no damage to this language network (Stuart *et al.*, 2002; Chon *et al.*, 2013; Maruta *et al.*, 2014; Yamamoto & Kawabata, 2014; Chesters *et al.*, 2015; Cler *et al.*, 2017).

Intriguingly, while the changes in speech rate and error rate from NAF to DAF in the reading and spontaneous conditions were consistently significantly correlated with the PALPA-3 (Kay *et al.*, 1992) auditory input processing task in the healthy control participants, none of these same scores were significantly correlated in the combined nfvPPA and lvPPA group. This task requires fine-grained discrimination of phonemically proximal minimal pairs, e.g. "mip" vs "nip". It seems highly relevant that sensitivity to DAF in the control group was correlated with this measure, but not in the nonfluents. Taken together, this lack of a correlation in the nonfluent group lends support to the idea of deficient integration of auditory feedback, most likely due to damage along the dorsal language pathway, and may in itself

go some way to explaining the lack of sensitivity shown by this group here (Warren *et al.*, 2005; Maruta *et al.*, 2014; Henry *et al.*, 2016).

There are, clearly, several limitations with the work presented in this Chapter. First, although my combined patient cohort comprised 41 unique individuals, the numbers in my main groups of interest, lvPPA and nfvPPA, were very small. A corollary of this is that these findings should be regarded as somewhat preliminary – future work will need to corroborate and extend the research presented here, ideally with neuroanatomical correlations. Second, one potentially important consideration is the length of the delay I opted to use in this experiment. Studies conducted with children have suggested that younger children may be less affected by DAF than older children, perhaps reflecting a higher degree of cortical plasticity that is diminished with age (Chase *et al.*, 1961). Indeed, younger children aged 4-6 show maximum disruption to fluency under a delay of around 500ms, while in children aged 7-9, the maximal level for disruption is around 400ms (Chase *et al.*, 1961). This contrasts with the 200ms delay that has been shown consistently to represent maximum disruption in older individuals (Stuart *et al.*, 2002; Maruta *et al.*, 2014; Max & Maffett, 2015; Mitsuya *et al.*, 2017). However, other research has suggested that perhaps the opposite is true, and that youngest children are in fact the most affected by DAF, with older children and adults becoming less reliant on NAF for sensori-motor retuning of speech output, reflecting increasing language mastery (Siegel *et al.*, 1980).

In this Chapter, I attempted to explore whether delaying auditory feedback in a cohort of patients with nfvPPA and lvPPA would improve speech output, using the key metrics of speech fluency and rate of errors. My results did not support this hypothesis, although there was a suggestion that these two groups may show reduced sensitivity to the effects of DAF. If this finding is replicated in larger cohorts, it could have important implications in terms of: i) our understanding of breakdown along the dorsal language pathway in nfvPPA and lvPPA; ii) tracking efficacy of treatments in these conditions, and iii) as an early, dynamic perceptual 'stress-test' that may be particularly sensitive relative to traditional cognitive measures in the earliest stages of these nonfluent syndromes. In my final experimental Chapter, I explore this idea of dynamic stress tests of the language network still further.

6. Processing of degraded speech stimuli

6.1. Chapter summary

In this Chapter, I focus more specifically on linguistic components of speech perception, using the paradigm of sinewave-degraded speech in a cohort of 27 patients with all three of the main syndromic variants of PPA relative to 11 patients with typical Alzheimer's disease and 17 healthy controls. Sinewave speech represents a perceptual transformation that initially renders speech signals unintelligible, but that is spontaneously and rapidly adjusted to by the healthy brain. Here, participants were required to identify two different sinewave versions of speech stimuli: i) spoken three-digit numbers, and ii) spoken geographical locations. Behavioural task performance was then correlated with grey matter volume in a voxel-based morphometry analysis. Relative to healthy control participants, patients with nfvPPA and lvPPA showed deficient processing of sinewave speech signals: in the lvPPA group, this covaried with phonological working memory capacity, whilst in nfvPPA there was no such relationship with working memory. Patients with svPPA, by contrast, showed intact processing of the degraded speech tokens, but deficient integration of semantic knowledge. Neuroanatomical correlates of key behavioural signatures emerged along the dorsal and ventral streams proposed to underlie speech perception, and results are discussed in terms of residual plasticity for perceptual learning, syndromic stratification, and auditory processing deficits corroborating the picture presented in Chapters 3-5.

6.2. Introduction

The work presented in the previous two chapters provides support for the notion that all three major PPA syndromes are associated with deficits of auditory speech signal processing. As discussed in Chapter 1, speech perception represents a computationally demanding perceptual process: the listener must identify the speech signal from a cacophony of background noise, parsing it into an auditory object, and mapping this representation to lexical and conceptual representations (Griffiths & Warren, 2004; Hickok & Poeppel, 2007; Hardy *et al.*, 2016). Decades of functional imaging research have increased our understanding of speech processing in the healthy brain (Scott *et al.*, 2000; Hickok &

Poeppel, 2007), and it is widely accepted that early spectrotemporal analysis of heard speech takes place in posterior STG and PT, before diverging into a dorsal stream concerned with sensory/ phonological mapping to motoric representations, implicating fronto-temporo-parietal regions, and a ventral stream concerned with mapping sensory/ phonological representations to lexical conceptual representations, comprising medial and inferior temporal structures (Hickok & Poeppel, 2000, 2004, 2007; Warren *et al.*, 2005). Given the clinico-anatomical pictures of the PPA syndromes, there is considerable interest in exploring speech signal processing in PPA.

Importantly, speech perception is robust to gross distortions of the speech signal. Superimposing the temporal envelope of a speech signal onto a noise carrier (i.e. noise vocoding) does not destroy intelligibility (Shannon et al., 1995; Davis & Johnsrude, 2007). Sinewave speech (Remez *et al.*, 1981) represents a different type of distortion: the major formants of the speech signal are tracked and replaced by sinewaves (see Figure 6.1), giving a percept of "whistled" tones that are initially not understood as speech. However, rapid perceptual learning of sinewave speech has been consistently documented (Remez *et al.*, 1981, 1997, 1998, 2007; Liebenthal *et al.*, 2001; Bent *et al.*, 2011). A summary of research using sinewave speech manipulations is given in Table 6.1. Intriguingly, despite the dramatic distortions inherent to sinewave speech signals, listeners are still able to use the residual phonetic information to identify gender and even individual speakers (Fellowes *et al.*, 1997; Remez *et al.*, 1997; Sheffert *et al.*, 2002; Gonzalez & Oliver, 2005). The fact that noise-vocoding and sinewave speech both remain highly intelligible to trained listeners, despite intrinsic and fundamental differences in the manipulations (noise-vocoded speech comprises entirely slowly-modulating broadband noises with minimal traces of speech formants, while sinewave speech lacks any broadband acoustic energy, but does retain the rapidly changing spectrotemporal cues of speech formants) suggest that healthy individuals are able to rely on automatic perceptual learning mechanisms even where traditional speech cues are degraded or totally absent (Davis & Johnsrude, 2007). Recent evidence suggests that perceptual learning of degraded speech stimuli is associated with automatic plasticity in primary auditory cortex, with an observable neurophysiological effect in the sub-second range (Holdgraf *et al.*, 2016).

There are two complementary processes thought to underlie the automatic adaptation to initially unintelligible speech stimuli: perceptual learning, and top-down influence (Davis & Johnsrude, 2007). Perceptual learning refers to an automatic and rapid process of adaptation to a stimulus through experience of that stimulus: it is a process of familiarisation that occurs spontaneously in the healthy brain (Gibson, 1963). Higher-level, i.e. top-down influences on distorted speech perception improve perceptual adaptation to the degraded signal (Davis *et al.*, 2005; Davis & Johnsrude, 2007; Hannemann *et al.*, 2007; Obleser & Kotz, 2010, 2011; Sohoglu & Davis, 2016). In one such demonstration, Davis and colleagues showed that training healthy participants with clear nonword sentences produced no benefit on subsequent perception of noise-vocoded sentences, while those trained with English sentences did experience a boost in perceptual learning of the subsequent noise-vocoded sentences (Davis *et al.*, 2005). Parsimoniously, it seems likely that efficient processing of distorted speech requires two related systems: a) a phonological working memory (PWM) store to allow for perceptual retuning of the heard signal (i.e. perceptual learning); and b) top-down semantic interpretation of the signal.

Here, I used the paradigm of sinewave speech to explore residual plasticity for perceptual learning of distorted speech signals in the vulnerable and disintegrating language networks of patients with major syndromes of PPA, referenced to a group of patients with typical Alzheimer's disease and to healthy older individuals. I applied a sinewave manipulation to two different semantic categories of speech signals: three-digit numbers and geographical locations. Numbers represent a special class of semantic knowledge, and previous research has demonstrated that number knowledge is well-preserved relative to other categories in svPPA (Rossor *et al.*, 1995; Crutch & Warrington, 2002; Domahs *et al.*, 2006; Julien *et al.*, 2010). Similarly, knowledge of country and city names represents a special module of conceptual knowledge pertinent to geographical spatial encoding (Incisa Della Rocchetta *et al.*, 1998; Crutch & Warrington, 2003, 2010) that may be less vulnerable to the anterior temporal lobe atrophy associated with svPPA than other semantic categories (Hoffman & Crutch, 2016).

These manipulations were designed with the intention of a) stratifying performance across PPA syndromes and b) allowing me to consider differences between "bottom-up"

auditory perceptual processing of stimuli relatively devoid of specific semantic associations (numbers) versus "top-down" associative integration of semantic knowledge (geographical locations). The geographical locations stimuli were subdivided factorially to allow consideration of location category (cities vs countries), geographical relatedness (near vs far), and syllable length (bisyllabic vs trisyllabic). Given the importance of PWM in the decoding of degraded speech (Davis & Johnsrude, 2007), and its critical involvement in lvPPA (Gorno-Tempini et al., 2008, 2011; Rohrer et al., 2010b; Henry et al., 2016), I critically considered the impact of PWM capacity on performance on these tasks.

With these manipulations, I was able to make certain key predictions about how each patient group would perform on each task, in paradigms designed to capture "bottom-up" apperceptive vs "top-down" semantic/ predictive processing of degraded speech signal information. Performance on key behavioural measures here was taken forward into a voxel-based morphometry analysis, allowing me to identify the critical neuroanatomical substrates required for performance of these tasks in PPA.

6.3. Key predictions

- Patients with lvPPA and nfvPPA would show bottom-up speech processing deficits corroborating results presented in Chapters 3-5 and previous evidence (Rohrer *et al.*, 2010b; Hailstone *et al.*, 2012; Hardy *et al.*, 2015; Grube *et al.*, 2016; Henry *et al.*, 2016).
- These deficits would be associated with corresponding neuroanatomical substrates in early speech areas including posterior superior temporal gyrus and planum temporale (Hickok & Poeppel, 2007; Gorno-Tempini *et al.*, 2008; Rauschecker & Scott, 2009; Rohrer *et al.*, 2010b; Henry *et al.*, 2016).
- Patients with svPPA would show rapid perceptual learning of the distorted speech signal, representing preserved cortex in these early auditory processing areas, but exhibit reduced top-down associative integration of semantic content (Lambon Ralph *et al.*, 2010, 2016).

Table 6.1. Summary of previous literature using sinewave speech distortions.

Authors (Year)	Design	Findings
(Benson *et al.*, 2006)	n=25 (n=12 fMRI) healthy younger participants. Passive listening fMRI where participants heard either SWS phonemes or reversed SWS phonemes.	Two brain regions, in bilateral STS, extending more posteriorly on the left activated more for the SWS condition.
(Dehaene-Lambertz *et al.*, 2005)	n=19 (fMRI), n=12 (ERP) healthy younger participants. Participants listened to SWS phonemes without explicitly being told they were speech sounds, and asked to perform a basic forced-choice task. Then they were told it was speech and asked to do it again.	Behaviourally, explicit knowledge that sounds were speech improved accuracy. For the EEG, MMR response was faster for the speech condition, implying a more efficient network for speech processing. fMRI showed that the posterior temporal lobe along left STS was more activated in speech than non-speech condition, including left supramarginal gyrus.
(Fellowes *et al.*, 1997)	n=79 healthy younger participants. In four experiments, listeners were asked to ascertain sex or identity of speakers in SWS.	Results imply that perceivers can differentiate talkers as well as words from phonetic properties of speech.
(Gonzalez & Oliver, 2005)	n=111 healthy younger participants. Participants asked about gender and identity of a talker as a function of number of channels in spectrally reduced speech (SWS and noise-band), with between three and 16 channels.	Participants were able to accurately detect gender and identity with just three SWS channels, implying that F0 and spectral properties of the natural voice provide strong cues for speaker and gender identity.
(Hillenbrand *et al.*, 2011)	n=71, healthy younger participants. All participants were given a SWS vowel intelligibility test and then assigned to one of four training conditions: feedback, sentence transcription, triad (SWS-clear-SWS), irrelevant control (gender decision)	All training improved accuracy, with the largest increase in the triad condition. Additional training produced significant improvements, but reached asymptote at around 74% (up from 55%).
(Lee & Noppeney, 2014)	n=41 (n=21 musicians). All participants judged audiovisual synchrony of speech, SWS and music at 13 AV stimulus onset asynchronies.	Musicians had narrower temporal integration windows for both music and SWS. Amount of practice significantly correlated with sensitivity to temporal misalignment.

(Lee & Noppeney, 2011)	n=31 healthy younger participants. Participants presented with SWS in visual, audio, and audiovisual modalities.	Distinct patterns of activity identified for audio-visual speech perception along dorsal frontotemporal circuitry.
(Loebach & Pisoni, 2008)	n=155 healthy younger participants. Participants allocated to one of five conditions: modified rhyme test (MRT), phonetically balanced words, meaningful sentences, anomalous sentences, environmental sounds put through an 8-channel sinewave vocoder. All had explicit training and performed a pre- and post-training task.	Participants trained on isolated words performed significantly better on the MRT than other groups. Participants trained on sentences (anomalous or meaningful) performed significantly better on anomalous sentences than other groups.
(Loebach *et al.*, 2008)	n=78 healthy younger participants. Participants trained on SWS (8-channel) using transcription, talker identification, or gender identification tasks, incorporating pre- and post-training testing and high probability, low probability and anomalous sentences (as designated by the terminal word).	On average, participants performed better on anomalous sentences than meaningful sentences. Participants in the talker ID and transcription conditions performed significantly better than participants in the gender ID condition, on post-test and generalization.
(Remez *et al.*, 1997)	n=50, healthy younger participants. A series of three experiments indexing whether listeners could accurately identify individual speakers in SWS.	Listeners must have been using phonetic information preserved in SWS in order to distinguish/ identify talkers.
(Remez *et al.*, 1998)	n=138, healthy younger participants. Auditory (sinewave replicas of single formants in isolation) and visual signals (video of space talking) played in tandem and participants asked for coherence judgements.	A sinewave replica of the second formant was more intelligible than any other formant.
(Remez *et al.*, 2001)	n=46, healthy younger participants. Participants listened to two isolated 2nd-formant patterns in an S/D task. Then an isolated 2nd-formant pattern followed by a SWS word and asked whether the pattern was a component of the word.	Participants were unable to verify the auditory form of the 2nd formant in SWS, implying that SWS evokes auditory perceptual processing in which acoustic elements are bound together.
(Remez *et al.*, 2007)	n=165, healthy younger participants. Participants listened to natural, SWS, and both reversed, spoken by 10 individual speakers with American or British accents. Sounds presented in pairs and participants had to rate the subjective likeness of the two talkers.	Participants broadly accurate for natural and SWS conditions, implying perceptual similarity in a group of talkers is largely preserved over acoustic transformation to SWS. Accuracy in the reversed conditions significantly worse, though there was still some subjective similarity.

(Serniclaes *et al.*, 2001)	n=36 children, 19 dyslexics, 17 average readers. All children were given a same/ different paradigm for SWS phonemes, and SW nonspeech.	Dyslexic children better at discriminating acoustic differences between stimuli belonging to same category - they were less categorical than average readers.
(Sheffert *et al.*, 2002)	n=44, healthy younger participants. Over five experiments, listeners were trained to 70% accuracy to identify 10 individual talkers from natural, sinewave or reversed speech sentences.	Talker-specific knowledge acquired during perceptual learning of sinewaves generalized to novel, natural, and sinewave sentences, i.e. listeners are able to abstract specific attributes of a talker's speech from sinewave - individual talker attributes are carried by segmental properties as well as vocal timbre.
(Viswanathan *et al.*, 2014)	n=62, healthy younger participants. Participants exposed to background noises comprising SWS, natural speech, and reversed version of both, looking at the irrelevant sound effect.	SWS produced less of an effect than natural speech, suggesting that speech-like properties of background noise are important beyond changing state complexity for ISE.

6.4. Materials and methods

6.4.1. Participants

Nine patients with nfvPPA (six female; mean age 69.6 ± 9.2 (SD) years), 11 patients with svPPA (four female; mean age 64.8 ± 7.2 years), seven patients with lvPPA (one female; mean age 66.3 ± 6.1 years), and 11 patients with tAD (six female; mean age 69.7 ± 8.8 years) were recruited in line with the procedures outlined in Section 2.1. Cerebrospinal fluid tau/ abeta profiles were available for five of the seven patients with lvPPA, all of which were consistent with Alzheimer's pathology based on local reference ranges (total tau: beta-amyloid 1-42 ratio > 1). Seventeen healthy elderly individuals (nine female; mean age 67.7 ± 5.2 years) also participated. Demographic, clinical and basic neuropsychological data for all participants are summarized in Table 6.2.

6.4.2. Experimental stimuli

All stimuli were recorded as digital wavefiles (sampling rate 44.1 kHz) in a quiet recording booth at University College London using Audacity® software (www.audacityteam.org). Two lists of stimuli were recorded: a) three-digit numbers and b) geographical locations. The numbers were recorded by a young male speaker (myself) and locations were spoken by a young female speaker (SJR), both speaking with a standard southern English accent. Different speakers were used to mitigate against perceptual learning performance transferring automatically across tasks. Sinewave replicas of these "clear" recordings were made using Praat software (version 6.0.27; http://www.fon.hum.uva.nl/praat/) with a script written by Chris Darwin (http://www.lifesci.sussex.ac.uk/home/Chris_Darwin/Praatscripts/SWS). The script tracks and replaces the centre frequencies of three formants of the target stimulus with sinewave tones. A graphical depiction of the transformation is given in Figure 6.1, and examples of the stimuli are given on the enclosed CD in Audio Files 6.1–6.4 (see Supplementary Table 2).

Table 6.2. Demographic, clinical and neuropsychological characteristics of participant groups.

	Controls	nfvPPA	svPPA	lvPPA	AD
Demographic and clinical					
No. (M:F)	8:9	3:6	7:4	6:1	5:6
Age (yrs)	67.7 (5.2)	69.6 (9.2)	64.8 (7.2)	66.3 (6.1)	69.7 (8.8)
Handedness (R:L:A)	16:0:1	8:1:0	11:0:0	7:0:0	10:1:0
Education (yrs)	16.2 (2.6)	14.9 (3.3)	14.5 (3.2)	15.1 (2.3)	14.2 (1.8)
MMSE (/30)	29.7 (0.5)	**24.4 (5.1)**	**23.3 (8.1)**	**18.4 (8.0)**	**18.0 (6.0)**
Symptom duration (yrs)	NA	3.6 (1.3)	5.2 (1.9)	3.3 (1.3)	6.1 (3.0)
PTA best ear (N:Mil:Mod)	4:11:0[b]	1:6:1[a]	4:6:0[a]	3:2:1[a]	2:6:0[c]
General intellect: IQ					
WASI Verbal IQ	127.6 (5.9)	**76.4 (17.7)**	**67.5 (22.4)**	**60.6 (8.3)**	**91.8 (19.3)**
WASI Performance IQ	121.7 (13.7)	**100.3 (21.8)**	110.1 (21.8)	**79.4 (13.1)**	**84.7 (20.3)[a]**
Episodic memory					
RMT Words (/50)	48.4 (1.9)	**40.3 (7.3)[b]**	**33.4 (5.7)[d]**	**31.0 (7.3)[b]**	15.7 (3.5)*[a]
RMT Faces (/50)	44.5 (4.4)	39.1 (4.0)[b]	**35.0 (6.2)[c]**	**31.7 (5.2)**	18.2 (3.2)*[a]
Working memory					
Digit span forward (max)	7.2 (1.0)	**4.6 (1.4)**	6.0 (1.3)	**4.0 (1.3)[a]**	**5.8 (1.5)**
Spatial span forward (max)	5.5 (0.8)[b]	**4.8 (1.2)**	5.5 (0.9)	**3.3 (0.8)**	NA
Executive skills					
Digit span reverse (max)	5.1 (1.1)	**3.0 (0.9)[a]**	5.4 (2.1)	**2.6 (0.9)[b]**	**3.8 (0.8)[a]**
Spatial span reverse (max)	5.4 (0.9)[b]	**3.8 (1.5)**	5.2 (1.2)	**3.0 (1.0)**	NA
Letter fluency (total)	18.4 (5.1)	**6.2 (6.0)**	**10.2 (4.5)[a]**	**4.5 (6.5)[c]**	**9.9 (6.0)**
Category fluency (total)	25.6 (5.4)	**9.7 (4.9)**	**17.6 (37.2)[a]**	**5.0 (7.5)**	**6.3 (4.9)**
Trails A (s)	31.8 (8.0)	**71.3 (36.9)**	**45.1 (37.2)**	**79.2 (37.6)[b]**	**92.8 (40.6)[b]**
Posterior cortical skills					
GDA Calculation (/24)	13.6 (4.1)	**6.0 (6.4)[a]**	15.0 (7.3)[b]	**3.0 (2.2)[c]**	**3.4 (4.4)[c]**
VOSP Object Decision (/20)	18.9 (1.0)	**17.4 (1.9)**	**16.2 (3.1)**	**15.3 (2.6)**	**15.5 (2.3)**
Neurolinguistic skills					
Auditory input processing					
PALPA-3 (/36)	35.1 (1.1)[b]	34.6 (2.3)	35.3 (1.0)	**31.1 (5.2)**	NA

Word retrieval					
GNT (/30)	27.1 (2.5)	**13.8 (4.8)[a]**	**1.2 (2.2)[e]**	**9.3 (10.3)**	**12.7 (9.2)[a]**
BNT (/30)	29.4 (0.6)[b]	**22.0 (5.0)**	**6.4 (5.2)[b]**	**9.9 (8.5)**	NA
Comprehension					
BPVS (/51)	48.3 (5.6)	**33.3 (14.9)**	**9.5 (14.8)**	**29.3 (7.3)**	**40.1 (5.5)[a]**
Concrete synonyms (/25)	24.5 (0.6)[b]	**19.0 (4.2)[a]**	**16.6 (3.3)[d]**	**17.7 (2.8)**	NA
Abstract synonyms (/25)	24.5 (0.8)[b]	**19.3 (4.5)[a]**	**15.6 (3.6)[d]**	**17.8 (4.0)[a]**	NA
PALPA-55 (/24)	23.9 (0.4)[b]	**19.1 (4.5)**	22.3 (2.1)[c]	**15.7 (4.9)**	NA
Speech repetition					
Polysyllabic words (/45)	44.8 (0.9)[b]	**35.1 (3.6)[a]**	48.9 (0.6)	**34.5 (2.6)**	NA
Short sentences (/10)	9.7 (0.6)[b]	**4.0 (2.9)[b]**	**7.8 (1.7)[b]**	**4.6 (2.2)**	NA
Spelling					
BST (/30)	26.6 (1.6)[b]	**14.2 (8.0)**	**13.0 (7.5)[a]**	**13.0 (7.3)[a]**	NA

Significant differences ($p<0.05$) from healthy control values are indicated in **bold**. *AD patients were administered the short version of the RMT tasks so a direct comparison with healthy controls here was not possible. Reduced numbers of participants are indicated: [a]n-1; [b]n-2; [c]n-3.

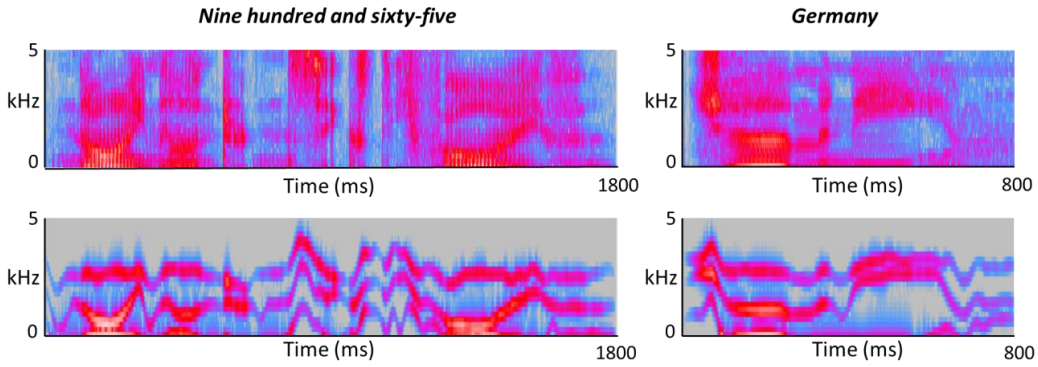

Figure 6.1. Broadband time-frequency spectrograms of clear and sinewave stimuli. Naturally-spoken stimuli are shown in the top panels; corresponding sinewave replicas are displayed on the bottom panels. Frequency is depicted on the y-axis, in kilohertz (kHz) and time is depicted on the x-axis, in milliseconds (msec); the sinewave replica retains the centre frequencies of the formant contours but omits the spectral detail evident in natural speech.

6.4.3. Design and procedure

6.4.3.1. Numbers

Number stimuli comprised 20 unique three-digit sinewave numbers and a separate list of 10 clear numbers. In both the test and clear conditions, each number was scored out of three; the participant was given one point for each correct digit.

Participants were seated opposite me, and told that they would hear a series of three-digit numbers. In a training phase, I spoke a series of three-digit numbers aloud and asked the participant to write down or repeat the numbers; whichever the participant found easiest. Once I was confident that the participant had understood the task requirements, I gave the participant a pair of headphones and made sure that they were placed comfortably over their ears. Volume was set to a minimum level of 70dB for all participants and adjusted higher if required.

At the start of the test phase, I said to the participant, “Now I’m going to play you some more numbers, but this time they’ve been distorted or changed so that they sound really quite strange. I want you to listen really carefully because over time you will get better at understanding what is being said. I’d like you to write down or repeat the number you think you hear, but it’s perfectly normal if at first you’re not sure: just put a question mark or say so and move on to the next number”. The order of the numbers within each list was randomised for each participant.

6.4.3.2. Locations

Forty sinewave locations were played to participants, who were again required to transcribe or repeat the location that they heard. Half of the stimuli were geographically proximal to London (n=20; English cities, European countries), and half were relatively further away (n=20; American cities, countries from outside of Europe). I also manipulated syllable length factorially, so that half of the locations were bisyllabic and half were trisyllabic. After the test phase, participants were required to transcribe or repeat 16 "clear" locations that had been used as sinewave stimuli in the previous phase. To assess semantic knowledge of the geographical stimuli, a two-alternative forced-choice task was administered after the participant had completed the listening part of the experiment.

The locations section always followed immediately after the numbers section had been completed. There was no practice phase for this task, and I ensured that each participant understood the task before commencing testing. I said to each participant, "This time, instead of hearing numbers, you're going to hear the names of cities or countries being spoken aloud. The cities could be English or American, and the countries could be European, or from anywhere else in the world. I'd like you to write down or repeat the name of the city or country that you hear. To start with, these will be in the strange distorted sounds that we were using before, so again it's a difficult task and don't worry if you find it really hard at first". After the listening part of the experiment, for each of the locations presented in sinewave speech, the participant was asked i) if it was a city or a country, and ii) if it was English/ American (for cities) or European/ not European (for countries), giving a total of 80 items.

6.4.4. Analysis of clinical and background neuropsychological data

Demographical, clinical, and background neuropsychological data for all participants were analysed in accordance with the approach outlined in Section 2.9.1.

6.4.5. Analysis of sinewave data

For the analysis of the experimental behavioural data in this Chapter, I used a series of multiple regression models repeated with and without certain key variables where appropriate.

6.4.5.1. Numbers

For the numbers tasks, I ran four different main analyses: looking at total score on the clear and sinewave tasks separately, and learning rate and performance over time for the sinewave numbers only. The learning rate variable was calculated by taking score on items 1-5 away from score on items 16-20. Higher scores on this variable therefore reflected a higher rate of learning. The 'standard' model for each of these incorporated MMSE score as a measure of disease severity, digit span as a measure of phonological working memory and diagnosis:

$$y_i = intercept + \beta(MMSE_i) + \beta(Digit\ Span_i) + \beta(diagnosis_i) + \varepsilon_i$$

Performance over time on this task was assessed using a repeated measures ANOVA that used score in four 'bins' of five items as a repeated measures variable that again covaried for MMSE and digit span.

6.4.5.2. Locations

For the locations task, the standard model included MMSE, digit span, score on the task assessing geographical knowledge and diagnosis:

$$y_i = intercept + \beta(MMSE_i) + \beta(Digit\ Span_i) + \beta(Geographical\ knowledge_i) + \beta(diagnosis_i) + \varepsilon_i$$

Running these same models with and without digit span allowed me to assess the effect of phonological working memory capacity on behavioural task performance.

For the semantic control task assessing participants' geographical knowledge, performance was compared in a simple regression model only incorporating overall score as dependent variable and diagnosis as independent variable, with planned comparisons assessing differences between the healthy control group and each patient group, and differences between the svPPA group and each other patient group. No covariates were included in this analysis as I wanted to assess 'pure' differences across groups, with a view to using this variable as a covariate in subsequent analyses.

Finally, to compare performance on sinewave number and locations processing directly, I used the difference between scores on these two tasks (converted to percentages) as dependent variable in a model incorporating MMSE, geographical knowledge, clear number performance, forward digit span and diagnosis as independent variables. Again, I dropped forward digit span and clear number performance in a stepwise fashion.

6.4.6. Brain MRI Acquisition and VBM preprocessing

Volumetric brain MR images were acquired for all patients in accordance with the general methods described in Section 2.6 and preprocessing for VBM was carried out in line with the methods described in Section 2.7.

6.4.7. Analysis of neuroanatomical data

I ran three separate major VBM analyses, using total score on the numbers task, learning rate on the numbers task, and total score on the locations task. The measure of learning rate on the sinewave numbers processing task was generated by taking score on items 1-5 away from score on items 16-20 in each participant. Higher scores here represent higher rate of perceptual learning. All three variables were included in separate full-factorial VBM analyses examining the interaction between diagnosis and behavioural task performance on voxel grey matter intensity in a model incorporating TIV and age as nuisance covariates for each patient group. I also incorporated forward digit span as a proxy for disease severity and to control for PWM capacity. SPMs were generated in accordance with the details outlined in Section 2.9.2.

Here I used pre-defined regions of interest based on neuroanatomical predictions from previous studies (see Figure 6.2). I defined a posterior temporal lobe region, comprising posterior MTG, STG, and PT, all of which have been previously implicated in the processing of intelligible speech and in mapping meaning onto speech sounds (Dehaene-Lambertz *et al.*, 2005; Benson *et al.*, 2006; Davis & Johnsrude, 2007; Hickok & Poeppel, 2007; Leff *et al.*, 2008; Price, 2010; Hartwigsen *et al.*, 2017), a parietal region known to be involved in auditory short-term memory and rehearsal of speech, comprising SPL, angular gyrus, and SMG (Ravizza *et al.*, 2004; Dehaene-Lambertz *et al.*, 2005; Benson *et al.*, 2006; Seghier, 2013; Hartwigsen *et al.*, 2014; Clark *et al.*, 2017), and a motor region consisting of IFG and precentral gyrus that has previously been implicated in creating a motoric/ somatotopic representation of speech as it would be produced (Tettamanti *et al.*, 2005; Davis & Johnsrude, 2007; Takeichi *et al.*, 2009; Obleser & Kotz, 2010; Wild *et al.*, 2012; Specht, 2013).

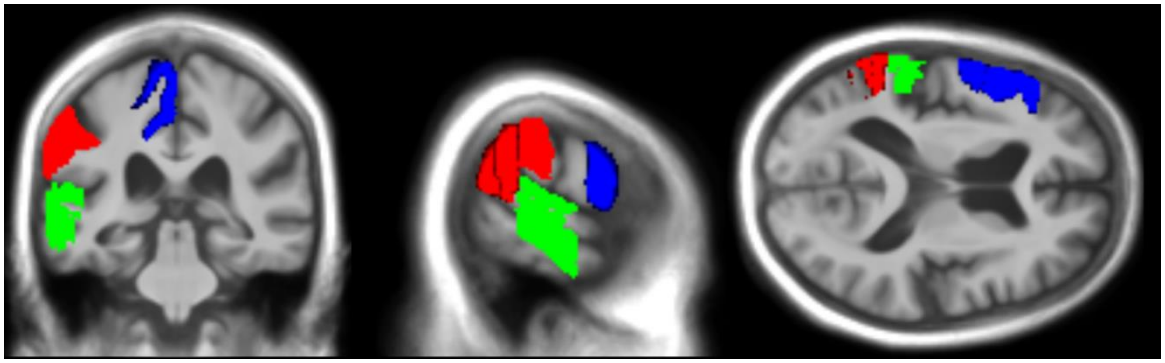

Figure 6.2. Representative sections of neuroanatomical volumes used for VBM small-volume corrections. Small volumes were derived from prior anatomical hypotheses (see text), and volumes were limited to the left hemisphere only. Each contrast was assessed within each small volume separately. Blue = IFG and precentral gyrus; red = SMG, angular gyrus and SPL; green = posterior MTG, posterior STG and PT.

6.5. Results

Background demographic, neuropsychological and clinical data for all participant groups are presented in Table 6.2. Results on the experimental tasks are presented in Table 6.3.

6.5.1. General participant characteristics

Groups did not differ overall in terms of age ($F(1,53) = 0.05$, $p = 0.822$), handedness ($\chi2 = 5.89$, $p = 0.659$), gender ($\chi2 = 5.39$, $p = 0.249$), peripheral hearing ability ($\chi2 = 11.72$, $p = 0.164$) or education ($F(1,53) = 1.49$, $p = 0.228$). Patient groups did not differ in terms of symptom duration ($F(1,36) = 3.82$, $p = 0.059$), but there was a significant main effect of diagnosis on MMSE score ($F(1,36) = 6.12$, $p = 0.018$) that was driven by lower scores in the lvPPA and tAD patient groups. Forward digit span differed significantly between groups ($F(1,52) = 8.49$, $p = 0.005$), driven here by reduced span lengths in the nfvPPA, lvPPA and tAD groups relative to the svPPA and healthy controls.

6.5.2. Processing of clear speech numbers

The initial model including forward digit span as a covariate was significant ($F(6,45) = 10.07$, $p < 0.001$, $R^2 = 0.573$). This was driven by significantly worse performance in the nfvPPA group ($t = -2.17$, $p = 0.035$). Dropping forward digit span as a covariate, the model remained highly significant ($F(5,47) = 11.17$, $R^2 = 0.543$), and both the nfvPPA ($t = -3.07$, $p = 0.004$) and lvPPA ($t = -3.36$, $p = 0.002$) groups performed significantly worse than controls (see Table 6.3), but did not differ significantly from one another, $t = -0.63$, $p = 0.531$.

Table 6.3. Group performance on experimental tasks

	Controls	nfvPPA	svPPA	lvPPA	tAD
Clear numbers (/30)	29.9 (0.0)	23.8 (0.9)	30.0 (0.0)	22.1 (1.4)	29.8 (0.1)
†**Sinewave numbers (/60)**	55.3 (0.6)	28.4 (2.9)	52.0 (1.0)	26.6 (4.0)	47.1 (0.8)
Trials 1-5 (/15) [Bin 1]	12.6 (0.7)	5.5 (8.4)	10.1 (1.0)	5.9 (2.1)	9.2 (0.8)
Trials 6-10 (/15) [Bin 2]	14.0 (0.3)	7.4 (1.4)	13.7 (0.6)	7.0 (2.4)	11.5 (1.1)
Trials 11-15 (/15) [Bin 3]	14.2 (0.2)	7.8 (1.8)	14.1 (0.5)	7.6 (2.4)	12.9 (0.4)
Trials 16-10 (/15) [Bin 4]	14.5 (0.2)	7.8 (1.9)	14.0 (0.5)	6.1 (1.8)	13.5 (0.4)
†**Learning rate***	1.8 (0.6)	2.3 (1.4)	3.9 (1.1)	0.3 (0.9)	4.3 (0.9)
Clear locations (/16)	16.0 (0.0)	14.7 (0.6)	15.9 (0.1)	14.1 (0.9)	16.0 (0.0)
†**Sinewave locations (/40)**	35.4 (0.7)	24.6 (3.0)	25.3 (1.4)	28.1 (1.8)	28.1 (1.8)
Near (/20)	18.6 (0.6)	16.1 (1.0)	16.0 (0.9)	13.0 (2.2)	17.4 (0.7)
Far (/20)	16.2 (0.5)	8.6 (4.5)	8.9 (0.9)	6.9 (2.3)	10.7 (1.3)
Bisyllabic (/20)	17.2 (0.4)	11.6 (1.2)	12.3 (0.7)	9.7 (2.2)	13.0 (0.9)
Trisyllabic (/20)	18.2 (0.4)	13.1 (1.9)	13.0 (1.2)	10.1 (2.4)	15.1 (1.0)
Geographical knowledge (/80)	79.8 (0.1)	76.4 (1.7)	70.7 (3.4)	73.5 (2.4)	76.0 (0.8)

The Table shows performance by participant group on the key experimental tasks of interest. *This variable was calculated by taking score on trials 1-5 away from score on trials 16-20. †Indicates variables that were used in the VBM analysis. Significant group differences are not coded here as several different models with different covariates were used to analyse each variable: please see text for details.

6.5.3. Processing of sinewave speech numbers

Given the group differences that emerged for the processing of clear speech numbers, performance on this task was incorporated into the standard model also covarying for forward digit span score and MMSE, with diagnosis as independent variable and overall score on the sinewave speech numbers task as dependent variable. This model was significant ($F(7,43) = 19.86$, $p < 0.001$, $R^2 = 0.764$), and the nfvPPA group emerged as performing significantly worse than control participants ($t = -2.18$, $p = 0.035$). Running the model without including digit span as a covariate was still highly significant ($F(6,45) = 28.78$, $p < 0.001$, $R^2 = 0.793$), and the nfvPPA group again emerged as the only group performing significantly worse than control participants ($t = -2.88$, $p = 0.006$). Finally, dropping forward digit span and performance on the clear numbers processing task from the model explained slightly less of the total variance ($F(5,46) = 18.53$, $p < 0.001$, $R^2 = 0.668$), and the lvPPA group also emerged as significantly more impaired than the healthy controls ($t = -2.60$, $p = 0.012$), as were the nfvPPA group again ($t = -4.38$, $p < 0.001$), although the difference between the two groups was not significant ($t = -1.01$, $p = 0.317$); see Figure 6.3A; Table 6.3.

The interaction between diagnosis and change in score on the sinewave numbers task over time approached significance in a repeated measures model covarying for MMSE, clear numbers performance and forward digit span ($F(12,138) = 1.73$, $p = 0.067$). This was driven by a lack of improvement in performance over time in the lvPPA group: relative to score on the first five items (bin 1), scores in bins 2, 3, and 4 were significantly improved in each of the other diagnostic groups (all $p < 0.05$); the lvPPA group showed marginally improved performance in the third time bin relative to bin 1 ($p = 0.045$), but no other differences to baseline performance. Dropping clear numbers performance from this model did not change this pattern of results. Dropping forward digit span and clear number performance from the model led to a significant interaction between diagnosis and change in score over time ($F(12,141) = 1.83$. $p = 0.048$), and the pattern of performance over time within each group echoed the previous model; here, however, none of the timepoints in the lvPPA group reflected an improvement on baseline performance. Figure 6.3B shows raw performance over time by group, unadjusted for any covariates; data are also presented in Table 6.3.

With regard to learning rates across participant groups, in the standard model covarying for MMSE and forward digit span, the overall model was not significant, $F(6,44) = 1.94$, $p = 0.095$, $R^2 = 0.209$. The control group had a rate of learning that appeared relatively modest (1.8 point improvement), reflecting the fact that they scored relatively highly on items 1-5 compared to the other participant groups. To enable more meaningful interpretation of analyses, here I referenced each patient group to the AD participants as my neurodegenerative control cohort. No patient groups had a significantly lower rate than AD participants. The model incorporating MMSE, forward digit span and clear numbers performance was also not significant, $F(7,43) = 1.64$, $p = 0.151$, $R^2 = 0.211$), and no patients had a significantly lower rate than AD participants. The next model, which did not included digit span or clear numbers performance, trended toward significance, $F(5,46) = 2.38$, $p = 0.054$, $R^2 = 0.205$, and here the lvPPA group were significantly worse than ADs ($t = -2.26$, $p = 0.029$).

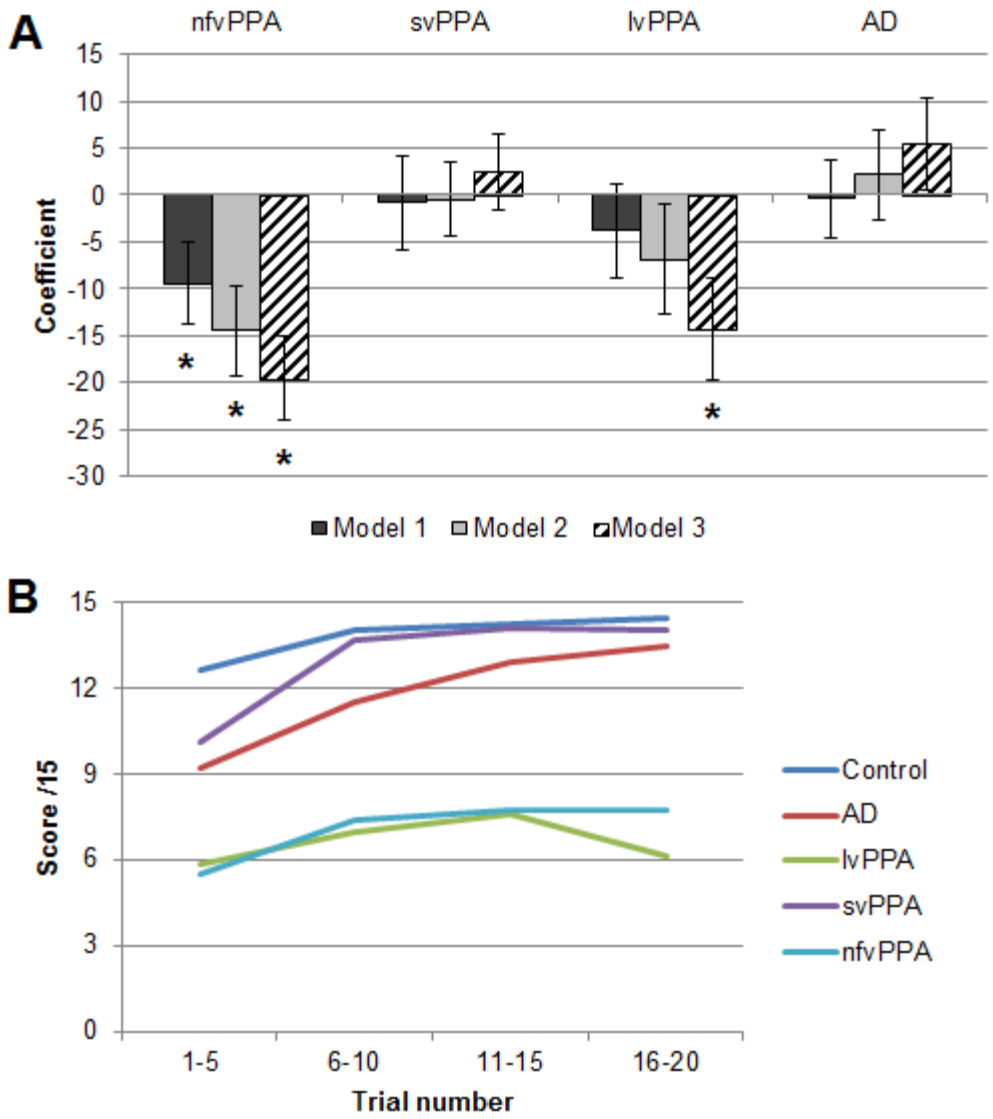

Figure 6.3. Behavioural results on the sinewave numbers processing task. A) Bar charts depicting coefficients from three models regressing diagnostic group membership against overall performance on the sinewave numbers processing task across the testing session. All models covary for MMSE score, Model 1 additionally covaries for forward digit span and clear number processing performance; Model 2 covaries for forward digit span, and Model 3 does not covary for digit span or clear number performance. Zero represents performance of the healthy control group, and all other diagnoses are referenced to this; raw data for all participant groups are presented in Table 6.3. *significantly different from controls, $p < 0.05$. Error bars represent standard error. **B)** Line charts showing performance of each group on the sinewave numbers processing task, split into four time 'bins'. Error bars have been omitted to aid visual interpretation; please see Table 6.3 for information on variance associated with each group and timepoint.

6.5.4. Processing of clear speech locations

Overall performance on the clear locations task (see Table 6.3) assessed using the standard regression model was significant overall ($F(7,44) = 4.12$, $p = 0.002$, $R^2 = 0.396$). There were, however, no significant group differences between any of the patient groups vs healthy controls (all $p > 0.05$); this overall significance was explained by a main effect of digit span ($t = 2.68$, $p = 0.010$). Running the model again without including digit span again resulted in a significant overall model ($F(6,46) = 4.01$, $p = 0.003$, $R^2 = 0.343$), and here both the nfvPPA ($t = -2.20$, $p = 0.033$) and lvPPA ($t = -2.10$, $p = 0.041$) groups were significantly impaired relative to healthy control participants, though not significantly different from one another ($t = -0.41$, $p = 0.684$).

6.5.5. Performance on geographical knowledge control task

Performance on the geographical knowledge control task was significantly affected by diagnosis ($F(4,50) = 4.12$, $p = 0.006$, $R^2 = 0.248$). This was driven by significantly worse performances relative to healthy control participants in the lvPPA ($t = -2.33$, $p = 0.024$) and svPPA ($t = -3.91$, $p < 0.001$) groups. The svPPA participants were also significantly worse relative to patients with nfvPPA ($t = -2.06$, $p = 0.044$) and tAD ($t = -2.09$, $p = 0.041$).

6.5.6. Processing of sinewave speech locations

Performance on the sinewave speech locations task (see Table 6.3) assessed using the standard model was significant overall ($F(7,43) = 13.65$, $p < 0.001$, $R^2 = 0.690$). This was explained by significantly worse performance in the svPPA group relative to healthy controls ($t = -4.12$, $p < 0.001$); no other patient groups differed significantly from the healthy control participants. Dropping forward digit span from the model was still highly significant ($F(6,45) = 12.45$, $p < 0.001$, $R^2 = 0.624$), and here the nfvPPA ($t = -3.03$, $p = 0.004$) and lvPPA ($t = -2.23$, $p = 0.031$) groups were affected in addition to the svPPA group ($t = =2.71$, $p = 0.009$).

Next, I considered differential performance on locations that were more geographically proximal (English cities, European countries) relative to those that were further away (American cities, non-European countries). In a model covarying for forward digit span, MMSE, and performance on the geographical knowledge control task, using

difference between score on processing of near vs far locations as dependent variable, the overall model was significant ($F(7,43) = 4.65$, $p < 0.001$, $R^2 = 0.431$). This was driven by significantly worse performance on the far vs near locations in the AD ($t = 2.27$, $p = 0.028$) and svPPA ($t = 3.93$, $p < 0.001$) groups, relative to the healthy controls.

Finally, I considered differential performance for locations that were trisyllabic relative to those that were bisyllabic. In a model covarying for forward digit span, MMSE, and geographical knowledge, using difference between score on processing of trisyllabic vs bisyllabic locations as dependent variable, the overall model was not significant ($F(7,43) = 1.11$, $p = 0.375$, $R^2 = 0.153$).

6.5.7. Differential processing of sinewave speech numbers vs locations

The overall model incorporating MMSE, geographical knowledge, clear number performance, forward digit span and diagnosis was significant ($F(8,41) = 9.28$, $p < 0.001$, $R^2 = 0.664$). Only the svPPA group was significantly different to healthy controls here ($t = 5.10$, $p < 0.001$), reflecting much better performance on processing of sinewave numbers than locations.

The model remained highly significant without including clear numbers performance ($F(7,42) = 6.60$, $p < 0.001$, $R^2 = 0.524$), and here the svPPA group showed the same pattern of results as before ($t = 4.40$, $p < 0.001$), while in the nfvPPA group, a significant difference emerged ($t = -2.26$, $p = 0.029$), reflecting better performance on processing of sinewave locations than numbers.

The model remained significant after dropping digit span ($F(6,44) = 8.28$, $p < 0.001$, $R^2 = 0.530$), and the same group differences as in the previous model emerged. In follow-up t-tests assessing within-group differences here, the AD, control, and svPPA groups all performed significantly better on the numbers processing task (all $p <0.05$), while in the nfvPPA group there was a trend toward better performance in the processing of sinewave locations ($p = 0.085$).

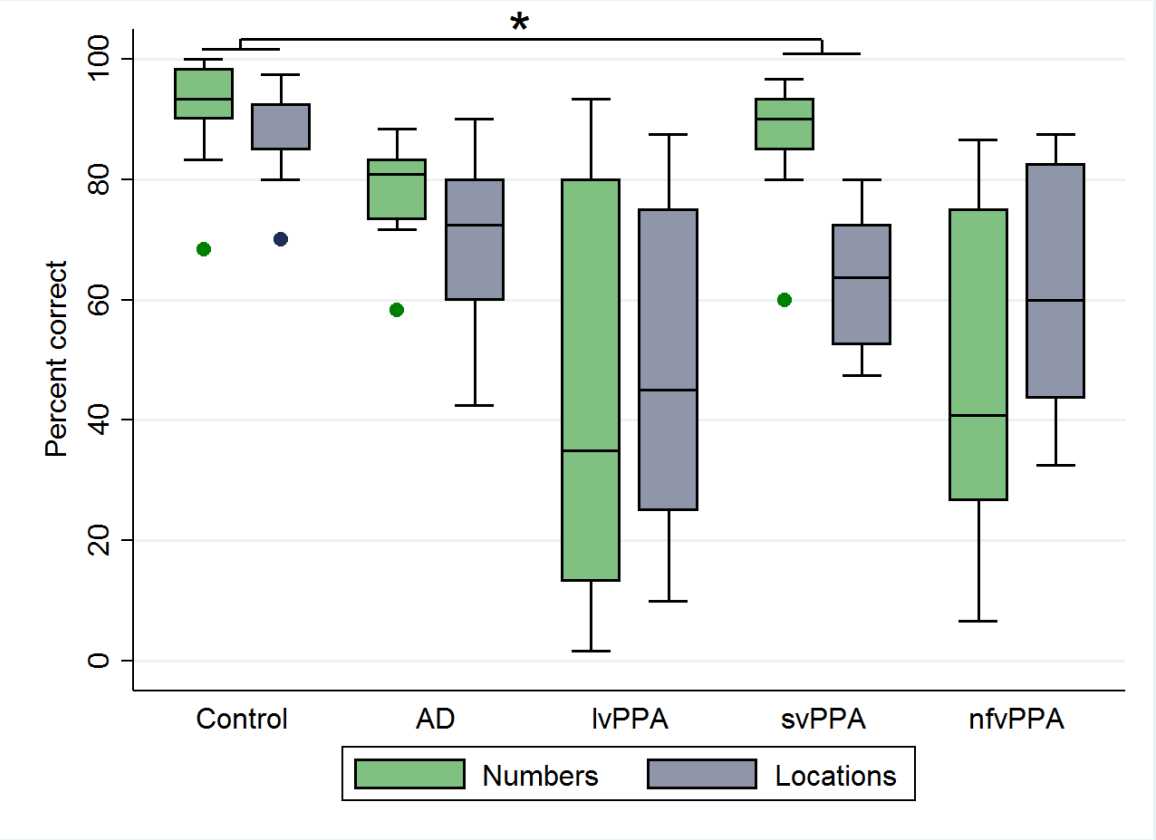

Figure 6.4. Performance on the sinewave locations task. Box plot showing performance on processing of sinewave numbers (green) vs sinewave locations (navy); for display purposes, both variables have been converted to percentage scores. *difference between processing of sinewave numbers and locations significantly different to healthy controls, $p < 0.001$.

6.5.8. Neuroanatomical data

Statistical parametric maps of grey matter regions associated with performance on the sinewave speech processing tasks are shown in Figure 6.5; local maxima of grey matter change correlated with experimental psychoacoustic task performance are summarised in Table 6.4.

No correlations emerged within any of the patient groups for overall score on the sinewave numbers task. However, improvement on the processing of sinewave numbers (i.e. learning rate) was positively associated with grey matter volume in left MTG in lvPPA and nfvPPA, more posteriorly in nfvPPA ($p<0.05_{FWE}$ within the pre-specified region of interest). The lvPPA group additionally showed a positive correlation with grey matter volume in left precentral gyrus ($p<0.05_{FWE}$ within the pre-specified region of interest). No correlations emerged at the specified threshold within the AD or svPPA groups here.

Processing of sinewave locations was positively associated with grey matter volume in left MTG in AD ($p<0.05_{FWE}$ within the pre-specified region of interest), while performance on the same task was positively correlated with grey matter volume in left SMG in the svPPA patient group ($p<0.05_{FWE}$ within the pre-specified region of interest). No significant loci within the regions of interest specified emerged for the nfvPPA or lvPPA groups for this contrast.

Table 6.4. Structural neuroanatomical associations of perceptual processing of sinewave speech in the patient groups.

Group	**Region**	**Cluster** (voxels)	**Peak** (mm)			**t-value**	**p-value**
			x	y	z		
Numbers							
No correlates in any group							
Learning rate (numbers)							
nfvPPA	L MTG post[a]	31	-58	-36	-8	4.26	0.050
lvPPA	L MTG mid[a]	19	-62	-18	-27	5.30	0.008
	L PrG[b]	254	-14	-21	76	5.13	0.038
Locations							
AD	L MTG mid[a]	72	-56	-16	-24	4.56	0.031
svPPA	L SPL[c]	49	-20	-50	69	6.61	0.002

The Table summarises statistically significant positive associations between grey matter volume and the relevant sinewave speech processing measure (see text for details), based on a VBM analysis of brain MR images. All values were significant at $p<0.05_{FWE}$ within the prespecified neuroanatomical small volume correction in the left hemisphere (see Figure 6.2): [a]comprised posterior STG, MTG and PT; [b]comprised PrG and IFG; [c]comprised SMG, Angular gyrus, and SPL.

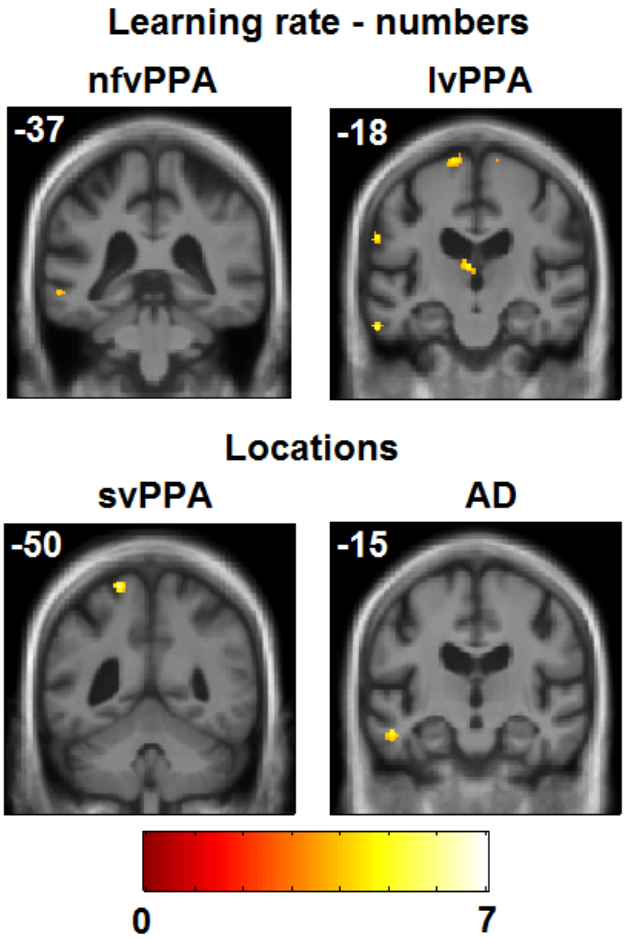

Figure 6.5. SPMs of sinewave speech processing

6.6. Discussion

In this Chapter, I have demonstrated behavioural and neuroanatomical correlates of the defective analysis of degraded speech signals across all three major PPA syndromes, referenced to a neurodegenerative control group of patients with AD. Here, all groups showed *some* capacity for perceptual learning, but patients with lvPPA and nfvPPA showed deficient "bottom-up" apperceptive processing of sinewave speech, while patients with svPPA showed intact perception of the distorted speech stimuli, but impaired "top-down" associative/ predictive processing of degraded speech signal information, in line with models of degraded speech perception in the healthy brain (Davis & Johnsrude, 2003, 2007; Sohoglu *et al.*, 2012; Sohoglu & Davis, 2016). Neuroanatomical correlates were identified for the slower perceptual learning rates seen in the nfvPPA and lvPPA groups in left MTG, and additionally in the left precentral gyrus in lvPPA only. For overall performance on the sinewave locations task, neuroanatomical correlates were identified again in left MTG in the AD group, and in left SPL for patients with svPPA. Taken together, the results presented in this Chapter substantiate the emerging picture of the two nonfluent PPA syndromes being associated with deficient early auditory perceptual processing.

Deficient processing of clear speech numbers was observed in the nfvPPA cohort. This deficit remained even when covarying for auditory short-term memory performance, suggesting that the deficit here was separable to any phonological working memory problem. Patients with lvPPA were also impaired on this task, but here their deficits were accounted for by phonological working memory capacity, in line with previous reports on this syndrome (Gorno-Tempini *et al.*, 2008; Wilson *et al.*, 2010b).

A similar syndromic pattern was observed for the processing of sinewave speech numbers: here, however, I covaried for clear number processing performance, so the deficit that emerged in the nfvPPA group was additional to the more basic processing of clear numbers alone. The lvPPA group, by contrast, only emerged as significantly impaired relative to controls on this task when the regression model did not incorporate digit span and clear numbers performance as covariates. The relationship with phonological working memory in this patient group is extremely important. The present data do not clarify whether the deficits seen here are completely attributable to phonological working memory capacity,

or if they reflect an interaction with phonological working memory as an aspect of dynamic phonological representation. Analogously, work on music perception and nonverbal sound processing in lvPPA and other dementia syndromes has suggested that phonological working memory impairment may account for early auditory processing deficits in these domains (Goll *et al.*, 2010a; Golden *et al.*, 2017). In lvPPA, one might argue that rather than phonological working memory capacity *per se*, it is this dynamic phonological representation system that is predominantly affected, going some way to explain the disparate constellation of symptoms such as phonemic paraphasias, repetition length effects, and word-finding pauses in these patients. Differentiating between capacity and representation in the context of lvPPA are beyond the scope of the present study, but suggest an exciting avenue for future research (see Section 7.3.1 for a further discussion of this point).

Critically, however, there was evidence of at least some perceptual learning in all of the patient groups. Patients with svPPA showed remarkably quick adaptation to the degraded number speech tokens (though critically not the locations), while those with nfvPPA and lvPPA showed a slower rate of learning (see Figure 6.3). It is not clear why this improvement seemed to tail off in the lvPPA patients in the last trials on the task: I would have anticipated a linear profile of improvement, and I think it likely that the poorer performance in the fourth time bin here reflects fatigue or other confounding effects, rather than representing a key index of degraded speech signal decoding. The fact that both the nfvPPA and lvPPA groups did show perceptual learning and improvement over time (albeit at a much slower rate to that seen in AD, svPPA or healthy controls) does suggest a degree of residual plasticity within this vulnerable language network that may be targeted with future cognitive rehabilitation strategies.

In terms of the task assessing processing of sinewave speech locations, only the patient group with svPPA emerged as significantly impaired relative to healthy control participants. Crucially, the patients with svPPA were impaired even after controlling for their background geographical knowledge of the sinewave locations, suggesting that this deficit was not merely driven by a pure semantic deficit. This category of knowledge was deliberately chosen to minimise any impact of more basic semantic impairment, and I would argue that the poor performance on this task reflects an inability in svPPA to use prior

knowledge (in this case, geographical knowledge) to determine the most probable interpretation of the distorted auditory stimulus: a deficit at the level of predictive pattern recognition. A similar Bayesian mechanism has been proposed for visual object perception (Kersten & Yuille, 2003), and Davis and Johnsrude argue that such a mechanism could support perceptual retuning to degraded speech stimuli by helping the speech system to adapt to novel and changing linguistic environments (Davis & Johnsrude, 2003). It is particularly noteworthy that the basic 'bottom-up' processing of sinewave speech was completely intact in the svPPA group, reflected by their healthy control-level performance on the sinewave numbers processing task (see Figure 6.2). This dissociation between performance on the degraded numbers and location stimuli echoes previous studies of short-term memory differences and verbal learning, which suggest that numerical cognition is relatively spared in svPPA (Jefferies *et al.*, 2004). The patients' inability to integrate semantic knowledge here could reflect a similar mechanism to that discussed in Chapter 4: an inability to compute coherent object concepts via sensory signal analysis (Lambon Ralph *et al.*, 2010, 2016; Clark *et al.*, 2017).

Considering performance on processing of locations geographically proximal to London relative to those that were further away, participants with svPPA and tAD were significantly impaired relative to controls on locations that were more distant from London. This finding is broadly consistent with previous research implying that geographical knowledge is impaired in patients with AD (Beatty & Bernstein, 1989; Beatty & Salmon, 1991).

The patient groups with nfvPPA and lvPPA were also impaired on this sinewave locations processing task when the model did not incorporate forward digit span as a covariate. With regard to the nfvPPA patients' performance here, accurate perception of these degraded speech stimuli is likely to be driven by two complementary processes: a 'bottom-up' mechanism responsible for interpreting primitive grouping cues such as rhythm, and a 'top-down' experience-driven mechanism sensitive to the higher-level linguistic characteristics of speech (Davis & Johnsrude, 2007); based on my results here it seems plausible that both routes are affected in nfvPPA. This is consistent with previous work suggesting that patients with nfvPPA have a 'double-hit' of impaired bottom-up perceptual

processing and top-down predictive mechanisms (Cope *et al.*, 2016). This explanation is parsimonious in accounting for the overall deficit in processing of sinewave speech numbers in nfvPPA, and the reduced rate of perceptual learning shown by the same patients over time.

A similar neuroanatomical locus in MTG was identified in both the nfvPPA and lvPPA groups for the processing of sinewave numbers, and in the AD group for processing of sinewave locations. MTG has previously been implicated in the processing of meaningful speech (Hickok & Poeppel, 2004; Hall *et al.*, 2005; Price, 2010), and prevailing evidence suggests that this region serves as an interface between sound-based representations of speech signals and widely distributed conceptual representations, i.e. it is a component of the ventral stream responsible for mapping sensory/ phonological representations to lexical conceptual representations (Démonet *et al.*, 1992; Davis & Johnsrude, 2003; Hickok & Poeppel, 2004; Hall *et al.*, 2005; Price, 2010). The correlation reported here for the learning rate on the sinewave numbers processing task could therefore go some way to accounting for the behavioural deficit seen in these patient groups, suggesting that the fundamental problem slowing the perceptual learning seen in the nonfluent patient groups was in mapping distorted speech signals to appropriate semantic constructs.

However, it is somewhat surprising that no correlates in the lvPPA or nfvPPA groups were identified in STS/STG, given the plethora of evidence suggesting that both syndromes are associated with critical damage to this area of cortex (Rohrer *et al.*, 2010b; Gorno-Tempini *et al.*, 2011; Henry *et al.*, 2016), and the role that this region is known to play in early spectrotemporal analysis of speech signals (Griffiths & Warren, 2002; Warren *et al.*, 2005; Hickok & Poeppel, 2007). One possibility is that inclusion of forward digit span in the VBM models accounted for variance associated with damage to these cardinal regions. Alternatively, as these critical temporo-parietal areas are considered as a focal point for atrophic profiles in nfvPPA and lvPPA, it is possible that a complete lack of variance here meant the regression models used in the VBM lacked sensitivity to correlate behavioural task performance with an area of uniform atrophy. It is plausible that PT should be completely engaged across all speech conditions: as discussed in Section 7.2, VBM allows for identification of regions that are critical for performance of a behavioural task. It seems

likely that using the same paradigm with different imaging methodologies (MEG/ fMRI) would yield complementary functional signatures along the STG/S.

An additional neuroanatomical correlate was identified in the lvPPA group in left precentral gyrus. This area has previously been associated with atrophy in lvPPA (Ossenkoppele *et al.*, 2015), and is typically thought to be a key node in the frontal-motor network for speech production that is likely to form part of the dorsal language network involved in sensory/ phonological mapping to motoric representations (Hickok & Poeppel, 2007). Indeed, mounting evidence in the healthy brain suggests that speech motor circuitry is also recruited during speech perception: left precentral gyrus shows dissociable functional activation profiles reflecting phonetic distinctive features of passive listening to speech sounds (Pulvermuller *et al.*, 2006). Similarly, functional connectivity to bilateral precentral gyri in healthy control participants is associated with improved performance on prosody intonation identification (Rota *et al.*, 2011), and in dyslexia, abnormal activation patterns are seen in left precentral gyrus on phonological processing tasks (Corina *et al.*, 2001). In the context of PPA, the same locus has previously been associated with deficits in tasks involving phonological perception and production (Wilson *et al.*, 2010b; Henry *et al.*, 2016). Additionally, this region is part of a network implicated in number cognition (Dehaene *et al.*, 1996; Venkatraman *et al.*, 2005), and the numerical nature of this task may have overburdened the already damaged circuity here, although as discussed above this task did not require arithmetic or number cognition *per se*.

The neuroanatomical correlate identified in the left SPL for performance on this task was slightly surprising, given that damage to this region is not often reported in the context of svPPA, although there are documented cases (Rossor *et al.*, 2000). Furthermore, the function of the SPL is typically regarded as directing visuospatial attention (Caminiti *et al.*, 1996; Vandenberghe *et al.*, 2001). However, left SPL has previously been implicated in regard to language processing (Shapiro *et al.*, 2006), and converging functional neuroimaging evidence from healthy controls and psychiatric patients suggests that this region may play a critical role in decoding distorted inputs, including speech signals (Bishop & Miller, 2009; Hill & Miller, 2010; Zheng *et al.*, 2016). All of the patients in the svPPA group transcribed their responses by writing, and it is also possible that the anatomical association

in left SPL reflects impairment at the level of writing to dictation (Segal & Petrides, 2012). However, this would not explain the specificity of the deficit for the locations task relative to the numbers, and I think a more appropriate explanation is that this region represents a hub necessary for the integration of spectrotemporal auditory object properties with semantic constructs.

The work presented in this Chapter has several limitations that suggest opportunities for future research. First, the sinewave manipulation I employed here was essentially binary: the stimuli were presented in clear speech, or sinewave speech. Recent research suggests that training procedures for degraded speech stimuli that start off with relatively little signal distortion may afford more opportunities for perceptual learning than conditions where severe distortions are presented immediately, as in my paradigm here (Gabay *et al.*, 2017). Future work aimed at exploiting, and exploring residual plasticity in the nfvPPA and svPPA syndromes, should perhaps explore whether a graded approach to perceptual learning of distorted speech stimuli could alter the learning curves displayed in Figure 6.2. Second, whilst I have identified neuroanatomical loci that may be critical within the neurodegenerative syndromes included here for the processing of distorted speech stimuli, this approach provides no information as to the temporal signatures associated with sinewave speech processing in each disease. Magnetoencephalography (MEG) is emerging as one of the most sensitive markers of early cognitive dysfunction in neurodegenerative contexts (Josef Golubic *et al.*, 2017), and the dynamic stimuli presented in this Chapter would be perfectly suited to MEG given the temporal and spatial sensitivity the technique now allows.

Nevertheless, I think the findings reported here are exciting for three reasons: i) they corroborate and extend previous work suggesting a fundamental auditory perceptual processing deficit in the nfvPPA and lvPPA syndromes (Rohrer *et al.*, 2010b; Hailstone *et al.*, 2012; Golden *et al.*, 2015b; Hardy *et al.*, 2015; Grube *et al.*, 2016; Henry *et al.*, 2016); ii) they add support to the notion of svPPA representing a disease affecting associative-level processing, suggesting that the deficits seen here speak to a more fundamental mechanism of pattern recognition and coherent object formation (Bozeat *et al.*, 2000; Lambon Ralph *et al.*, 2010; Hsieh *et al.*, 2011); and iii) they provide support for the notion of residual plasticity

within the damaged and disintegrating language network in nfvPPA. This represents a fundamentally new direction focussed on capacity rather than deficits that could have implications for development of novel biomarkers and future rehabilitation strategies. A refinement of the paradigm could represent a dynamic perceptual 'stress test' for each of the major PPA syndromes.

7. General discussion

7.1. Summary of findings

This thesis sought to characterise deficits in auditory signal decoding in PPA, and where possible to relate these behavioural deficits to underlying structural and functional neuroanatomy. Specific deficits were associated with the different PPA phenotypes: broadly speaking, nfvPPA and lvPPA were associated with 'bottom-up' early perceptual and apperceptive deficits, while impairments seen in svPPA were more attributable to 'top-down' associative deficits. Neuroanatomical correlates in the experiments detailed in Chapters 3, 4 and 6 point towards a distributed fronto-temporo-parieto-subcortical network of regions within and beyond the canonical language networks that subserve these psychoacoustic processing deficits.

The work of Chapter 3 corroborated previous findings suggesting that both nfvPPA and lvPPA are associated with impairments in early auditory perceptual processing (Bozeat *et al.*, 2000; Goll *et al.*, 2010a; Hailstone *et al.*, 2011; Rohrer *et al.*, 2012; Grube *et al.*, 2016), characterised here by dysfunction at the level of processing phonemic structure, signal information content (entropy), and temporal regularity, while patients with svPPA show impaired processing of phonemic spectral structure and entropy but not temporal regularity. In a combined VBM analysis of the FTLD-PPA groups, performance on the temporal regularity task was associated with grey matter volume in left supplementary motor area and right caudate, while phonemic processing correlated with grey matter in left supramarginal gyrus. It is worth noting that here I used stimuli designed to probe the generic "building blocks" of speech signals, addressing a more fundamental level of deficit/ mechanism than previous work, and specifically manipulating speech signal characteristics for the first time.

Using similar stimuli in the context of fMRI, different functional neuroanatomical signatures were identified for each of the major PPA subtypes in Chapter 4. Separable patterns of activation were found relative to healthy controls: in nfvPPA in medial Heschl's gyrus in response to any sound and in anterior cingulate in response to temporal irregularity; in svPPA in caudate and anterior cingulate in response to increased entropy; and in lvPPA in

posterior STG/STS in response to phonemic spectral structure. Together, the experiments detailed in Chapters 3 and 4 identify perceptual deficits for auditory processing of key components of speech signals, correlating these deficits with structural and functional neuroanatomical substrates across the PPA spectrum.

The findings I present in Chapter 5 suggest that nfvPPA and lvPPA may be less susceptible to the effects of delayed auditory feedback – a transformation of normal auditory feedback that disrupts fluency, reduces speech rate and increases speech errors in healthy participants. These data should be regarded as preliminary and interpreted with a degree of caution, but do suggest that damage to structures in the dorsal language pathway may negate sensori-motor adaptation to normal auditory feedback, and could go some way to accounting for some aspects of the speech phenotype associated with both lvPPA and nfvPPA.

Finally, in Chapter 6 I moved beyond the characterisation of fixed deficits to address dynamic processing and residual plasticity. Here, I used the paradigm of sinewave speech to degrade normal speech in a manner that requires rapid and spontaneous perceptual learning: a computationally demanding task that is even more taxing in patients with disintegrating language networks, and has wide potential relevance as a paradigm of "challenging listening conditions". Here, patients with nfvPPA and lvPPA showed deficient "bottom-up" processing of sinewave speech signals, while patients with svPPA showed intact processing of degraded speech tokens, but deficient "top-down" integration of semantic knowledge. Neuroanatomical correlates for key behavioural signatures here were identified along the dorsal and ventral pathways of the language network. Critically, this experiment provided evidence of residual capacity for perceptual learning in all syndromes, but also allowed for differentiation by syndrome.

7.2. Structure vs function: the differing contributions of VBM vs fMRI

The relationship between structural neuroanatomy and functional neuroanatomical signatures is important given the use of these contrasting methodologies in this thesis: VBM in Chapters 3 and 6, and fMRI in Chapter 4. I would argue that VBM can be considered as an extension of lesion analysis methods that establish *critical* anatomical associations/ substrates/ mechanisms at network level, whereas fMRI delineates the networks *engaged* in

processing. As a corollary of this, VBM more closely indexes behaviour, while fMRI more closely tracks the underlying pathophysiology. Indeed, the functional activation profile shown in Chapter 4 by the nfvPPA group for anisochronous signals was not correlated with out-of-scanner perceptual assessment of speech stimuli, and was moreover right-lateralized, perhaps indicating motor recoding of syllable timings or recruitment of a generic mechanism for the decoding of signal regularities (Nastase *et al.*, 2014), underlining the fundamental difference here between VBM and fMRI. The key point is that the anatomical profiles delineated by VBM and fMRI need not necessarily converge, as in the data presented across Chapters 3 and 4.

7.3. Impaired auditory signal decoding in PPA

The work presented in this thesis corroborates the growing body of literature suggesting that the major PPA syndromes are characterised by nonverbal and meta-linguistic auditory processing impairments (Bozeat *et al.*, 2000; Goll *et al.*, 2010a, 2010b, 2011; Hailstone *et al.*, 2011; Rohrer *et al.*, 2012; Golden *et al.*, 2015b, 2017; Grube *et al.*, 2016; Hardy *et al.*, 2016). The four major experiments presented here suggest that these deficits stratify syndromic groups, and Figure 7.1 depicts an updated schematic representation of the dual streams model of speech perception (Hickok & Poeppel, 2000) that incorporates findings from this thesis. The model is replicated in triplicate with the critical node(s) for each syndrome highlighted in red.

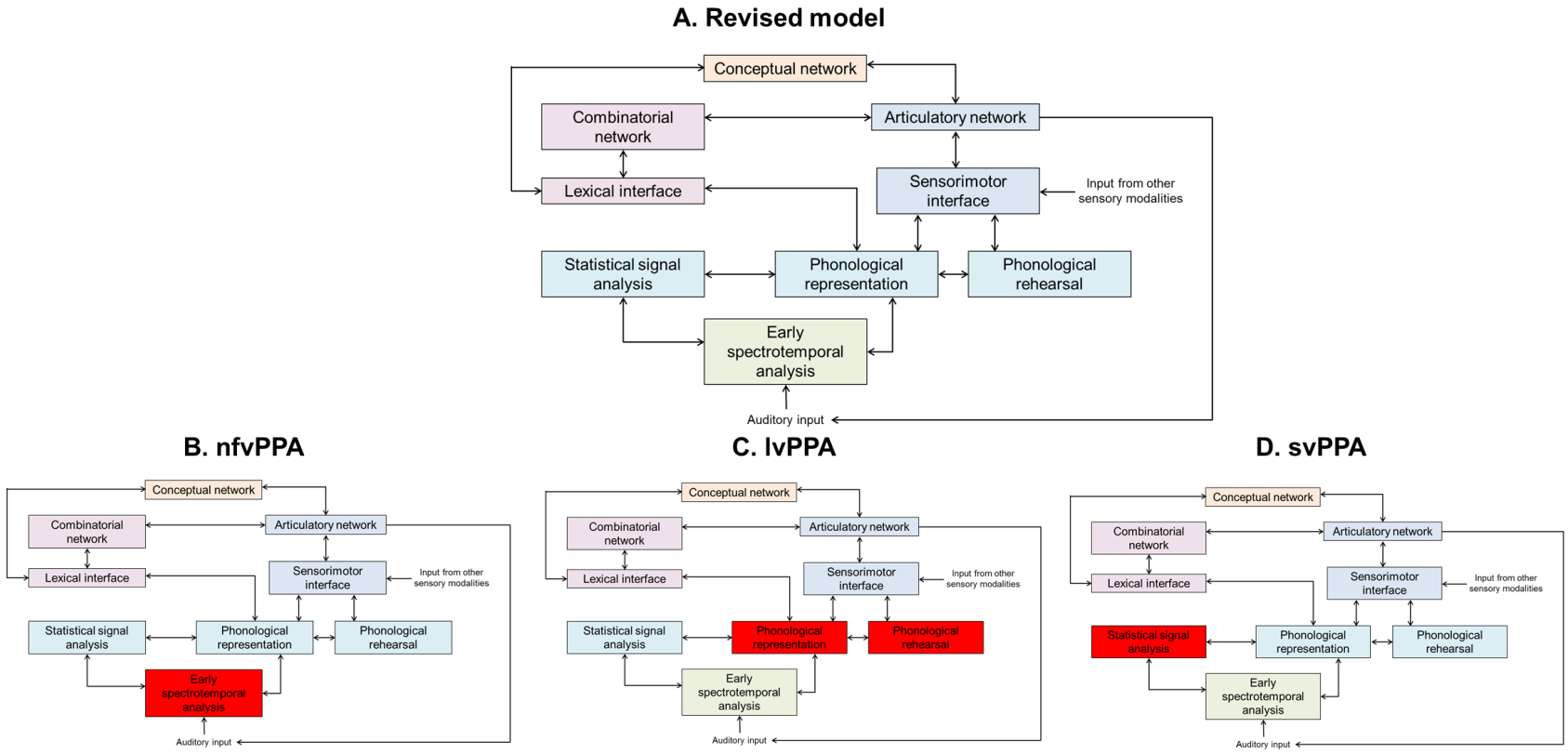

Figure 7.1. Reproduction of Figure 1.4 with additional support from findings in this thesis. A) This model incorporates an additional stage of "statistical signal analysis", and distinguishes between "phonological representation" and "phonological rehearsal" (all turquoise boxes). Pink boxes represent nodes in the proposed ventral stream, while those in blue represent the proposed dorsal stream (Hickok & Poeppel, 2007). The green box denotes the earliest stage of cortical speech processing, while the orange box depicts the widely distributed conceptual network. The model also incorporates the proposed link from articulation to auditory input, i.e. "auditory feedback" (Warren *et al.*, 2005). Red boxes in panels B-D represent the level of impairment for a particular syndrome based on findings from this thesis.

7.3.1. The nature of the deficits seen in nfvPPA and lvPPA

The clinical presentations of patients with either of the two nonfluent PPA syndromes can be very similar, especially in the early stages, perhaps explaining why lvPPA has only been recognised as a separate syndrome since the turn of the century (Gorno-Tempini *et al.*, 2004, 2008; Rohrer *et al.*, 2010b). In this thesis, both patient groups showed deficient early perceptual analysis of incoming auditory signals consistent with deficits at the level of spectrotemporal processing (Figure 7.1): behavioural deficits were reported in Chapter 3 for the processing of temporal regularity, phonemic spectral structure and entropy. The deficit for entropy processing here I think is more likely to reflect a fundamental impairment of pitch pattern analysis than the computational mechanism discussed above in relation to svPPA. These early spectrotemporal deficits are broadly consistent with a large body of previous research (Bozeat *et al.*, 2000; Goll *et al.*, 2010a; Hailstone *et al.*, 2011; Rohrer *et al.*, 2012; Grube *et al.*, 2016), although it is perhaps significant that the study by Grube and colleagues found no core auditory processing deficits in their (albeit small) sample of four patients with lvPPA. One possible explanation for this discrepancy is that Grube et al used completely non-linguistic stimuli: the auditory sequences I used in Chapters 3 and 4 were all based on spoken syllables.

This raises the possibility that the deficits I observed in lvPPA may reflect impairment at a different level to early spectrotemporal processing. Phonological working memory impairment is a defining feature of lvPPA (Gorno-Tempini *et al.*, 2008; Rohrer *et al.*, 2010b; Henry *et al.*, 2016), but it is possible that this is caused by a more basic problem at the level of dynamic phonological transcoding, so that these phonemic representations are malformed before they enter the so-called ‘phonological loop’ in classical models of working memory (Baddeley, 2010). It is possible that while early spectrotemporal processing is impaired in nfvPPA, it may be relatively unimpaired in lvPPA: my data do not allow for disentangling of spectrotemporal processing vs phonological representation given that my stimuli in Chapters 3 and 4 did have linguistic properties. However, it seems likely that across the different levels of spectrotemporal analysis, there is a core deficit at the level of temporal pattern processing.

Phonological working memory was clearly a critically important factor with regard to the deficit in processing degraded speech signals in lvPPA in Chapter 6: covarying for working memory meant that this group of patients did not emerge as significantly different to control participants on any of the sinewave speech tasks. What is unclear here is whether this reflects aberrant phonological rehearsal, representation, or (most likely), an interaction of the two. Parsimoniously, however, a deficit at the level of phonological representation in lvPPA could go some way to explaining the disparate constellation of leading symptoms, such as word-finding pauses, phonemic paraphasias, and repetition length effects.

7.3.2. Signal analysis and computation of coherent object concepts in svPPA

Evidence presented in Chapters 3-6 suggest that "bottom-up" early perceptual and apperceptive processing is intact in svPPA, but Chapters 3, 4, and 6 suggest that "top-down" associative integration is impaired. This is consistent with a plethora of previous evidence suggesting that svPPA is a disease of pan-modal conceptual degradation (Bozeat *et al.*, 2000; Hodges, 2000; Snowden, 2004; Knibb & Hodges, 2005; Garrard & Carroll, 2006; Luzzi *et al.*, 2007; Piwnica-Worms *et al.*, 2010; Goll *et al.*, 2012b).

The work presented in this thesis suggests that these deficits, at least in the auditory domain, may be attributable to an inability to compute coherent object concepts via auditory signal analysis. The model presented in Figure 7.1 proposes that patients have intact capacity for spectrotemporal analysis (reflecting largely spared cortex in the STG), but impaired ability to extract global statistical regularities from the auditory signal that are used to form and evaluate semantic concepts via the ventral stream (see Figure 7.1: this is necessarily bidirectional - generic conceptual degradation results in impaired concepts against which to evaluate these statistical properties). This was demonstrated partially in Chapter 3: patients with svPPA showed impaired ability to differentiate between sequences of high and low entropy, while the work presented in Chapter 4 suggested that this behavioural deficit was associated with functional signatures in a fronto-cingulo-striatal network likely to be relevant to predictive coding and minimising of uncertainty in the healthy brain (Kiehl *et al.*, 2000; Magno, 2006; Lee *et al.*, 2011; Ide *et al.*, 2013; Fan, 2014; Nastase *et al.*, 2014, 2015). Chapter 6 suggests that this account is pertinent to mapping sounds to meaning with regard to lexical stimuli. Here, when the stimuli to be decoded had limited and

specific semantic associations (numbers), perception was as good as in healthy control participants. However, when the computational demands were difficult (mapping the distorted token to a geographical location), a deficit emerged that was only partially attributable to the loss of conceptual knowledge intrinsic to this syndrome. It seems likely that in this study, patients with svPPA were able to form an accurate percept of the degraded speech token, but crucially in the presence of this sensory noise were not able to adequately integrate prior knowledge, i.e. they were not able to use statistical information present in the signal to predict plausible candidates for that token, and were therefore unable to match sound to meaning. These findings are consistent with recent work suggesting that patients with semantic aphasia may be affected at a level of 'semantic integration' – over and above object identification (Thompson *et al.*, 2017).

Broadly, this deficit at the level of pattern-matching across Chapters 3, 4 and 6, reflects inefficient formation of predictions. 'Predictive coding' describes the generation and updating of hypotheses predicting sensory input, the central driver being to minimise prediction error across hierarchically organised generative brain networks (Rao & Ballard, 1999; Friston & Kiebel, 2009). This model has been used to explain perceptual learning of degraded speech in the healthy brain (Sohoglu & Davis, 2016), and my data imply that extraction of statistical regularities from incoming auditory signals is aberrant in svPPA, which results in inappropriate or malformed predictions, ultimately manifesting in deficient associative processing of incoming stimuli. Clearly, my results here are pertinent only to the auditory domain, but it seems plausible that this generic mechanism could reflect a key deficit in svPPA in computing statistics from incoming information in any sensory modality (Holland & Lambon Ralph, 2010; Lambon Ralph *et al.*, 2016).

7.3.3. Trans-syndromic effects

Whilst a critical aim and indeed key finding of this thesis was in regard to stratification of the PPA phenotypes according to auditory processing deficits, there are certain commonalities in terms of mechanisms and processes that suggest a degree of unification across the three syndromes.

The work I presented in Chapter 3 identified a common neuroanatomical profile associated with processing of the building blocks of speech signals that I used in this

experiment. Here, I found that temporal pattern processing was associated with grey matter volume in left SMA and right caudate in a combined group of svPPA and nfvPPA patients. Phonemic processing here correlated with grey matter in left SMG, while entropy processing correlated with grey matter volume in right putamen. The fundamental theoretical differences in VBM relative to fMRI are discussed briefly in Section 7.2, but it is worth also noting that my findings in the fMRI study presented in Chapter 4 suggested that a generic mechanism of cortical inefficiency might in fact underpin the psychoacoustic deficits observed in the previous Chapter. This pathophysiological 'theme' of inefficient decoding mechanisms is reflected by aberrant activation profiles in svPPA in response to low entropy stimuli, in nfvPPA in response to isochronous stimuli, and in lvPPA in response to phonemic structure. In Section 4.6, I argue that in Bayesian terms, loss of computational efficiency across the PPA syndromes might manifest in imprecise coding of speech signal attributes.

Taken together, the findings here corroborate previous research suggesting that there is an interacting hierarchy of levels of spectrotemporal processing, with temporal pattern processing and early spectrotemporal analysis affected in nfvPPA, extraction of information content and statistical pattern processing affected in svPPA, and phonological transcoding or representation impaired in lvPPA. Crucially, however, these modular impairments occur within an interacting processing hierarchy, and ultimately manifest in common structural and neuroanatomical signals such as those depicted in Chapters 3 and 4. A generic mechanism of residual plasticity for perceptual learning was observed across all PPA syndromes included in Chapter 6, suggesting that there are trans-syndromic patterns of adaptive perceptual learning, as well as trans-syndromic patterns of pathophysiological signatures of auditory signal decoding.

7.4. Clinical translation

7.4.1. Relating findings to patients' day-to-day experiences

My findings have clinical resonance in helping to account for the symptoms reported by patients with all PPA syndromes. These results may also have significance for clinical counselling: understanding why particular situations or environments represent

significant challenges can help with management of those situations as and when they occur.

Patients with lvPPA often report that they find it more difficult to hear other people talking in an environment with lots of background noise, and my research suggests that in addition to problems with auditory scene analysis associated with posteromedial default mode network dysfunction seen within the Alzheimer's disease spectrum (Golden *et al.*, 2015a, 2015c), early perceptual deficits at the level of analysis of phonemic spectral structure is a concomitant issue for these patients. Auditory scene analysis has not been specifically studied across the PPA spectrum, but sinewave speech may tap into a relevant mechanism here.

Nonfluent variant PPA is typically described as a speech output disorder, in terms of speech production and agrammatism, but patients often report that they find it much easier to understand information if it is presented visually, rather than verbally. This may also extent to increased reliance on lip-reading in these patients: my own impression is that during repetition tasks, patients with nfvPPA show worse performance if the experimenter covers their mouth when they give the target words. My results again support the idea that there is a core early auditory processing deficit associated with nfvPPA, which could have significant implications for cognitive assessment of patients: much test administration is currently performed verbally.

My findings in regard to svPPA highlight the importance of top-down processing for disambiguating and accurately comprehending speech. The story emerging here suggests that although svPPA patients can reliably and accurately form percepts of speech stimuli, even under challenging listening conditions, top-down integration of associative conceptual knowledge may be impaired, meaning that patients are still unable to comprehend speech signals in noisy auditory environments.

7.4.2. Syndromic stratification and disease tracking

The essential aim of the work described in each of the experimental Chapters in this thesis has been to identify behavioural signatures of auditory processing specific to each of the three major PPA syndromes, and where possible to relate these signatures to underlying neuroanatomy. My work has shown that it is indeed possible to stratify patient

groups in this manner, suggesting that stimuli and paradigms of the kind I have used here could one day be used to aid diagnosis and stratification of syndromes. Each of the patients included in my studies were, by necessity, already diagnosed with one of the PPA syndromes: an exciting extension of the work presented here would be to see if ability to process degraded speech stimuli, for instance, could facilitate clinical diagnosis.

The PPAs are clinically, anatomically, and pathologically heterogeneous. Intrinsically different proteinopathies can give rise to the same clinical phenotype, as in nfvPPA (Josephs *et al.*, 2006; Rohrer *et al.*, 2011; Elahi & Miller, 2017), and stratification of proteinopathies in life will be of central importance as potential disease-modifying drug therapies emerge. Ultimately, the hope is that the research presented in this thesis will form the basis for identification of brain mechanisms that support auditory signal decoding to eventually stratify the specific neural architectures that underpin specific proteinopathies (Warren *et al.*, 2013).

There is a need for dynamic stimuli that can probe and ultimately overburden the vulnerable or failing language network right at the earliest stage of PPA – identification of syndromes at the very earliest stages is crucial, as brain dysfunction and atrophy are known to precede cognitive decline in neurodegenerative contexts (Jack & Holtzman, 2013; Rohrer *et al.*, 2015). Procedures such delayed auditory feedback (Chapter 5) and sinewave speech processing (Chapter 6) could form the basis for future speech-based 'stress tests' to assess early language dysfunction and treatment response. There is also interest not only in syndromic stratification, but in identifying common biomarkers that cut across syndromes.

Finally, novel tests based around auditory processing could be advantageous relative to traditional tests that rely on language, as these can transcend and cut across problems associated with different languages in different countries. Clinical trials in PPA are likely to require large, multicentre, international collaborations: using nonlinguistic instruments could be hugely beneficial here.

7.4.3. Non-pharmacological interventions

Cognitive therapies are gaining some traction in the context of PPA, but these typically centre on higher-level linguistic processes such as anomia (Bier *et al.*, 2009; Savage *et al.*, 2014), often in the context of transcranial direct current stimulation (Roncero

et al., 2017). Themes of this thesis may inform non-pharmacological interventions. The work presented in Chapter 5 suggests that DAF may improve rate of spontaneous speech in patients with nfvPPA and lvPPA, while results presented in Chapter 6 suggest that there is at least some capacity for residual plasticity even within the disintegrating language networks of patients with nfvPPA and lvPPA. If the perceptual learning for degraded speech stimuli shown in these patient groups can be harnessed and transferred to improved performance in terms of auditory word comprehension, this could form the basis for cognitive retraining therapies.

7.5. Limitations

The conclusions put forward here are inevitably subject to certain general limitations. First, although every chapter here reports on a cohort of at least 27 individual patients, the individual syndromic group sizes are small. This is a problem inherent to single-centre cross-sectional work of this kind, especially in the context of PPA, which represents an extremely rare set of neurodegenerative syndromes. Larger patient cohorts, ideally recruited by collaborating specialist centres, and ideally with molecular and/ or histopathological correlation might enable further pathophysiological stratification of syndromes.

Second, all of the experimental work presented in this thesis is cross-sectional. If any of the behavioural stimuli presented here are to emerge as cognitive/ auditory processing biomarkers there is a key need to use longitudinal study designs to assess their potential in detecting and tracking disease in individual patients across disease stages.

Third, behavioural work of this kind, in patient groups characterised by comprehension deficits, is necessarily reductionist. The speech signal stimuli employed in Chapters 3 and 4, for instance, used an extremely restricted range of phonemic carriers: future work could explore the effect of a more representative set and examine the interaction of phoneme identity with other experimental parameters. Here, it would be advantageous also to consider cross-modal sensory inputs: in the real-world, we are rarely confronted by audio input without concurrent visual stimulation.

7.6. Future directions

In light of the nosological difficulties that surround PPA, and mounting neuropsychological and functional and structural neuroanatomical evidence for nonverbal auditory processing deficits in these syndromes, it may be timely to re-evaluate the 'language-led' dementias as more fundamental disorders of auditory signal decoding. Future research – work that I hope to undertake myself after my PhD – needs to investigate the precise nature of these auditory deficits. It is possible that some of the more dynamic stimuli presented here could be used as sensitive diagnostic clinical tests in the future, and it remains to be seen whether individual proteinopathies are associated with distinct auditory processing profiles in the PPA syndromes. This is an extremely exciting avenue for future work with clinical trials in PPA on the horizon.

The differentiation between nfvPPA and lvPPA can be hard to make clinically. Ancillary molecular information from cerebrospinal fluid can be helpful in determining Alzheimer's pathology – associated with lvPPA in the majority of cases (Rohrer *et al.*, 2011; Spinelli *et al.*, 2017) – but a significant minority of patients with nfvPPA have Alzheimer's pathology (Rohrer *et al.*, 2011). Work presented in Chapters 4 and 6 here suggests that there are behavioural and neuroanatomical differences between the syndromes relevant to processing of auditory speech signals, and a critical avenue for future research is to identify candidate markers that dissociate the syndromes with a higher degree of accuracy than is currently possible, alongside molecular and histopathological correlation.

As noted throughout this thesis, there is considerable heterogeneity across PPA in terms of clinical presentation, neuroanatomy, and molecular pathology. Perhaps as many as 40% of PPA patients do not meet current consensus criteria for any of the three variants (Sajjadi et al., 2012), though estimates do vary across centres (Rohrer et al., 2011; Spinelli et al., 2017). If, as argued here, the PPAs represent disorders of auditory signal decoding, rather than being language-led syndromes *per se*, it is possible that extensive phenotyping of auditory processing characteristics will be able to characterise this group of PPA not-otherwise-specified (PPA-NOS) patients better than the current diagnostic criteria (Gorno-Tempini *et al.*, 2011).

8. References

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9. Appendix

Supplementary Table 1. Participation by participants across Chapters

					Chapter			
ID	Group	Age	Gender	Handedness	3	4	5	6
1	Control	74	M	R	✓	✓	✓	✓
2	Control	67	M	R	✓	✓	✓	✓
3	Control	79	F	R	✓	✓		
4	Control	59	F	R	✓	✓		✓
5	Control	66	M	R	✓	✓		✓
6	Control	68	F	R	✓			
7	Control	71	M	R	✓	✓	✓	✓
8	Control	66	F	L	✓	✓		
9	Control	70	M	R	✓	✓	✓	✓
10	Control	70	M	A	✓	✓	✓	✓
11	Control	72	M	R	✓	✓		
12	Control	67	F	R	✓	✓	✓	✓
13	Control	69	F	R	✓	✓	✓	✓
14	Control	67	F	R	✓	✓		
15	Control	70	M	R	✓	✓		
16	Control	71	M	R	✓	✓		
17	Control	78	F	R	✓			✓
18	Control	65	F	R	✓			
19	Control	71	F	R	✓		✓	✓
20	Control	69	M	R				✓
21	Control	66	F	R			✓	✓
22	Control	57	M	R			✓	✓
23	Control	71	F	R			✓	✓
24	Control	71	F	R				✓
25	Control	57	F	R			✓	✓
26	Control	73	F	R			✓	
27	lvPPA	62	F	R	✓	✓		
28	lvPPA	62	M	R	✓	✓		
29	lvPPA	72	F	R	✓	✓		
30	lvPPA	58	M	R	✓	✓		✓
31	lvPPA	66	M	R	✓		✓	✓
32	lvPPA	56	M	R	✓	✓		
33	lvPPA	74	F	R	✓			
34	lvPPA	66	M	L	✓	✓	✓	✓
35	lvPPA	78	M	R			✓	✓
36	lvPPA	67	M	R			✓	✓
37	lvPPA	61	M	R			✓	✓

38	lvPPA	65	F	R			✓	✓
39	lvPPA	86	M	R			✓	
40	nfvPPA	56	M	R	✓	✓		
41	nfvPPA	65	F	R	✓	✓		✓
42	nfvPPA	72	F	R	✓	✓		
43	nfvPPA	63	M	R		✓		
44	nfvPPA	71	M	L	✓	✓		
45	nfvPPA	67	F	R	✓	✓		✓
46	nfvPPA	76	M	R		✓		
47	nfvPPA	79	M	R	✓	✓		
48	nfvPPA	83	M	R	✓	✓		
49	nfvPPA	72	M	R	✓	✓		
50	nfvPPA	84	F	R	✓	✓		
51	nfvPPA	63	F	L	✓	✓		
52	nfvPPA	84	F	R			✓	✓
53	nfvPPA	70	M	R			✓	✓
54	nfvPPA	74	F	L			✓	✓
55	nfvPPA	63	F	R			✓	✓
56	nfvPPA	55	F	L			✓	✓
57	nfvPPA	64	F	L			✓	✓
58	nfvPPA	82	F	R			✓	✓
59	svPPA	59	F	R	✓	✓	✓	✓
60	svPPA	64	M	R	✓	✓	✓	✓
61	svPPA	57	F	R	✓	✓	✓	✓
62	svPPA	66	M	R	✓		✓	✓
63	svPPA	69	M	L	✓	✓		
64	svPPA	71	M	R	✓	✓	✓	✓
65	svPPA	60	M	R	✓	✓		
66	svPPA	63	F	R	✓	✓		✓
67	svPPA	65	M	R	✓	✓		✓
68	svPPA	60	M	R		✓		
69	svPPA	64	M	R				✓
70	svPPA	70	M	R			✓	✓
71	svPPA	51	M	R				✓
72	svPPA	78	F	R			✓	✓
73	svPPA	74	M	R			✓	
74	tAD	64	F	R			✓	✓
75	tAD	63	F	R			✓	✓
76	tAD	67	F	R			✓	✓
77	tAD	62	M	R			✓	✓
78	tAD	73	M	R				✓
79	tAD	74	F	R			✓	✓
80	tAD	84	M	R			✓	✓

81	tAD	87	F	R			✓	✓
82	tAD	65	F	R			✓	✓
83	tAD	62	M	R			✓	✓
84	tAD	66	M	L			✓	✓
85	tAD	71	F	R			✓	
86	bvFTD	65	M	R			✓	
87	bvFTD	75	F	R			✓	
88	bvFTD	58	M	R			✓	
89	bvFTD	78	M	R			✓	
90	bvFTD	53	M	R			✓	
91	bvFTD	60	M	R			✓	
92	bvFTD	63	M	R			✓	
93	bvFTD	71	M	R			✓	

Participants are ordered by group. The shaded boxes indicate which patient groups were not recruited to the experimental cohort represented by the column heading. A tick denotes that the participant was recruited to that experimental cohort. ID numbers are not sequential and serve no other purpose than to differentiate between participants and display the extent of overlap between studies.

Supplementary Table 2. Description of audio files on enclosed CD

Track No.	File name	Description
Chapter 3		
1	Audio File 3.1	Isochronous sequence “ab”
2	Audio File 3.2	Anisochronous sequence “ab”
3	Audio File 3.3	Low entropy sequence “fu”
4	Audio File 3.4	High entropy sequence “fu”
5	Audio File 3.5	Natural phonemic structure sequence “ba”
6	Audio File 3.6	Rotated phonemic structure sequence “ba”
Chapter 4		
7	Audio File 4.1	Natural, isochronous, high entropy sequence
8	Audio File 4.2	Rotated, anisochronous, low entropy sequence
Chapter 6		
9	Audio File 6.1	Sinewave speech number example
10	Audio File 6.2	Clear speech number
11	Audio File 6.3	Sinewave speech location example
12	Audio File 6.4	Clear speech location

9.1. Division of labour

The work described in this thesis was conducted by CJDH with assistance from other researchers based at the Dementia Research Centre, UCL. Contributors are detailed below.

9.1.1. Chapter 3: Behavioural and neuroanatomical correlates of speech analysis

Experimental design: CJDH, JDW
Construction of tests: CJDH, JDW
Data collection: CJDH, CRM, CNC, LLR, RLB, EVB
Data analysis: CJDH

9.1.2. Chapter 4: Functional neuroanatomy of speech signal decoding

Experimental design: CJDH, JDW, JA
Construction of stimuli: CJDH, JDW
Data collection: CJDH, CRM, LLR, CNC, RLB, EVB
Data analysis: CJDH, SO, JA, CF

9.1.3. Chapter 5: Delayed auditory feedback

Experimental design: CJDH, JDW, RLB
Construction of tests: CJDH, RLB
Data collection: CJDH, RLB, CM, LLR
Data analysis: CJDH

9.1.4.Chapter 6: Processing of degraded speech stimuli

Experimental design: CJDH, JDW
Construction of tests: CJDH, SJR
Data collection: CJDH, RLB, CRM, LLR
Data analysis: CJDH

9.2. Publications

9.2.1. Publications arising as a direct result of the work conducted in this thesis

Hardy, C. J. D., Agustus, J. L., Marshall, C. R., Clark, C. N., Russell, L. L., et al. 2017. Behavioural and neuroanatomical correlates of auditory speech analysis in primary progressive aphasias. Alz Res Ther, 9(1), p. 53.

Hardy, C. J. D., Agustus, J. L., Marshall, C. R., Clark, C. N., Russell, L. L., et al. 2017 Functional neuroanatomy of speech signal decoding in primary progressive aphasias. Neurobiol Aging, 56, 190–201.

Hardy, C. J. D., Marshall, C. R., Golden, H. L., Clark, C. N., Mummery, C. J., et al. 2016 Hearing and dementia. J Neurol, 263(11).

9.2.2. Other substantial contributions

Hardy, C. J. D., Buckley, A. H., Downey, L. E., Lehmann, M., Zimmerer, V. C., et al. 2015. The Language Profile of Behavioral Variant Frontotemporal Dementia. J Alzheimers Dis, 50(2), 359–71.

Marshall, C. R., Hardy, C. J. D., Rossor, M. N. and Warren, J. D. 2016 Teaching NeuroImages: Nonfluent variant primary progressive aphasia: A distinctive clinico-anatomical syndrome. Neurology, 87(23), p. e283.

Warren, J. D., Hardy, C. J., Fletcher, P. D., Marshall, C. R., Clark, C. N., et al. 2016. Binary reversals in primary progressive aphasia. Cortex, 82, 287–289.

Cohen, M. H., Carton, A. M., Hardy, C. J., Golden, H. L., Clark, C. N., et al. 2016. Processing emotion from abstract art in frontotemporal lobar degeneration. Neuropsychologia, 81.

Thompson, A. E., Clark, C. N., Hardy, C. J., Fletcher, P. D., Greene, J., et al. 2016. Two cases of food aversion with semantic dementia. Neurocase, 22(3).

Clark, C. N., Nicholas, J. M., Agustus, J. L., Hardy, C. J., Russell, L. L., Brotherhood, E. V., Dick, K. M., Marshall, CR., Mummery, C. J., Rohrer, J. D., & Warren, J. D. 2017. Neuropsychologia, in press.