

Hearing impairment in dementia: defining deficits and assessing impact

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Doctor of Philosophy (PhD)

I, Jeremy Colin Spencer Johnson confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

## Abstract

The association between hearing impairment and dementia has emerged as a major public health challenge, with significant opportunities for earlier diagnosis, treatment and prevention. However, the nature of this association has not been defined. We hear with our brains, particularly within the complex soundscapes of everyday life: neurodegenerative pathologies target the auditory brain and are therefore predicted to damage hearing function early and profoundly. Here I present evidence for this proposition, based on structural and functional features of auditory brain organisation that confer vulnerability to neurodegeneration, the extensive, reciprocal interplay between ‘peripheral’ and ‘central’ hearing dysfunction, and recently characterised auditory signatures of canonical neurodegenerative dementias (Alzheimer’s disease and frontotemporal dementia).

In chapter 3, I examine pure tone audiometric thresholds in AD and FTD syndromes and explore the functional interplay between the auditory brain and auditory periphery by assessing the contribution of auditory cognitive factors on pure tone detection. In chapter 4, I develop this further by examining the processing of degraded speech signals, leveraging the increased importance of top-down integrative and predictive mechanisms on resolving impoverished bottom-up sensory encoding. In chapter 5, I use a more discrete test of phonological processing to focus in on a specific brain region that is an early target in logopenic aphasia, to explore the potential of auditory cognitive tests as disease specific functional biomarkers. Finally, in chapter 6, I use auditory symptom questionnaires to capture real-world hearing in daily life amongst patients with dementia as well as their carers and measure how this correlates with audiometric performance and degraded speech processing.

I call for a clinical assessment of real-world hearing in these diseases that moves beyond pure tone perception to the development of novel auditory ‘cognitive stress tests’ and proximity markers for the early diagnosis of dementia and management strategies that harness retained auditory plasticity.

## Impact Statement

Hearing loss has emerged as the most significant modifiable mid-life risk factor for dementia; to fully realise any potential risk reduction through remediation of hearing loss, we require a fuller understanding of this relationship. The work in this thesis posits the central role of the brain in decoding and analysing the complex soundscapes of daily listening that goes far beyond the simple detection of sounds by the ears. In other words, we hear with our brains. The theoretical considerations and experimental findings explored in this thesis suggest that auditory cognitive dysfunction is likely to be an early consequence of neurodegenerative dementias and affords primacy to the neural consequences of pathogenic protein accumulation in the causal relationship between hearing loss and dementia. These findings could be of significant future benefit to several important areas both within and outside academia.

Future research using physiologically grounded techniques should substantiate the central role of neurodegenerative disease in the interaction between hearing loss and dementia and be used to clarify the neural mechanisms underlying how the brain compensates for degraded auditory input via peripheral hearing loss and how these might inform future therapeutic targets. Longitudinal studies of at-risk populations would further develop this understanding and raise the exciting prospect of novel auditory ‘cognitive stress tests’ for detecting the early stages of neurodegeneration. In turn, these could be used to create novel physiological biomarkers of disease evolution, residual plasticity and therapeutic response. Such markers could represent red flags for targeting population-based screening and recruitment into dementia prevention trials from primary care settings and could be developed into ‘digital biomarkers’ that are highly scalable. Additionally, they may prove to be more effective at tracking functional changes related to disease modifying therapies that are on the horizon.

To date, a full assessment of the wide gamut of auditory cognitive symptoms experienced in daily life by patients with dementia has received little attention and is sorely needed; the work in this thesis is a potential starting point and should inform future work. Such an assessment would help to raise awareness among clinicians across disciplines as well as the wider public about the role of the brain in hearing, how dementia impacts this and the limitations of audiometric assessment, based on their poor correlation with daily life hearing. These will be key to earlier recognition and referral of patients with cognitive changes that will aid early diagnosis as well as informing future interventions, such as the development of physiologically informed ‘smart hearing aids’.

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## Abbreviations

$A\beta$	Amyloid-beta
AD	Alzheimer's disease
AG	angular gyrus
mAIAD	modified Amsterdam Inventory for Auditory Disability and Handicap
BPVS	British Picture Vocabulary Scale
bvFTD	behavioural variant frontotemporal dementia
C9orf72	chromosome 9 open reading frame 72
CI	confidence interval
CSF	cerebrospinal fluid
DARTEL	diffeomorphic anatomical registration through exponentiated lie algebra
fMRI	functional magnetic resonance imaging
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
FWE	family-wise error
GDA	Graded Difficulty Arithmetic
GNT	Graded Naming Test
GRN	progranulin
HG	Heschl's gyrus
IFG	inferior frontal gyrus
MAPT	microtubule associated protein tau
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
MTG	middle temporal gyrus

MTL	mesial temporal lobe
nfvPPA	nonfluent variant primary progressive aphasia
OFC	orbitofrontal cortex
OAE	Otoacoustic emission
PAL	Paired Associate Learning test
PET	Positron emission tomography
PMC	Pre-motor cortex
PPA	primary progressive aphasia
RMT	Recognition Memory Test
ROI	region of interest
SD	standard deviation
SMA	supplementary motor area
SMG	supramarginal gyrus
STG	superior temporal gyrus
svPPA	semantic variant primary progressive aphasia
TDP-43	transactive response DNA binding protein 43
TIV	total intracranial volume
TPJ	temporo-parietal junction
VBM	voxel-based morphometry
VOSP	Visual Object and Spatial Perception battery
WASI	Wechsler Abbreviated Scale of Intelligence
WMS	Wechsler Memory Scale

## Epigraph

“Sometimes you have to go on when you don't feel like it, and sometimes you're doing good work when it feels like all you're managing is to shovel shit from a sitting position.”

Stephen King



# 1 General Introduction

## 1.1 Scope and nature of the problem

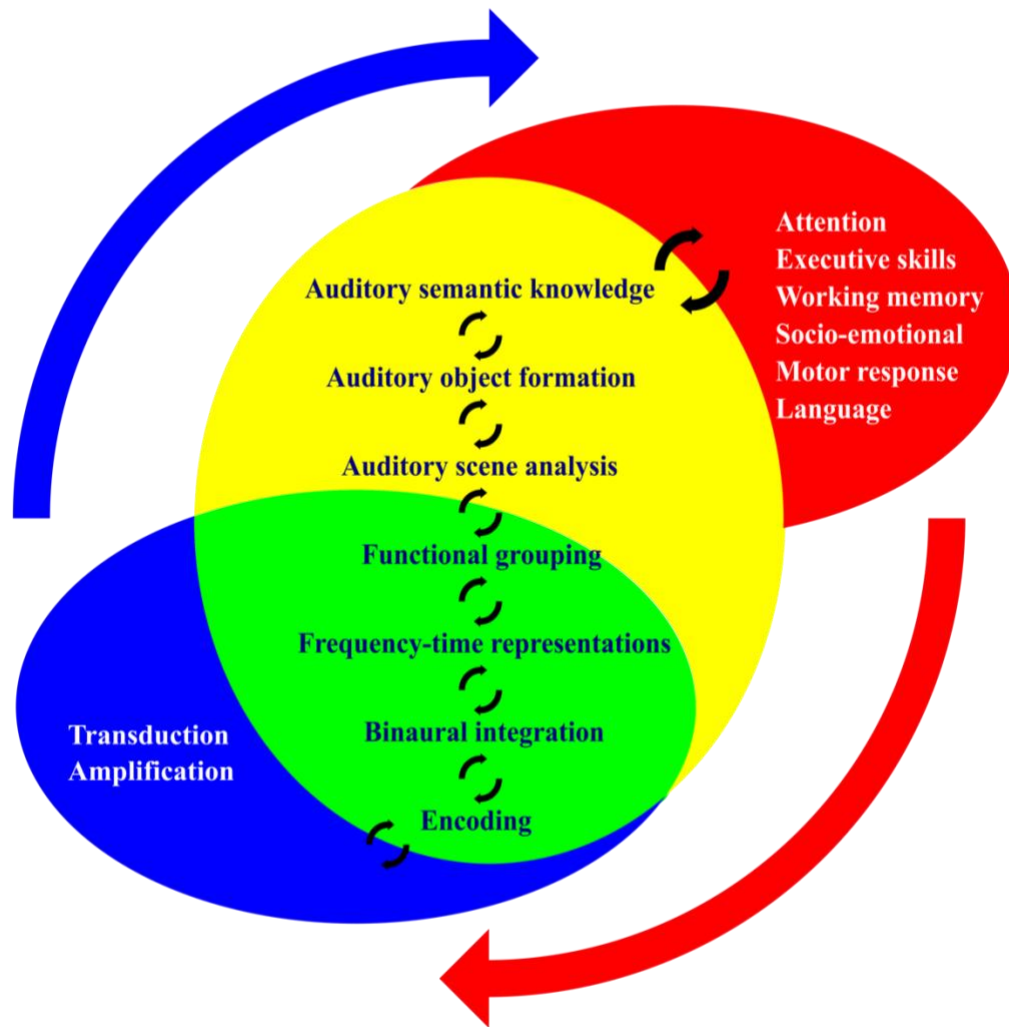
Hearing impairment in mid-life is a major clinical issue and a leading association of cognitive decline and is estimated to account for 9% of cases of incident dementia (Gates and Mills, 2005; Lin *et al.*, 2011; Gallacher *et al.*, 2012; Deal *et al.*, 2016; Taljaard *et al.*, 2016; Livingston *et al.*, 2017; Loughrey *et al.*, 2018), presenting significant potential opportunities for dementia diagnosis, treatment and prevention (Dawes *et al.*, 2015; Taljaard *et al.*, 2016; Livingston *et al.*, 2017). But how are hearing impairment and dementia related? Hearing loss of any cause tends to limit social engagement and quality of life (Graydon *et al.*, 2019), amplifies the effects of cognitive impairment and may confound or delay diagnosis of dementia (Panza *et al.*, 2015; Wayne and Johnsrude, 2015). Conversely, diagnosis of hearing loss and compliance with hearing aids are hindered by cognitive impairment (Dawes *et al.*, 2015). There may, however, be a more fundamental pathophysiological basis for the association: hearing is a complex cognitive function that, alongside other cognitive functions, is directly vulnerable to the pathophysiological processes that cause dementia (Wayne and Johnsrude, 2015; Hardy *et al.*, 2016; Griffiths *et al.*, 2020).

Recent studies addressing the link between hearing impairment and dementia have focussed predominantly on audiometric pure tone detection, the ability to detect quiet sounds (Lin *et al.*, 2011; Loughrey *et al.*, 2018). However, most natural auditory environments or ‘scenes’ comprise mixtures of sounds that change over time, and listening – perception and understanding of sounds – is a highly active cognitive process (Bendixen, 2014; Friston *et al.*, 2020) (Figure 1.1). Consider, for example, the everyday scenario of following a conversation in a crowded room. After substantial ‘pre-cognitive’ processing in the auditory brainstem (Cope *et al.*, 2015), the incoming auditory signal must be deconstructed (by ‘auditory scene analysis’: (Goll *et al.*, 2012a, Golden *et al.*, 2015c; Hardy *et al.*, 2016)) into discrete and stable percepts or ‘auditory objects’ corresponding to voices and speech features, separate from background noise (Griffiths and Warren, 2004, Goll *et al.*, 2010b). Such auditory objects must be matched to stored representations and expectations to achieve recognition and ultimately, an appropriate behavioural response. These processes collectively constitute ‘auditory cognition’ (Figure 1.1) and depend critically on neural computations in auditory cortical and linked processing networks: the auditory brain (Figure 1.2).

Evidence that neurodegenerative pathologies target the auditory brain and produce ‘central’ hearing deficits disproportionate to any peripheral hearing loss was first produced some time ago (Kurylo *et al.*, 1993; Strouse *et al.*, 1995). More recently, a diverse array of ‘central’ auditory deficits has been described in these diseases (Mahoney *et al.*, 2011; Rohrer *et al.*, 2012; Fletcher *et al.*, 2015, Golden *et*

*al.*, 2015c; Grube *et al.*, 2016; Hardy *et al.*, 2016), ranging widely beyond ‘deafness’ (impaired sound detection) to encompass altered auditory perception, understanding and behavioural responses, with far-reaching consequences for hearing function in daily life. To date, however, the role of the auditory brain in linking hearing impairment to cognitive decline has been largely overlooked.

Here I argue that the auditory brain is integral to the development and expression of hearing impairment in dementia. My case rests on three interwoven lines of evidence: the structural and functional characteristics of auditory brain organisation targeted by neurodegenerative diseases; the known extensive interplay between so-called ‘peripheral’ and ‘central’ hearing mechanisms; and mounting data on auditory cognitive dysfunction as a prominent, early and specific manifestation of canonical dementia syndromes.



**Figure 1.1 Processes and interactions in 'peripheral' and 'central' hearing**

The Figure diagrams the functional organisation of the auditory processing hierarchy and the interplay of hearing with more general cognitive functions. Ellipses indicate the broad domains of peripheral hearing (blue; anatomically, the peripheral hearing apparatus which receives incoming sounds, cochlea and auditory nerve), pre-cognitive auditory processing (green; chiefly the auditory brainstem), auditory cognition (yellow; auditory cortex and its cerebral connections) and general cognitive functions (red; see Figure 1.2 for neuroanatomy). Listed within the ellipses are some key stages in the analysis of auditory information: 'peripheral' and 'central' hearing processes lie on a functional and anatomical continuum, with reciprocal connections between successive processing stages (black arrows). This organisation implies that pathologies (such as neurodegenerative proteinopathies) predominantly targeting auditory cognitive (and general cognitive) processing stages may have cascading effects at other processing stages. Certain additional functional properties that operate across auditory processing stages, such as nonlinear signal coding and plasticity, are likely to be particularly vulnerable to the effects of neurodegenerative pathologies (see text). External red and blue arrows here signify general mechanisms by which hearing dysfunction of any cause may promote cognitive decline, and

the converse; these mechanisms are likely to be mutually reinforcing and may additionally compound more specific effects of auditory brain dysfunction, with the potential to establish pathophysiological 'vicious cycling.'

## 1.2 The auditory brain: structural and functional substrates for neurodegeneration

The auditory system has evolved to allow adaptive behavioural responses to complex, dynamic acoustic environments (Griffiths *et al.*, 2001; Pickles, 2015). This is directly reflected in the structural and functional organisation of the brainstem pathways and cerebral networks that constitute the auditory brain (Griffiths *et al.*, 2001; Poremba, 2003; Griffiths and Hall, 2012; Pickles, 2015). However, its structural and functional characteristics confer specific vulnerabilities to neurodegenerative pathologies.

Anatomically, the hierarchy of auditory processing relays and in particular the large-scale cerebral networks that process sound information (Figure 1.2) are highly distributed. The spread of pathogenic proteins in neurodegenerative dementias (Figure 1.2) targets these networks rather than the peripheral organs of hearing. Though histopathological data remain limited, neurodegenerative pathologies may preferentially involve auditory association cortex and cortico-cortical projections rather than primary sensory cortex (Esiri *et al.*, 1986; Lewis *et al.*, 1987, Baloyannis *et al.*, 2011*b*, *a*), thereby striking the integrative mechanisms that are most critical for auditory object analysis.

The transformation of the basic time and frequency information that arrives at the ears into categorical, multi-dimensional cortical representations is achieved by a multi-level computational hierarchy of dedicated neural circuitry. Sound processing begins at the cochlea, which actively filters the incoming broadband acoustic waveform into component narrowband frequencies along the basilar membrane (Guinan, 2018; Oxenham, 2018). A hierarchy of processing stages in the ascending brainstem and subcortical auditory nuclei allows acoustic frequency and timing data to be integrated into sensory featural representations over timescales ranging from milliseconds to hundreds of milliseconds (Malmierca and Hackett, 2010; Pickles, 2015). Accurate auditory signal transduction (for example, during spatial hearing or speech perception) is dependent on this precise integration of frequency-based (spectral) and time-based (temporal) information (Griffiths *et al.*, 2001; Bizley *et al.*, 2009): any pathology that damages relevant neural circuits is likely to disrupt such processing early in its course. As the auditory signal passes up the processing hierarchy, it is transformed non-linearly such that it is no longer a direct replica of the incoming signal encoded at the periphery (Wang, 2007; Gaucher *et al.*, 2013); due to the intrinsically temporal nature of sound, this transformation of auditory information is particularly evident in the time domain and supports the extraction of invariant auditory object features and cross-modal integration. The resulting percept is normally robust to noisy variations in the sensory signal, however, its non-linear nature means that even small perturbations of neural circuit function due to neurodegenerative disease may have disproportionately large perceptual and behavioural consequences.

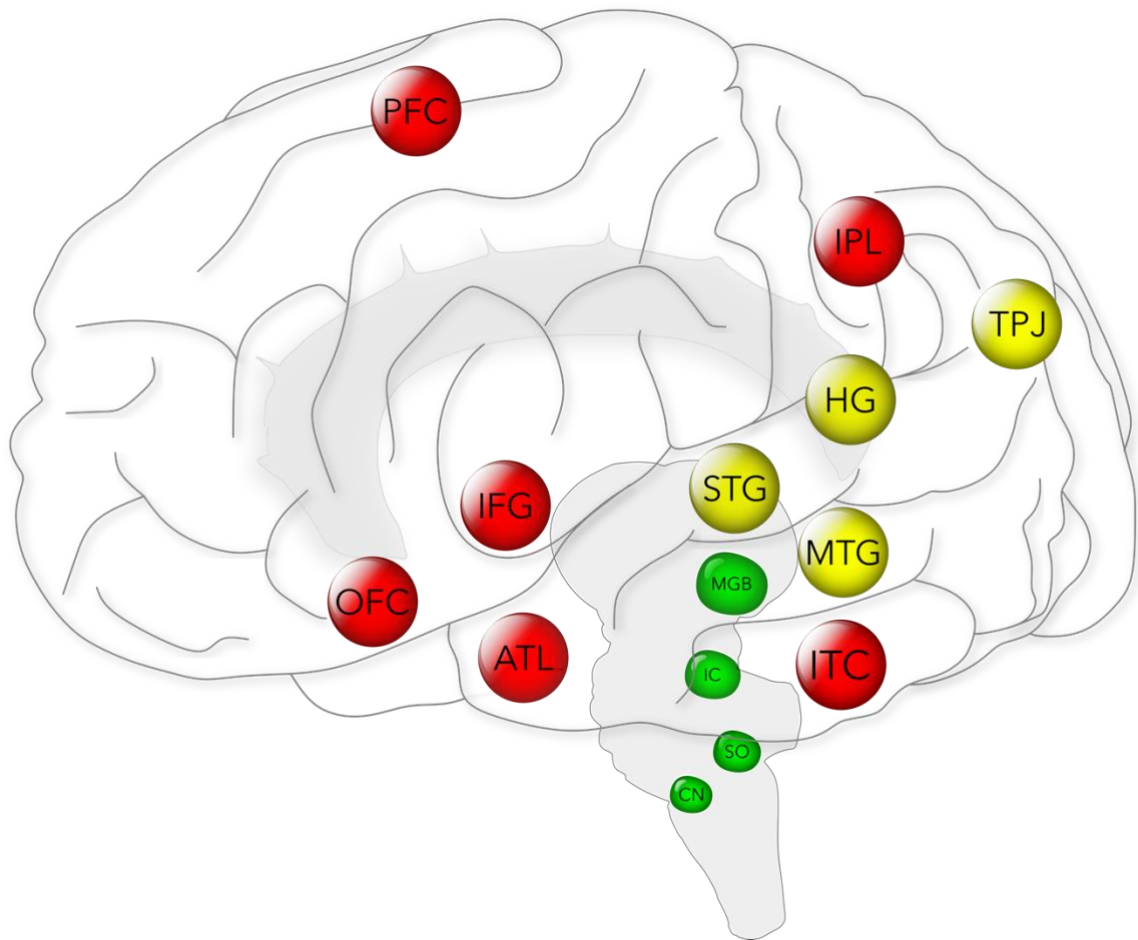
Two additional, related guiding principles of auditory system operation that are critical for adaptive functioning in complex, dynamic auditory environments are reciprocity and functional plasticity. Reciprocity provides a feedback mechanism that allows for the rapid and dynamic changes in auditory neural sensitivity that underwrites functional plasticity. In turn, plasticity (for example, perceptual learning of degraded speech (Hardy *et al.*, 2018)) enables dynamic neural adaptation to auditory experience.

Reciprocity is mediated by recursive, afferent-efferent feedback between processing stages (Terreros and Delano, 2015) that supports auditory change detection and top-down tracking of behaviourally relevant sound sources (Shamma and Micheyl, 2010; Zion Golumbic *et al.*, 2013; Bendixen, 2014; Malmierca, 2014), as well as predictive decoding and ‘filling-in’ of ambiguous and varying auditory inputs, such as degraded speech (Malmierca, 2014; Simon, 2015; Donhauser and Baillet, 2020) (see Figure 1.1). Each stage instantiates a mechanism whereby ‘top-down’ feedback via efferent pathways can modulate incoming, feed-forward afferent traffic, based on prior learning and expectations, behavioural goals and attentional resources. Efferent traffic in the auditory system is extensive (Snyder and Elhilali, 2017; Yakunina *et al.*, 2019): the most accessible example is the medial olivocochlear efferent pathway which tunes cochlear responses to transient sounds in background noise (Lopez-Poveda, 2018; Marian *et al.*, 2018; Yasin *et al.*, 2018) and modulates otoacoustic emissions ((OAE) the sonic reflections measured by intracanalicular microphones that signal presynaptic cochlear function (Kemp, 2002; Guinan *et al.*, 2012; Guinan, 2018). Attentional modulation reflects the interaction of bottom-up change detection and top-down tracking mechanisms (Buschman and Miller, 2007; Näätänen *et al.*, 2012; Bizley and Cohen, 2013, Kaya and Elhilali, 2017a); it operates at multiple levels and timescales of the auditory processing hierarchy, and is particularly critical for parsing the auditory scene, reconciling deviant or ‘surprising’ auditory events with expectations and behavioural goals (Tervaniemi *et al.*, 2009; Shamma and Micheyl, 2010; Zion Golumbic *et al.*, 2013; Simon, 2015, Kaya and Elhilali, 2017a).

The interaction of afferent and efferent influences is fundamental to our perception of a coherent auditory world (Costa-Faidella *et al.*, 2017; Kondo *et al.*, 2017); this interaction underpins auditory adaptation and plasticity and tunes the sensitivity of the cochlea and afferent auditory pathways dynamically according to auditory experience, current environmental contingencies and behavioural set (Suga and Ma, 2003; Lesica and Grothe, 2008; Chandrasekaran *et al.*, 2009; Skoe and Kraus, 2010; Antunes and Malmierca, 2011; Rabbitt and Brownell, 2011; Ayala and Malmierca, 2015; Malmierca *et al.*, 2015; Yasin *et al.*, 2018; Lopez-Poveda, 2018; Marian *et al.*, 2018). The principles of neural plasticity and feed-forward/feedback coupling together enable predictive decoding and perceptual learning of

ambiguous auditory inputs, such as degraded speech (Billig *et al.*, 2013; Hardy *et al.*, 2018): a sine qua non of adaptive, context-dependent behaviour.

These functional principles are evident throughout the auditory system (Russo *et al.*, 2005; Barascud *et al.*, 2016; Guinan, 2018) and are highly sensitive to synaptic neurochemical (particularly cholinergic) modulation, especially under challenging listening conditions (Dhanjal *et al.*, 2013; Kuchibhotla *et al.*, 2017; Minces *et al.*, 2017). They are therefore potentially highly susceptible to neurodegenerative pathologies that disrupt synaptic and neurotransmitter pathway integrity. Moreover, the characteristics of nonlinear stimulus coding, extensive efferent regulation of afferent pathways and pervasive plasticity (though not specific to audition) are much more marked in the auditory system than in other sensory systems, notably vision (King and Nelken, 2009). Impaired functional adaptation of auditory brainstem pathways has perceptual consequences in patients with mild cognitive impairment (Bidelman *et al.*, 2017), suggesting that indices of auditory plasticity may be sensitive and dynamic markers of neurodegenerative pathologies.



**Figure 1.2 The auditory brain in health**

Major anatomical regions that mediate the processes underpinning hearing (see Figure 1) are represented as spheres overlaid in a left lateral view of the brain. These regions are anatomically and functionally linked into large-scale, distributed networks. The colour convention follows that in Figure 1 (green, pre-cognitive auditory processing in brainstem pathways, enclosed by the grey filled outline; yellow, auditory cognition in auditory cortices; red, general cognitive processes in connected cerebral regions); note however that there is no simple, one-to-one correspondence between particular brain regions and individual 'tiers' of the processing hierarchy outlined in Figure 1. Brain regions are designated as follows: **ATL**, antero-mesial temporal lobe (also encompassing amygdala and hippocampus); **CN**, cochlear nucleus (ventral and dorsal); **HG**, Heschl's gyrus (medial portion contains primary auditory cortex); **IC**, inferior colliculus; **IFG**, inferior frontal gyrus (closely associated with insular cortex, deep to the cerebral surface); **IPL**, inferior parietal lobe; **ITC**, inferior temporal cortex; **MGB**, medial geniculate body; **MTG**, middle temporal gyrus; **OFC**, orbitofrontal cortex; **PFC**, prefrontal cortex; **SO**, superior olive (its main projection in the lateral lemniscus has several additional, small associated nuclei); **STG**, superior temporal gyrus; **TPJ**, temporo-parietal junctional cortex. Also shown in grey filled



outline is the cingulate gyrus, projected from the medial surface of each cerebral hemisphere: this signifies linked deep medial prefrontal and parietal cortices that also participate importantly in integrative and modulatory cognitive processes relevant to hearing.

### 1.3 ‘Peripheral’ and ‘central’ hearing: a false dichotomy and a double hit

The anatomical and functional interactions of auditory processing stages (Figures 1.1 and 1.2) suggest that any sharp distinction between ‘peripheral’ and ‘central’ hearing is likely to be a false dichotomy. Pure tone audiometry (PTA), the mainstay of standard clinical audiological assessment, is generally interpreted as an index of ‘peripheral’ (cochlea and auditory nerve) hearing. However, PTA thresholds are affected by attention (Musiek *et al.*, 2017), executive function (Gates *et al.*, 2010) and brainstem pathologies that do not directly involve the cochlea (Cope *et al.*, 2015), reflecting the known role of top-down influences on cochlear sensitivity (Terreros and Delano, 2015). Furthermore, PTA does not fully predict ability to hear speech in noise (the principal hearing complaint of older listeners, (Anderson *et al.*, 2011; Guest *et al.*, 2018; Holmes and Griffiths, 2019)). Conversely, ‘central’ hearing functions that rely on high-fidelity signal coding at brainstem level (such as speech intelligibility) are tuned by efferent synaptic functional adaptation at the cochlea (Pressnitzer *et al.*, 2008) and auditory agnosia is modulated by peripheral hearing loss (Coebergh *et al.*, 2020). Neurodegenerative diseases that principally involve cortical and subcortical pathways may therefore significantly impact hearing functions canonically attributed to the peripheral sense organs; indeed, elevated PTA thresholds have recently been documented in the nonfluent-agrammatic variant of primary progressive aphasia (nfvPPA), a primary cortical degeneration (Hardy *et al.*, 2019). On the other hand, anatomical involvement of subcortical auditory relays by neurodegenerative pathology does not necessarily lead to a perceptual deficit (Hughes *et al.*, 2014).

Moreover, neurodegenerative diseases typically target the ageing brain, and healthy ageing itself affects multiple stages of auditory processing, ranging from cochlea to cortex (Bendixen, 2014; Bidelman *et al.*, 2014; Roth, 2015; Henry *et al.*, 2017; Zhao *et al.*, 2019). Some of these effects (in particular, degeneration of synapses between inner hair cells and auditory nerve fibres) are undetectable or ‘hidden’ on standard PTA and may therefore be underestimated (Wu *et al.*, 2019); other effects (such as attentional suppression of irrelevant sensory information) may only emerge under challenging listening conditions or for particular tasks, such as tracking fine-grained temporal information in speech (Henry *et al.*, 2017). Increased cognitive effort and engagement of task-relevant capacities (in auditory cortex or executive control systems) may compensate to a degree for the widespread effects of ageing on auditory signal processing (Profant *et al.*, 2015; Meister *et al.*, 2016; Glick and Sharma, 2017, Bidelman *et al.*, 2019a), however, if compensatory mechanisms are compromised by neurodegenerative pathology, this ‘double hit’ may cause hearing loss to become functionally significant. Such decompensation would be relatively more likely under adverse listening conditions. In this context, neurodegenerative effects on auditory brain function might act as ‘proximity makers’ for incipient, more generalised cognitive decline.

## 1.4 Major dementias have diverse auditory phenotypes

The neurodegenerative diseases that cause canonical dementia syndromes have specific profiles of large-scale, cortico-subcortical network involvement, determined by the patterns of spread of pathogenic proteins ((Seeley *et al.*, 2009; Warren *et al.*, 2013; Vogel *et al.*, 2021), examples in Figure 1.3)). These pathologies have correspondingly diverse clinical phenotypes including prominent auditory cognitive deficits (Table 1.1).

### 1.4.1 Alzheimer's disease

#### 1.4.1.1 Typical Alzheimer's disease

Alzheimer's disease (AD) produces a core impairment of auditory scene analysis, not attributable to more elementary deficits of sound perception or generic cognitive capacities (Idrizbegovic *et al.*, 2011). Auditory scene processing deficits may predate onset of more generalised cognitive decline in people at risk of developing AD (Golob *et al.*, 2009; Gates *et al.*, 2011) and in both the typical amnesic and posterior cortical (visuospatial) syndromic presentations of AD (Goll *et al.*, 2012*a*, Golden *et al.*, 2015*c*; Hardy *et al.*, 2020), suggesting that such deficits are a functional marker of AD pathology. This interpretation would corroborate neuroanatomical findings linking impaired auditory scene analysis to dysfunction and atrophy of the temporo-parietal 'default mode' network that is essential to AD pathogenesis ((Goll *et al.*, 2012*a*; Warren *et al.*, 2012, Golden *et al.*, 2015*c*, *a*), Figure 1.3, Table 1.1).

More generally, auditory phenotypic features of AD may signify a unifying deficit in encoding sound sources and patterns as distinct auditory objects (Griffiths and Warren, 2004, Goll *et al.*, 2010*b*, 2011; Hailstone *et al.*, 2012, Hardy *et al.*, 2017*b*). Such a deficit might ultimately underpin environmental sound agnosia in AD (Coebergh *et al.*, 2020) and impaired phonological processing (most saliently in the logopenic variant described below: (Johnson *et al.*, 2020)), amplified by abnormalities of auditory working memory (Dhanjal *et al.*, 2013).

#### 1.4.1.2 Logopenic variant primary progressive aphasia

Logopenic variant primary progressive aphasia (lvPPA) is increasingly formulated as the language-led variant of AD within the primary progressive aphasia spectrum as the majority of cases are underpinned by AD pathology, although some exceptions exist (Rohrer *et al.*, 2010*b*; Spinelli *et al.*, 2017; Marshall *et al.*, 2018). The core language features of lvPPA are prominent word-finding difficulty with resulting speech pauses, phonological errors and on examination, impaired repetition of phrases despite intact repetition of single words. Motor speech output and grammar are spared (Gorno-Tempini *et al.*, 2011, Johnson *et al.*, 2021*b*). Atrophy in lvPPA shows some overlap with AD, but typically shows early and extensive involvement of speech processing regions including the temporo-parietal junction as well as

involvement of the middle temporal gyrus (MTG); in contrast to AD there is also relative sparing of structures in the mesial temporal lobes (MTL) and functionally, default mode network activity is initially undisturbed (Figure 1.3 (Gorno-Tempini *et al.*, 2008, Rohrer *et al.*, 2010b; Warren *et al.*, 2012; Whitwell *et al.*, 2015; Win *et al.*, 2017)). The areas targeted in lvPPA are key speech sound decoding regions, activating stored phonological representations to link to verbal semantic stores (Leyton *et al.*, 2014; Marshall *et al.*, 2018; Ruksenaite *et al.*, 2021). Disordered auditory phonemic object transcoding and markedly decreased auditory phonological working memory capacity are predicted from first principles and have some experimental support (Table 1.1 (Gorno-Tempini *et al.*, 2008; Goll *et al.*, 2011, Hardy *et al.*, 2017b)).

## 1.4.2 Frontotemporal dementias

Frontotemporal dementia (FTD) subsumes a clinically, neuroanatomically and pathologically heterogeneous group of disorders that target overlapping, distributed cortico-subcortical networks traversing the frontal and temporal lobes (Convery *et al.*, 2019; Sivasathiseelan *et al.*, 2019), Figure 1.3, Table 1.1). Despite their comparative rarity, these disorders have disproportionate importance because they frequently strike people in the prime of life and collectively illustrate an overarching paradigm of neurodegenerative disease: the selective and specific vulnerability of neural systems to pathogenic protein aggregation. The auditory phenotypes of FTD reflect this specificity and diversity.

### 1.4.2.1 Non-fluent variant primary progressive aphasia

Non-fluent variant primary progressive aphasia (nfvPPA) is clinically defined as a motor-speech output disorder, with halting, effortful and unmelodious speech (aprosodic speech), accompanied by speech sound errors and distortions (apraxic speech). Single-word comprehension and object knowledge are spared, but there is both expressive and receptive agrammatism (Gorno-Tempini *et al.*, 2011, Johnson *et al.*, 2021b). Whilst nfvPPA is defined as an output disorder, auditory perceptual dysfunction is emerging as a core feature of nfvPPA (Goll *et al.*, 2010a, 2011; Grube *et al.*, 2016; Golden *et al.*, 2017; Hardy *et al.*, 2019)), including deficits of rhythm, pitch and timbre perception (Goll *et al.*, 2010a, 2011; Grube *et al.*, 2016) and sound detection (Hardy *et al.*, 2019), which is perhaps surprising. Sensory perception relies on the integration of sensory input with cognitive expectations that are derived from prior knowledge or experience. Predictive coding is a formalisation of how top-down generative expectations of the current state of the world are updated based on bottom-up prediction errors. The inferior frontal gyrus (IFG) is the core frontal language hub that projects to key peri-Sylvian regions involved in auditory pattern analysis and is the core region that degenerates in nfvPPA (Rohrer *et al.*, 2009; Seeley *et al.*, 2009; Grube *et al.*, 2016; Cope *et al.*, 2017, Hardy *et al.*, 2017a; Spinelli *et al.*, 2017; Henry *et al.*, 2018; Lombardi *et al.*, 2021). The key mechanism is therefore likely to be impaired auditory

pattern analysis in peri-Sylvian and connected prefrontal regions (principally IFG) that govern expectations about incoming sensory traffic ((Cope *et al.*, 2017, Hardy *et al.*, 2017a, b), Figure 1.3 and Table 1.1).

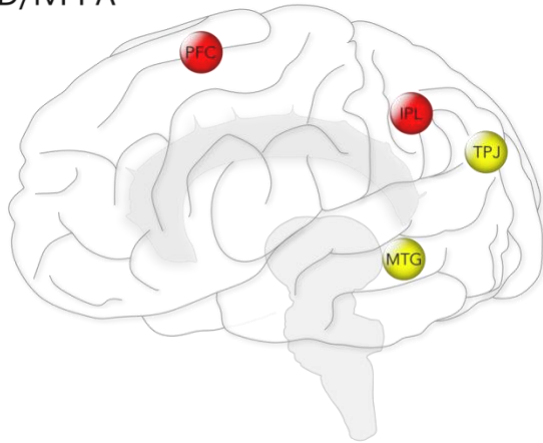
#### 1.4.2.2 Semantic variant primary progressive aphasia

In the semantic variant of primary progressive aphasia (svPPA), degeneration of the dominant anterior temporal lobe (ATL) destroys semantic knowledge (the general store of information about the world) resulting in anomia, with accompanying loss of object knowledge and impaired single-word comprehension, as well as ‘surface dyslexia’ (whereby irregular sounding words such as ‘yacht’ or ‘chaos’ are mispronounced). Speech production and repetition are spared (Gorno-Tempini *et al.*, 2011, Johnson *et al.*, 2021b). In contrast to nvPPA, svPPA typically spares elementary auditory pattern perception and auditory features are not defined in the diagnostic criteria for this syndrome. However, degraded semantic analysis of environmental sounds, voices and affective auditory signals have been described (Bozeat *et al.*, 2000, Goll *et al.*, 2010a, 2012b; Hailstone *et al.*, 2011; Fletcher *et al.*, 2015, Golden *et al.*, 2015b; Muhammed *et al.*, 2018). This profile reflects selective degeneration and functional reorganisation of the antero-medial temporal lobe (Figure 1.3 and Table 1.1) and its connections, including orbitofrontal cortices and auditory thalamus.

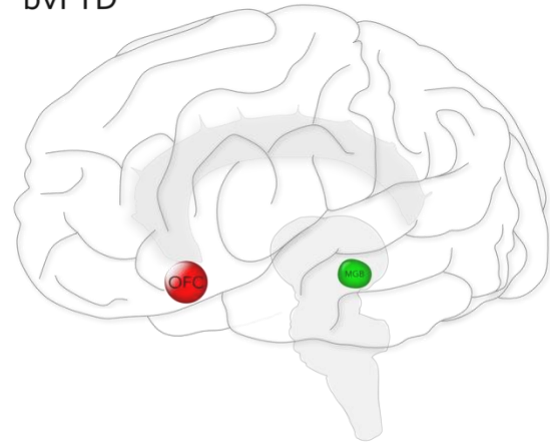
#### 1.4.2.3 Behavioural variant frontotemporal dementia

In the behavioural variant of frontotemporal dementia (bvFTD), the core clinical features are of progressive behavioural change, with abnormalities of social and emotional awareness and reactivity for which the patient lacks insight (Rascovsky *et al.*, 2011, Johnson *et al.*, 2021b). Although the core diagnostic features reflect behavioural change, inappropriate emotional reactions to voices, environmental sounds and music are often prominent (Omar *et al.*, 2011; Fletcher *et al.*, 2015): these are likely to be driven by impaired valuation and regularity decoding in complex auditory environments, linked to dysfunction of fronto-limbic and fronto-subcortical (Figure 1.3 and Table 1.1) neural circuits mediating reward and rule processing (Clark *et al.*, 2017, 2018).

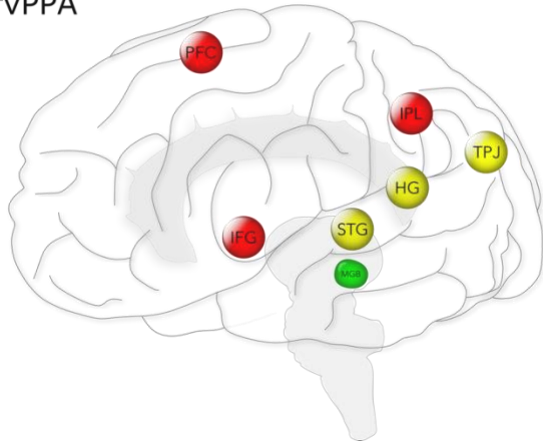
AD/lvPPA



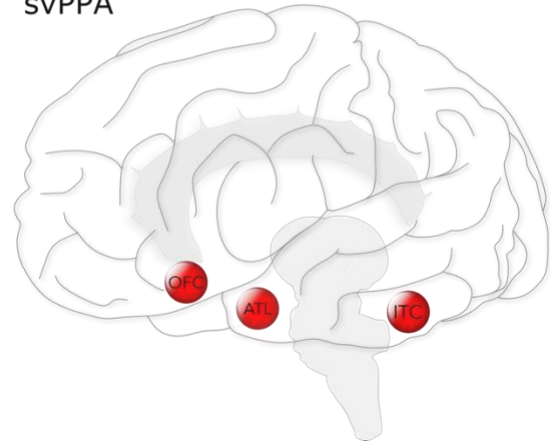
bvFTD



nfvPPA



svPPA



**Figure 1.3 Auditory brain networks across neurodegenerative diseases**

Key components of the brain networks implicated in hearing that are also predominantly targeted in representative neurodegenerative proteinopathies. These patterns of brain degeneration anticipate the differential involvement of particular auditory functions and therefore distinctive functional hearing profiles or ‘auditory phenotypes’ of these disorders (see text and table 1.1). Although the neuroanatomical patterns shown correspond to the distribution of most severe regional brain atrophy in each disease, dysfunction predates atrophy and additional connected brain regions may also be implicated in the pathogenesis of auditory symptoms. **AD**, typical Alzheimer’s disease; **lvPPA**, logopenic variant primary progressive aphasia; **nfvPPA**, nonfluent-agrammatic variant primary progressive aphasia; **svPPA**, semantic variant primary progressive aphasia.

Table 1.1 Auditory phenotypes of some major dementia syndromes

Syndrome	Core clinical features	Key auditory symptoms	Auditory deficits <sup>a</sup>	Proposed auditory diagnostic test <sup>b</sup>	Pathological neuroanatomy <sup>c</sup>
<b>AD</b>					
<b>Typical</b>	Episodic / topographical memory loss, parietal deficits	Difficulty tracking sound sources / information in busy acoustic environments, auditory disorientation, difficulty understanding less familiar accents, auditory agnosia, increased sound sensitivity	Scene analysis, localisation, attention, melody contour, accents, environmental sound recognition, working memory	Auditory stream separation, sound localisation / motion detection <sup>h</sup> , DLT <sup>1,2,3,4</sup>	Posterior cingulate, precuneus, lateral temporo-parietal cortex
<b>lvPPA<sup>d</sup></b>	Anomia, phonological and verbal working memory deficits	Similar to typical AD, more prominent derangement of phonemic processing	Phoneme perception, prosody perception, phonological working memory	Phoneme discrimination <sup>5i</sup>	Lateral temporo-parietal cortex
<b>FTD</b>					
<b>nvPPA</b>	Speech production deficits, agrammatism	Agnosia for environmental sounds / accents, word deafness <sup>e</sup>	Pure tone detection, perception of pitch interval / timbre / rhythm / prosody, accent comprehension	Temporal pattern discrimination <sup>6</sup>	Peri-Sylvian networks, prefrontal cortex

<b>svPPA</b>	Anomia and vocabulary loss, visual agnosias, behavioural changes similar to bvFTD	Musicophilia / sound aversion <sup>f</sup> , tinnitus, phonagnosia / nonverbal sound agnosia	Environmental sound / voice recognition, emotional recognition / reactivity, hedonic valuation, integration of semantic / affective information	Environmental sound recognition <sup>7</sup>	Auditory / multimodal association cortex in anterior temporal lobe, orbitofrontal cortex, insula
<b>bvFTD</b>	Socio-emotional, executive dysfunction with disinhibition, apathy, loss of empathy, obsessions and rituals, dietary and other behavioural abnormalities	Sound aversion / musicophilia <sup>f</sup> , phonagnosia <sup>g</sup>	Emotional recognition / reactivity, hedonic valuation, voice recognition <sup>e</sup> , integration of semantic / affective information	Vocal emotion recognition <sup>8</sup>	Auditory / multimodal association cortex in anterior temporal lobe, orbitofrontal cortex, insula, anterior cingulate, striatal circuits

The table summarises major clinical features, and auditory cognitive deficits, candidate auditory cognitive tests for early diagnosis and neuroanatomical associations in canonical dementia syndromes for which adequate data are available (see also Figure 1.3). Key: **a**, auditory domains affected based on behavioural test performance; **b**, based currently on experimental studies (examples referenced below) with a view (particularly for AD) to potential scalability, e.g., online administration - but provisional and require further clinical validation; **c**, major distribution of pathological changes in brain networks relevant to auditory deficits, as assessed using voxel-based morphometry, functional neuroimaging (chiefly fMRI) and/or post mortem material; **d**, underpinned by Alzheimer pathology in majority of cases; **e**, not usually severe; **f**, associated with altered autonomic responses to sound; **g**, particularly associated with right temporal lobe atrophy; **h**, can be delivered via headphones using virtual space stimuli; **i**, other auditory abnormalities analogous to typical AD; **AD**, Alzheimer's disease; **bvFTD**, behavioural variant frontotemporal dementia; **DLT**, dichotic listening test; **FTD**, frontotemporal dementia; **lvPPA**, logopenic variant of primary progressive aphasia; **nfvPPA**, nonfluent variant primary progressive aphasia; **svPPA**, semantic variant primary progressive aphasia. Examples of experimental studies employing proposed tests: 1, (Goll *et al.*, 2012a); 2, (Golden *et al.*, 2015c); 3, (Tuwaig *et al.*,



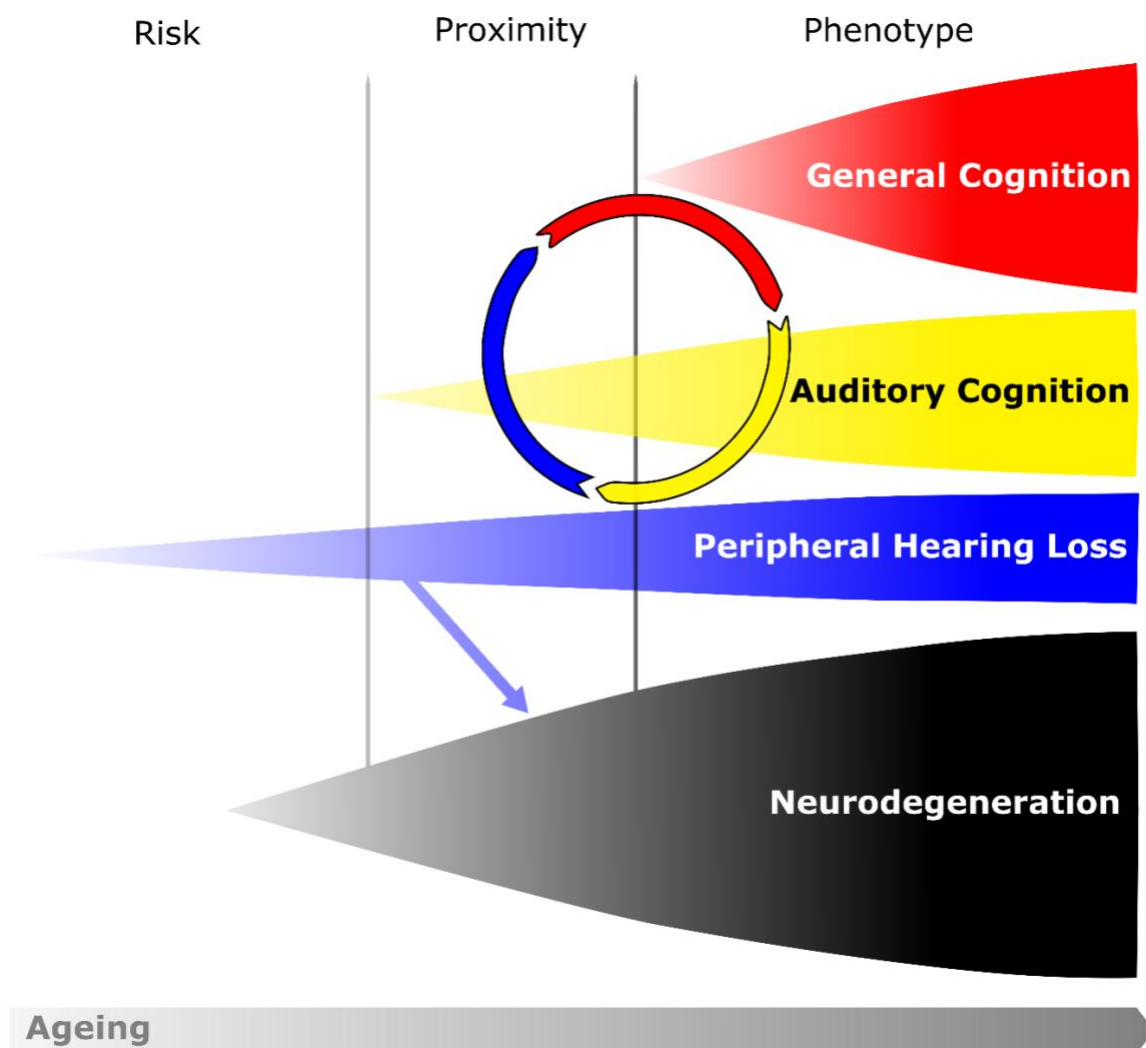
2017); 4, (Gates *et al.*, 2011); 5, (Johnson *et al.*, 2020); 6, (Grube *et al.*, 2016); 7, (Golden *et al.*, 2015b); 8, (Omar *et al.*, 2011).

## 1.5 Hearing impairment: cause, canary or corollary of dementia?

Alzheimer's disease has been the major focus of epidemiological studies assessing the risk of developing dementia in association with hearing loss (though the distinction from cerebrovascular and other pathologies is problematic (Lin *et al.*, 2011; Taljaard *et al.*, 2016; Livingston *et al.*, 2017; Loughrey *et al.*, 2018)). Several potential mechanisms have been proposed such as a common pathological substrate (e.g. vascular disease), hearing loss induced brain structural changes that increase the risk of neurodegeneration via cellular effects such as oxidative stress, altered gene expression (Frenzilli *et al.*, 2017; Park *et al.*, 2018) or changes in neural circuit function (Oxtoby *et al.*, 2017; Bidelman *et al.*, 2019a) and cognitive impairment through monopolisation of general cognitive mechanisms that would otherwise be deployed elsewhere (Wayne and Johnsrude, 2015; Griffiths *et al.*, 2020). Recently, a more specific interaction between changes in neural mechanisms important to auditory pattern analysis in the mesial temporal lobe (MTL) and AD pathology has been proposed. Three potential interactions are outlined in this model: first, neuronal overactivity could propitiate the accumulation and spread of AD pathology, second, synaptic changes secondary to AD pathology might be excitotoxic and third, hearing loss induces changes in gamma oscillatory activity in the MTL that exacerbates amyloid deposition in the hippocampus (Griffiths *et al.*, 2020). However, a direct causal effect has not been established: for example, peripheral hearing function was not associated with brain amyloid deposition (a relatively specific preclinical marker of AD) in a large cohort of cognitively healthy older people (Parker *et al.*, 2020) and such an effect would still not account for the majority of cases of dementia with hearing alterations. Additionally, recent work examining the association between age-related hearing loss and structural neuroimaging features of brain age did not show any significant correlation between brain age and untreated mild to moderate hearing loss (Rosemann and Thiel, 2021).

Whilst the possibility of a direct causal relation between hearing loss and neurodegeneration remains an open question, it is important to note that impoverished sensory fidelity due to peripheral hearing loss or disturbed subcortical auditory trafficking will potentially have effects both on auditory cognition and more general cognitive functions such as attention, executive processing and perceptual learning (Wayne and Johnsrude, 2015; Pichora-Fuller *et al.*, 2016; Dryden *et al.*, 2017; Pelle, 2018; Griffiths *et al.*, 2020; Heinrich *et al.*, 2020). The balance of these is likely to depend on an interaction between the specific stimulus and task demands with the underlying network phenotype of the neurodegenerative process(es) involved. These observations are not incompatible with a more direct effect of hearing loss as a driver of neurodegeneration. Indeed, hearing impairment might constitute a facilitating cause of neurodegenerative disease evolution, an early-warning 'canary' for impending cognitive disaster or an accompaniment of established dementia: these non-exclusive scenarios would have mutually reinforcing implications for auditory brain function.

Based on my review of the emerging literature, I suggest that alterations in ‘central’ hearing or auditory cognition may constitute an early warning signal of incipient dementia, due to the computational demands imposed by listening in challenging everyday acoustic environments. In support of this idea, predominantly central auditory deficits (involving, for example, dichotic listening) have been shown to predict CSF tau levels and regional atrophy profiles consistent with AD pathology in cross-sectional studies (Tuwaig *et al.*, 2017) and longitudinal development of a clinical syndrome compatible with AD (Gates *et al.*, 2011), while large genetic and neuropathological surveys have suggested changes in hearing (in particular, speech-in-noise perception) may be a preclinical marker of neurodegeneration (Brenowitz *et al.*, 2020*b, a*). I emphasise however, that deficits of peripheral and central hearing and more general cognitive functions are likely to interact strongly, with considerable potential for ‘vicious cycling’.



**Figure 1.4 A pathophysiological synthesis of hearing impairment and dementia**

This figure schematises proposed relations between development of peripheral hearing loss (blue), changes in auditory cognition (gold) and general cognitive function (red) and underlying neurodegeneration (black), based on emerging epidemiological and pathophysiological evidence. Hearing loss can be considered a potential causal risk factor for cognitive decline (Risk), a proximity marker for incipient dementia (Proximity) or a feature of the established dementia syndrome (Phenotype), according to the time window in which it occurs; the mechanisms of these effects are distinct but likely to be inter-dependent.

## 1.6 Rationale and hypotheses of this thesis

### 1.6.1 Motivations for the work in this thesis

The balance of neuroanatomical, physiological and clinical evidence suggests that the auditory brain plays a key role in the increasingly well documented association between dementia and hearing impairment. Degeneration of central auditory processing mechanisms (in particular, auditory cognitive dysfunction) will tend to amplify any degree of peripheral deafness and reduce compensatory capacity under natural (noisy) listening conditions. This reflects the extensive reciprocal interplay between afferent and efferent auditory processing pathways, making them exquisitely vulnerable to neurodegenerative proteinopathies. Moreover, neurodegenerative pathologies have distinct and relatively specific auditory cognitive phenotypes as well as generic effects on cognitive functions relevant to hearing, in line with the large-scale neural network signatures of these diseases. However, how peripheral hearing function relates to auditory and more general cognitive functions in dementia has not been established. This remains a key unresolved issue with important neurobiological and clinical implications.

Neurobiologically, central auditory dysfunction is likely to be a fundamental, early consequence of neurodegenerative dementias, due both to direct involvement of susceptible auditory processing networks by pathogenic protein spread and remote effects on highly interconnected structures. Diagnostically, hearing impairment might plausibly constitute a proximity marker for incipient cognitive decline and dementia, reflecting the heavy computational demands that auditory signal processing imposes on failing neural circuits. Logically, however, it is first necessary to determine auditory signatures of established clinical dementia diseases, before candidate early auditory markers of those diseases can be derived. This in turn will require a head-to-head comparison between diseases using a systematic battery of auditory cognitive tests. Developing a test battery to quantify the relative contributions of peripheral and central auditory deficits would allow accurate characterisation of auditory phenotypes in individual patients and could facilitate diagnosis of particular neurodegenerative pathologies (see Table 1.1). The available evidence suggests that tests that index degraded speech processing may be key components of such a battery, reflecting both the ready manipulability of spectral and temporal features of speech and the fundamental importance of speech perception under often challenging listening conditions to everyday communication.

With a view to clinical management, it will be crucial to capture the real-world impact of central hearing impairment, which is likely to be more profound than would be predicted by the degree of any peripheral hearing loss. Management approaches that focus solely on peripheral sound amplification are therefore likely to be of limited efficacy for improving hearing function in dementia. There is a clear

practical and pathophysiological motivation to address any potentially reversible component of peripheral hearing loss and ensuring compliance with hearing aids (Proctor *et al.*, 2020). Ultimately, however, the goal of management should be to minimise hearing-related disability in the complex listening environments of daily life – to treat the patient, not the audiogram or the neuropsychological test score. Personalised interventions directed to central auditory mechanisms such as ‘smart’ hearing aids (Koohi *et al.*, 2017), hearing-based behavioural therapies and auditory cognitive rehabilitation (Russo *et al.*, 2005) should be combined with education and environmental modification supported by a detailed assessment of functional disability. Pharmacological modulation of cholinergic and dopaminergic function to harness auditory plasticity has shown early promise in AD (Dhanjal *et al.*, 2013, Hardy *et al.*, 2017c): such approaches could herald a new era of physiologically informed, integrated management focussing on retained capacity rather than deficits and embracing both central and peripheral auditory impairment in dementia. Key first steps toward this goal will be to identify instruments that can capture daily life hearing symptoms sensitively and reliably in cognitively impaired people and the overall impact of such symptoms on the burden of care; and to assess how well such instruments correlate with candidate auditory cognitive tests that could serve as proxies for daily life hearing function.

### 1.6.2 Key aims and experimental hypotheses

Motivated by these unresolved issues around the relations between cognitive decline and hearing function in neurodegenerative pathologies, the overarching rationale for this thesis is to explore auditory cognitive function in AD and FTD syndromes using a range of auditory tests that target different aspects of the auditory hierarchy, with three core aims:

1. Explore the nature of the causal relationship between raised audiometric thresholds and dementia
2. Examine how canonical dementia syndromes drive specific auditory phenotypes and assess the potential of specific auditory cognitive tests (in particular, tests based on degraded speech processing) as functional biomarkers of disease
3. Capture the real-world consequences of auditory cognitive deficits and how they correlate with auditory cognitive tests

I have addressed these broad aims in four separate experiments, each with an overarching motivating question, specific aims and hypotheses, as summarised below.

### 1.6.2.1 Chapter 3: Pure tone audiometry

Question: What is the nature of the relationship between pure tone audiometric thresholds and auditory cognitive dysfunction?

Aims:

1. Measure and describe audiometric performance across canonical dementia syndromes in comparison to healthy older control participants
2. Assess the impact of general cognitive factors on audiometric thresholds
3. Explore how a measure of 'central hearing' (dichotic listening) interacts with audiometric performance

Hypotheses:

- Audiometric thresholds in nvPPA and to a lesser extent AD are raised in comparison to svPPA, bvFTD and healthy control participants
- Specific auditory cognitive measures will be correlated with audiometric performance
- Central hearing ability will account for a degree of the differences in audiometric thresholds, particularly in nvPPA participants

### 1.6.2.2 Chapter 4: Speech perception tests in dementia

Question: Are degraded speech tests more sensitive tests of auditory cognitive dysfunction than audiometric threshold and how specific are they?

Aims:

1. Measure performance on degraded speech tests across canonical dementia syndromes
2. Compare performance between novel and standard degraded speech tests
3. Make a preliminary assessment of the potential of degraded speech tests as sensitive and specific physiological biomarkers of neurodegenerative diseases

Hypotheses:

- Patients with dementia will perform significantly worse than healthy control participants on degraded speech tests, with nvPPA patients the most affected and patients with AD the least affected

- Novel tests that capture auditory cortical function will outperform standard degraded speech tests
- Degraded speech tests will be sensitive tests of auditory cognitive dysfunction, with a degree of syndromic specificity, particularly for patients with nvPPA

#### 1.6.2.3 Chapter 5: Phonological processing in dementia

Question: Are bespoke auditory cognitive tests effective as syndrome specific diagnostic tests?

Aims:

1. Assessment of phonological processing across the primary progressive aphasia and AD
2. Explore the syndromic specificity of a test of phonological processing as an auditory diagnostic tool in dementia

Hypotheses:

- Patients with lvPPA and to a lesser degree AD, will be significantly impaired on a phonemic discrimination task compared with healthy control participants and participants with svPPA and nvPPA
- Phonological processing is a syndrome specific auditory cognitive test that demonstrates the principle of using behavioural auditory cognitive tests as diagnostic tools and functional biomarkers

#### 1.6.2.4 Chapter 6: Auditory symptoms, disability and handicap in dementia

Question: How well do auditory symptom questionnaires capture real-world listening ability and carer burden?

Aims:

1. Assess real-world auditory function, disability and handicap across canonical dementia syndromes using an auditory symptom questionnaire suitable for administration to patients' carers.
2. Correlate real-world auditory symptoms with pure tone audiometric thresholds and the various degraded speech measures explored in chapter 4
3. Assess carer burden as frequent communication partners of people with dementia using a quality-of-life questionnaire
4. Measure the prevalence of hyperacusis across dementia syndromes using a hyperacusis questionnaire

Hypotheses:



- Dementia syndromes are associated with significant auditory disability and handicap that can be captured with auditory symptom questionnaires, with nvPPA patients showing the most severe disability and handicap
- Pure tone audiometry is a poor predictor of real-world hearing function will be weak, with degraded speech tests showing stronger correlations
- Carer burden will be significantly increased by frequent communication with dementia patients, with the greatest burden in carers for patients with nvPPA
- Hyperacusis will be more prevalent in patients with dementia, with patients with svPPA and AD being more severely affected.

## 2 Overview of methods

### 2.1 General considerations

The experiments presented in this thesis are a series of case-control studies that aimed to explore the core aims laid out in section 1.6.2 in the general introduction to this thesis. Experimental design and analytical approach were governed in part by group sizes, which were small. This was due to a combination of disease rarity (in the case of FTD syndromes), the difficulty of recruiting dementia participants to research studies (all dementia subtypes) and the duration of the PhD fellowship (3 years), as well as the unanticipated effect of the COVID-19 pandemic, which stopped recruitment 1 year earlier than originally planned. As such, multivariate approaches that might test the effects of group, sex and cognitive tests on hearing thresholds and complex-sound perceptual measures would be inappropriate given the large number of potential independent variables. With this in mind, general demographic and neuropsychological measures are presented to give an overview of the group profiles of study participants (Table 3.1), with specific demographic and neuropsychological scores incorporated into analyses based on a priori assumptions about potential nuisance confounds. Overall, this work should be regarded as preliminary, with an eye to the design of future larger scale studies that would offer greater statistical stability.

### 2.2 Recruitment and consent

Patients were recruited during an 18-month period between 2018 and 2020, principally from the Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, with a minority through direct referral to the research programme by external clinicians. Healthy older control participants were recruited from a local database of volunteers aged between 50 and 80. Ethics approval for all studies included was granted by the UCL/UCLH Research Ethics Committees and all participants gave informed consent in accordance with the Declaration of Helsinki (Study title: Brain signatures of auditory information processing in the degenerative dementias; Reference number: 06/Q0512/52; Approval granted 06/07/2006 and Study title: Longitudinal investigation of FTD and associated disorders (LIFTD); Reference number: 16/LO/0465; Approval granted 05/05/2016).

### 2.3 Diagnostic groupings

All subjects underwent detailed clinical assessment and volumetric T1 MR imaging, allowing correlation with the current consensus diagnostic criteria for Alzheimer's disease and related syndromes (Dubois *et al.*, 2014), canonical FTD syndromes and PPA accordingly (Gorno-Tempini *et al.*, 2011) (Rascovsky *et al.*, 2011), as well confirmation of the absence of other neurodegenerative disease(s) and to exclude any participants with significant vascular burden. Patients were included if they met the diagnostic criteria for probable AD (see appendix, table 2.1, (Dubois *et al.*, 2007)), "probable bvFTD" (see appendix,

table 2.2, (Rascovsky *et al.*, 2011)) or “imaging-supported” PPA (see appendix, table 2.3, (Gorno-Tempini *et al.*, 2011)), i.e. all syndromic cases were supported by appropriate brain imaging findings. FTD patients with genetic mutations had ‘definite’ FTD pathology. Where patients exhibited behavioural and language impairment, a combination of the ‘dominant’ clinical feature(s) and regional brain atrophy profile were used to assign a relevant grouping of bvFTD, svPPA, nvPPA or lvPPA. Patients presenting with behavioural features, but without evidence of relevant cerebral atrophy were excluded as possible bvFTD ‘phenocopies’ (i.e., behavioural change not related to proteinopathy driven neurodegeneration). Applying these criteria, it is anticipated that the majority of the included patients will have AD or FTD spectrum pathology at post-mortem (Perry *et al.*, 2017; Spinelli *et al.*, 2017). Five out of ten of the AD patients included in this study had positive AD biomarkers (3 CSF, 2 Amyloid-PET); CSF positivity was based on a total tau:beta-amyloid 1-42 ratio of  $> 1.0$  or a beta-amyloid 1-42/1-40 ratio of  $< 0.065$ . None of the patients in the AD group in whom they were measured had negative AD biomarkers. In the bvFTD group, four patients had C9 open reading-frame 72 (*C9orf72*) mutations, one patient had a microtubule-associated protein tau (*MAPT*) mutation and one patient had a progranulin (*GRN*) mutation. A number of visual rating scales for the radiological assessment and classification of cerebral white matter and cerebrovascular disease have been developed over the years, but their detailed use was beyond the scope of this work (Wardlaw *et al.*, 2013; Wahlund *et al.*, 2017). To reduce the potential confound of severe cerebrovascular disease, T2 FLAIR sequences were visually inspected for each participant and if there was extensive white matter disease they were excluded from the study.

## 2.4 Clinical assessment

Clinical assessment was performed with both patient and informant to provide reliable collateral information. Detailed demographic information was recorded including age, gender, handedness and education history, as well as family history of neurodegenerative disease. Age at clinical onset was estimated based on caregiver timing of first symptom onset. A comprehensive clinical assessment covered the following domains: behavioural, neuropsychiatric, linguistic, cognitive, motor, autonomic and ‘other’ symptoms (auditory, time and visual perception). Past and current medical history including active medications were also recorded. Neurological examination for evidence of amyotrophic lateral sclerosis, Parkinsonism and ‘Parkinson Plus’ features was performed. Bedside cognitive and linguistic assessment incorporating the Queen Square Screening Test for Cognitive Deficits and the Mini Mental State Examination (MMSE) were also included (Folstein *et al.*, 1975). All participants donated blood to screen for 18 previously identified disease-causing genetic mutations (Beck *et al.*, 2014). Where available, in vivo diagnosis of Alzheimer’s disease was confirmed using cerebrospinal fluid biomarkers (Ewers *et al.*, 2015) or amyloid-PET imaging (Mosconi *et al.*, 2010; Morris *et al.*, 2016).

## 2.5 Neuropsychological assessment

Detailed neuropsychological assessment by a trained research psychologist was completed with all patients. Standardised tests of general intellectual level and domain-specific cognitive performance were assessed as per Table 2.1. Test results were used to corroborate clinical and neuroimaging based syndromic categorization. In experiments weighted towards domain-specific performance, test scores were used as covariates during analysis as described in the relevant experimental chapters, e.g., forward digit span and working memory, or British Picture Vocabulary for semantic knowledge.

**Table 2.1 List of neuropsychological tests performed by all participants**

Tests by cognitive domain	Reference
<b>General Intellect</b>	
WASI Performance IQ	Weschler (1981)
WASI Verbal IQ	Weschler (1981)
National Adult Reading Test (NART)	Nelson (1982)
<b>Executive Function</b>	
WASI Block Design	Weschler (1997)
WASI Matrices	Weschler (1997)
Fluency – Letter and Category (Animals)	In-house Test
Trails Making Test (A & B)	Tombaugh (2004)
D-KEFS Colour-Word Interference Test	Delis, Kaplan and Kramer (2001)
<b>Working Memory</b>	
Digit Span Forward	Weschler (1987)
Digit Span Reverse	Weschler (1997)
Spatial Span Forward	Weschler (1987)
<b>Episodic Memory</b>	
Recognition Memory Test for Words	Warrington (1984)
Recognition Memory Test for Faces	Warrington (1984)
Camden Paired Associates Learning	Warrington (1996)
<b>Auditory Input Processing</b>	
PALPA-3	Kay et al. (1992)
<b>Naming</b>	
Graded Naming Test	Mckenna and Warrington (1980)
Boston Naming Test	Kaplan et al. (1983)
WASI Vocabulary	Weschler (1997)
<b>Language Comprehension</b>	
British Picture Vocabulary Test	Dunn & Whetton (1982)
Concrete Synonyms	Warrington et al. (1998)

Abstract Synonyms PALPA-55	Warrington et al. (1998) Kay et al. (1992)
<b>Speech Repetition</b>	
Word Repetition Graded Sentences	McCarthy and Warrington (1984) McCarthy and Warrington (1984)
<b>Other functions</b>	
Graded Difficulty Arithmetic Visual Object and Space Perception Task (VOSP)	Jackson and Warrington (1986) Warrington and James (1991)

## 2.6 Peripheral hearing assessment

### 2.6.1 Pure tone audiometry

We followed the British Society of Audiology (BSA) recommended procedure for pure-tone audiometry as per the 2018 guideline (BSA, 2018), using the dual-channel GSI Audiostar Pro (*GSI AUDIOSTAR PRO™ USER MANUAL*, 2013) audiometer. The BSA procedure is covered in more detail in chapter 3. All participants were tested in the same room, with an average ambient sound-level of 37 dB as measured via a calibrated, RadioShack Digital Sound Level Meter (CAT.NO.: 3300099). BSA guidelines for PTA suggest an ambient noise cut-off of 35 dB or less (BSA, 2018); to neutralize the +2 dB above recommended testing threshold in our room, all testing was performed via the GSI Audiostar Pro headphones with noise-reducing ear-cups calibrated and provided by the supplier.

### 2.6.2 Speech intelligibility index

The speech intelligibility index (SII) is a quantification of the proportion of information in the speech signal that is both audible and usable for the listener and is derived from the individuals pure tone audiogram. It is expressed as an index ranging between 0.0 and 1.0, with 1.0 representing full audibility and usability and 0.0 representing no audibility or usability. In general, SII and speech understanding have a monotonic relationship, however the SII is not a direct measure of intelligibility, but rather, the available information in a given setting (background listening conditions, individual hearing sensitivity, etc., (Rhebergen *et al.*, 2010)).

The GSI Audiostar Pro (*GSI AUDIOSTAR PRO™ USER MANUAL*, 2013) has an in-built function that automatically calculates the SII for each ear after adjusting for hearing threshold. Groupwise average SII was included as a covariate in the analysis of speech tests as a more functionally relevant and nuanced measure of the effect of peripheral hearing loss on speech test scores than pure tone audiometry.

## 2.7 Auditory stimulus presentation and experimental recording

### 2.7.1 Auditory stimuli

Test selection for inclusion in the experimental work in this thesis was predicated on the idea of sampling various stages and functions of the auditory hierarchy. A large number of previously used tests were considered, including tests of scene parsing, spatial processing, auditory attention, pitch and temporal analysis, object-level processing, semantic identification, emotion recognition and social recognition. Final selections were based on specific hypotheses about which tests were likely to best index various auditory cognitive functions as well as the predicted auditory cognitive characteristics of the various dementia syndromes represented in the experimental work. Three novel degraded speech tests were also created with a particular view to their potential as auditory cognitive ‘stress tests’, due to their heavy neurocomputational demands and the ease with which difficulty can be manipulated. These were piloted amongst healthy volunteers to explore task validity, floor and ceiling effects and appropriate paradigm design.

All stimulus manipulation was performed using Audacity®, Version 2.2.3. Detailed description of stimulus creation is given in chapter 4. All stimuli were stored as WAV files with a sample(Gorno-Tempini *et al.*, 2011, Johnson *et al.*, 2021b) rate of 44100Hz and 16-bit resolution. Within each test, sounds were matched for mean intensity (root-mean-square) over trials. All stimuli were presented binaurally using the dual-channel GSI Audiostar Pro (*GSI AUDIOSTAR PRO™ USER MANUAL*, 2013) audiometer at +50dB HL above the measured air conduction threshold average at each ear, as per convention; patients were given the opportunity to adjust the presentation level according to comfort if desired and the new presentation level was recorded. Testing was undertaken in the same room used for pure-tone audiometry described above. External stimuli were played from a MacBook Pro™ (2015 edition), using the inbuilt sound card and the Audio Stream Input/Output (ASIO) driver protocol for low-latency, high-fidelity interface. The MacBook Pro™ – GSI Audiostar Pro™ connection was via high-fidelity gold hardware cable.

#### **Dichotic digits test and Gaps-in-Noise**

Stimuli for the dichotic digits test (DDT) and the Gaps-in-Noise (GIN) test were taken from the original tests developed by Musiek *et al* (Musiek, 1983; Musiek *et al.*, 1991, 2005). Word lists for the Speech-in-Babble test (SiB) and were taken from Rosen *et al* (Rosen *et al.*, 2013), and provided with permission from Prof Doris-Eva Bamiou.

#### **Speech-in-Babble and Time-Compressed Speech (monosyllable)**

Speech in Babble (SiB) and time-Compressed Speech (monosyllable) both used pre-recorded, phonemically and phonetically balanced, consonant-vowel-consonant word lists previously recorded on compact disc and supplied to the Dementia Research Centre (DRC), by Professor Doris-Eva Bamiou, UCL (Bamiou *et al.*, 2015; Spyridakou *et al.*, 2020).

### **Spectrally filtered speech and Time-Compressed Speech (spondee)**

The same spondee word list was used for the spectrally filtered speech and time-compressed speech (spondee) tests. The word list was recorded by a male with a native Standard Southern English accent, using neutral intonation to reduce variance from prosodic cues. The words were recorded at the UCL Language and Cognition Department in a sound-proof booth, using a condensing microphone with a pop-shield to reduce sibilant artifact. Samples were recorded using the audio software platform Audacity®, Version 2.2.3.

#### **2.7.2 Experimental recording**

Pure tone audiometry and SII results were transcribed directly from the audiometer display with pen and paper and then transferred to Excel™. The DDT described in chapter 3 and each experiment described in chapter 4 were built using Experiment Builder™ version 2.3. The DTT and GIN stimuli were presented in a non-randomised fashion following their original recordings, with the participant asked to give the correct numerical response verbally, by finger count, by pointing to a number chart or writing the response as they preferred. Patients were familiarized with each experiment using practice examples prior to scoring responses. The spectrally filtered speech, time compressed speech tests and SiB test stimuli were delivered in a randomized '1-up, 1-down staircase' automatically terminating once average performance over the previous 8 trials was 0.5 (50%), i.e., chance levels. Participants were asked to either repeat the word they heard, or they could write their response if preferred/necessary (spelling errors were not penalised). All responses were inputted by me in real-time to reduce operator errors and no time limits were imposed. Results were outputted as a simple text file by Experiment Builder, before being tabulated in Excel prior to analysis in STATA 16™. For every participant, tests were presented in the same order: pure tone audiometry, GIN, DDT, spectrally filtered speech, time-compressed speech (mono), time-compressed speech (spondee) and SiB.

### **2.8 Auditory symptom questionnaires**

Auditory symptoms in dementia are typically poorly recognized by both patients and clinicians although they are present in many dementia syndromes (Hardy *et al.*, 2016). To better characterize and attempt to quantify auditory symptoms, disability and handicap in dementia, I administered the Modified Amsterdam Inventory for Auditory Disability and Handicap (Kramer *et al.*, 1995; Meijer *et al.*, 2003; Bamiou *et al.*, 2015). Caregiver burden was assessed using the Hearing in Significant Other Impact Scale

(Preminger and Meeks, 2012). The Hyperacusis Questionnaire (Khalifa *et al.*, 2002) was used to characterise symptoms of hyperacusis. Questionnaire selection was based on previous validation, any prior use in patients with auditory cognitive dysfunction and ease of use. Detailed descriptions of these questionnaires, the rationale for their choice and how they were administered are presented in chapter 6.

## 2.9 Structural brain imaging

For each participant visit, a sagittal 3-D magnetization-prepared rapid-gradient echo (MPRAGE) T1-weighted volumetric brain MR sequence (TE/TR/TI 2.9/2200/900 ms, dimensions 256 x 256 x 208, voxel volume of 1.1 x 1.1 x 1.1 mm) was acquired on a Siemens Prisma 3T MRI scanner using a 32-channel phased array head-coil. Structural scans were entered into a voxel-based morphometry analysis to assess the relationship between grey matter atrophy and performance on specific experimental tasks and to exclude any participants with significant vascular disease.

## 2.10 Statistical analysis

Statistical analysis of behavioural data was performed using Stata 16® with an analysis pipeline created and saved as a do-file. Brain imaging analysis was run in MATLAB R2020b™ using the SPM12 toolbox (<http://www.fil.ion.ucl.ac.uk/spm/>).

For comparison of two independent categorical variables (e.g. disease group and gender), Fisher's exact test was preferred over the Chi-square test due to small *n* in this dataset. This is because Fisher's exact test gives an exact *p*-value, whereas the Chi-square gives an approximate *p*-value that becomes exact if the sample size is large enough. I used the general rule of *n* < 10 per cell in the two-way contingency table used to calculate either test as a prompt to use Fisher's exact test.

For comparison of categorical variables with numerical variables (e.g. disease group and test score) linear regression was used where assumptions of the general linear model (GLM) were satisfied, i.e. linearity, normality of the residuals, equality of variance (homoscedasticity) and fixed independent variables measured without error. Because there was no reason to suspect clustered sampling (i.e., sampling was actually random) and because measures were not repeated for any subjects (therefore obviating the possibility of autocorrelation), the final assumption is met on the basis of the experimental design. A summary of the model diagnostics used to test assumptions of the GLM is included in Table 2.2.

For each experiment included in this thesis I investigated (1) main effect of disease group (independent variable) on test score (dependent variable) and, where this result was significant (2) between group comparisons of disease group vs test score. Estimates of effect sizes for each regression analyses were



calculated using Eta-squared. Eta-squared measures the proportion of variation in the dependent variable that is associated with membership of different groups of the independent variable (or variables when multiple are used in which case the partial eta-squared is calculated). It is useful for comparing effect sizes within a study, but cannot easily be compared between studies, because the total variability in a given study is dependent on study design and increases with the number of variables manipulated. Cohen's *d* is another method for calculating standardised effect sizes that are comparable across studies, however, it cannot be used when there are more than two independent samples and therefore was not used (Lakens, 2013).

Adjustment for potential confounding factors was performed by including nuisance variables as covariates in the regression model. Covariates were considered for inclusion if there were significant group differences of the nuisance variable (e.g. age) and on their relevance to the experimental design, for example, if the task was felt to place a significant burden on working memory, then a test of working memory (e.g. digit span) was included as a covariate. The number of covariates was limited by the size of the dataset and therefore one covariate per minimum of 10 subjects was used based on common convention to avoid over-fitting the data. Details of specific regression models used in data analyses are presented in the relevant experimental chapters.

Where model diagnostics showed violation of assumptions for the GLM, the non-parametric Kruskal-Wallis test was used for comparison of two or more independent samples and Mann-Whitney U test for between group comparisons.

Correlational analyses were performed using either Pearson's correlation with two continuous variables (and where assumptions were met: related pairs of observations, absence of significant outliers and linearity), or Spearman's correlation when one or both variables were categorical and/or assumptions for Pearson's correlation were violated.

**Table 2.2 Summary of model diagnostics**

Model diagnostic	Test(s)
Outliers and Leverage	Stem plot of studentised residuals Leverage vs residual-squared plot
Normality of residuals	Q-Q plot Kernel density estimate Bootstrapping 1000 repeats with replacement Shapiro-Wilk test
Homoscedasticity	Residual vs fitted plot Cameron & Trivedi's decomposition of IM-test Breusch-Pagan/Cook-Weisberg test
Linearity	Two-way scatter plot (single predictor) Standardised residual vs predictor plots (multiple predictors) Augmented component-plus-residual plot (multiple predictors)
Collinearity	Variance inflation factor
Model specifications	Linktest (predictor vs squared predictor) Ramsey RESET test

This table summarises the statistical analyses undertaken to ensure that the assumptions of the GLM were met.

## 3 Pure tone audiometry and dementia

### 3.1. Chapter Summary

#### 3.1.1 Aims

- Measure and describe audiometric performance across canonical dementia syndromes in comparison to healthy older control participants
- Assess the impact of general cognitive factors on audiometric thresholds
- Explore how a measure of 'central hearing' (dichotic listening) interacts with audiometric performance

#### 3.1.2 Methods

- A total of 37 patients with FTD (svPPA, nvPPA and bvFTD) and AD were assessed with 15 healthy older patients acting as a control group
- Pure tone audiometry was assessed following the standardised protocol from the British Society for Audiology in a quiet room, with additional sound reduction via noise reducing headphones
- Dichotic listening ability was assessed using the Dichotic Digits Test
- Cognitive functions were recorded using the neuropsychological test battery laid out in the general methods, chapter 2

#### 3.1.3 Results

- Audiometric thresholds were significantly higher in patients with AD, nvPPA and bvFTD compared with patients with svPPA and healthy control participants
- Age was the most consistent and largest predictor of audiometric thresholds throughout the cohort
- There was a significant interaction between specific cognitive measures (dichotic digits test and MMSE) and audiometric performance
- Dichotic digits score showed the most significant interaction with audiometric thresholds, with near complete elimination of the significance of group as a predictor of audiometric thresholds

#### 3.1.4 Conclusion

- Age is the most significant predictor of baseline audiometric thresholds in patients with dementia

- Dichotic listening has a significant effect on audiometric thresholds, suggesting that auditory specific cognitive factors significantly modulate audiometric performance

## 3.2 Introduction

Pure tone audiometry (PTA) refers to the method of measuring the minimum detection threshold in decibels (dB) at specific frequencies, following the presentation of a pure tone of that frequency. It is a standardized procedure that has been in use clinically for more than 50 years, with minimal changes to testing methodology over time. As discussed in the general introduction to this thesis, there is accumulating evidence that audiometric thresholds are correlated with cognitive impairment and dementia and predict an increased risk of developing dementia when measured longitudinally in mid-life (Lin *et al.*, 2011; Gallacher *et al.*, 2012; Deal *et al.*, 2016; Taljaard *et al.*, 2016; Livingston *et al.*, 2017; Loughrey *et al.*, 2018). Importantly, these effects persisted after adjustment for multiple demographic and health factors that are known to be predictive of baseline audiometric thresholds (Kiely *et al.*, 2012; Linssen *et al.*, 2014).

### Hearing loss and neurodegeneration

How loss of hearing sensitivity might be causally related to the development of dementia is of critical importance as it has mechanistic, diagnostic and therapeutic implications and multiple potential mechanisms have been proposed (for reviews see (Wayne and Johnsrude, 2015; Griffiths *et al.*, 2020). Age is by far the strongest predictor of baseline audiometric performance (Linssen *et al.*, 2014) and it has been noted that age-related hearing loss and AD share many common risk factors that are typically regarded as proxies of vascular risk such as obesity, diabetes and hypertension (Swords *et al.*, 2018). Additionally, pure tone audiometry is commonly held predominantly to reflect cochlear function, with vascular changes in the cochlear considered to be a core driver of age-related hearing loss (Roth, 2015; Kurata *et al.*, 2016). Of note however, and contrary to historical views (Schuknecht, 1955; Schuknecht and Gacek, 1993), there is robust evidence that audiometric profiles are generally poor predictors of cochlear pathology (Landegger *et al.*, 2016). A significant challenge to the theory that vascular disease is the common pathologic mechanism underlying audiometric threshold increase and dementia is the persistence of the effect after adjusting for vascular risk factors, as well as the fact that the majority of dementia cases in published series have been diagnosed as having AD, rather than vascular dementia (Livingston *et al.*, 2017; Griffiths *et al.*, 2020).

Accumulation of amyloid-beta ( $A\beta$ ) and tau tangles are the hallmark of AD, but whilst AD related pathological changes have been described in various cortical and subcortical structures (including the cochlea in gene-enriched mouse models of AD (Lewis *et al.*, 1987; Sinha *et al.*, 1993; Parvizi *et al.*, 2001; Baloyannis *et al.*, 2009, 2011a; Griffiths *et al.*, 2020)), there is little evidence that it affects the cochlea in humans, with no significant differences in distortion product otoacoustic emissions in AD patients compared with controls (Gates *et al.*, 2010). Similarly, auditory brainstem responses in patients with

AD did not correlate with cognitive performance (Gates *et al.*, 2010). Moreover, data from 368 healthy control subjects in a UK longitudinal ageing study showed that while audiometric thresholds were weakly associated with lower primary auditory cortex thickness, they did not predict in vivo  $A\beta$  deposition (using amyloid-PET imaging), white matter hyperintensity volume, hippocampal volume or AD pattern cortical thickness (Parker *et al.*, 2020). This is especially difficult to explain given that the estimated time from amyloid-PET positivity to AD levels of deposition is estimated to be approximately 20 years (Villemagne *et al.*, 2013), as well as the fact that brain volume changes in hearing impaired individuals have been taken as a proxy of neurodegeneration (Lin *et al.*, 2014). It is interesting to note that in the study by Lin *et al.*, when individuals who developed dementia within only 6 years of assessment were excluded, results were approaching borderline statistical significance ( $p = 0.04$ , (Lin *et al.*, 2011)). Moreover, in the same study, when analysis was restricted to AD only cases, excess risk was 1.20 per 10dB hearing loss, but with a confidence interval that crossed 1 ([95% CI: 0.94 – 1.53], (Lin *et al.*, 2011)). Finally, the idea of a common pathological substrate is predicated in part on the specificity of the pure tone audiogram as a putative index of cochlear or auditory nerve function, but lesions from brainstem to auditory cortex may alter audiometric thresholds (though in comparison to the characteristic high-frequency hearing loss of auditory ageing, ‘central deafness’ is typically profound and with additional neurologic signs (Musiek *et al.*, 2007, 2017; Cope *et al.*, 2015)).

Two related concepts invoke shared cognitive, rather than pathological substrates for degeneration. The first mechanism is a kind of disuse atrophy from impoverished sensory input (“sensory deprivation model”), causing secondary structural and functional changes in the brain that increase the risk of developing dementia. Interestingly, recent work examining the association between age-related hearing loss and structural neuroimaging features of brain age did not show any significant correlation between brain age and untreated mild to moderate hearing loss (Rosemann and Thiel, 2021). The second mechanism posits that cognitive impairment is secondary to increased cognitive demand (“cognitive load model”, or sometimes referred to as ‘cognitive energy’), whereby cognitive ‘resources’ (such as attention or working memory) are monopolised by auditory processing demands, thereby producing cognitive impairment (Wayne and Johnsrude, 2015; Pichora-Fuller *et al.*, 2016; Peelle, 2018; Griffiths *et al.*, 2020; Heinrich *et al.*, 2020)). A critical and unanswered question remains how either of these mechanisms generate the specific pathologic and brain network changes observed in various dementias. The three prospective longitudinal studies of audiometric thresholds and incident dementia either failed to subclassify dementia diagnosis, or failed to subclassify the (sometimes not insubstantial) cases that were labelled as having dementia but not AD (Lin *et al.*, 2011; Gallacher *et al.*, 2012; Deal *et al.*, 2016). The proportion of dementia cases diagnosed with DLB (the commonest dementia subtype in older people after AD) increases significantly with specialist cognitive assessment (Vann Jones and

O'Brien, 2014) and although FTD is disproportionately prevalent in very young onset dementia, the overall prevalence of FTD increases after 65 years of age (Harvey *et al.*, 2003; Coyle-Gilchrist *et al.*, 2016). FTD is also notoriously difficult to diagnose, even amongst specialists meaning the number of diagnosed FTD cases is likely to be an underestimate of the true prevalence. Assuming then that a not insignificant proportion of the incident dementia cases above had a non-AD and non-vascular cause, this begs the question of how presupposed, non-specific cochlear hearing loss interacts with 'generic' cognitive mechanisms in a way that somehow leads to a range of specific, pathogenic proteinopathies.

An extended concept that addresses this shortfall more directly is the idea of a specific interaction between AD pathology and dysfunctional hearing induced changes in MTL structure, which is the site of the earliest changes in AD (Braak and Braak, 1991; Griffiths *et al.*, 2020). These include the increased accumulation and spread of  $A\beta$  due to neuronal overactivity, pathologically driven synaptic changes that potentiate excitotoxicity and changes in MTL gamma oscillations that exacerbate deposition of  $A\beta$ . This concept is appealing for several reasons: first, it posits a specific mechanism by which hearing loss and AD pathology might interact at a neural level to promote neurodegeneration, that is supported by evidence from animal studies; second, it is neuroanatomically and pathologically precise, meaning that it is disease-specific; third, although it is disease-specific, the underlying principle might be applied to other neurodegenerative syndromes. Some open questions remain, such as whether pathological change is secondary to hearing induced neuronal changes, or vice versa, although as pointed out in the original hypothesis, this may be somewhat circular if the relationship is bidirectional (Griffiths *et al.*, 2020). Trying to unpick this may nonetheless be important as it has a bearing on what sort of interventions (such as hearing aids) are likely to be beneficial. Additionally, it does not directly address the possible impact neurodegenerative changes may have on peripheral hearing function via efferent mechanisms, which could give further insight into likely mechanisms. Finally, whilst meta-analysis estimates suggest approximately 9% of dementia cases are 'attributable' to mid-life hearing loss (Livingston *et al.*, 2017), clinical experience suggests the proportion of patients with AD complaining of altered hearing is likely to be much higher than this, which may mean the picture is incomplete.

A perspective that has perhaps received less attention and is the focus in this thesis, is how these pathological changes give rise to specific auditory brain dysfunction that determines dementia-specific auditory phenotypes from an early stage. A key emerging theme in AD is that pathological changes begin to accumulate decades before the onset of symptoms, with some evidence that this is also the case in Parkinson's disease, FTD, Huntington's disease and progressive supranuclear palsy, suggesting that this may be a common theme across all dementias (Aylward *et al.*, 1996; Dickson *et al.*, 2008; Evidente *et al.*, 2011; Bateman *et al.*, 2012; Villemagne *et al.*, 2013; Masters *et al.*, 2015; Rohrer *et al.*, 2015). Additionally, pathogenic changes target specific brain networks and evidence in AD shows that

the spread of tau-pathology correlates well with the clinical phenotype (Seeley *et al.*, 2009; Warren *et al.*, 2013, Johnson *et al.*, 2021a; Vogel *et al.*, 2021). With this in mind, I suggest that pathological changes are the main driver of auditory cognitive changes, that are amplified by any effect of peripheral hearing loss. This perspective is complementary to the ideas described above (and each of which may play a role), but answering this question directly is beyond the scope of this work. More generally however, some insight into this question can be gained by exploring what happens to audiometric thresholds across neurodegenerative diseases which exhibit a combination of domain-general and domain-specific cognitive changes, as well as syndrome specific neuropathology. This will also give information on the relative utility of audiometric threshold measurement in the diagnosis and management of dementia.

### **Cognition and hearing loss**

It is interesting that the impact of domain general cognitive processes on audiometric performance has been little studied given that it is a behavioural task. Cognitive ability is well established as playing an important role in degraded speech processing and best predicts speech in noise ability when combined with audiometric measures (explored in chapter 6 of this thesis, (Akeroyd, 2008; Füllgrabe *et al.*, 2015; Billings and Madsen, 2018; Holmes and Griffiths, 2019; Yeend *et al.*, 2019). Dual-task paradigms such as dichotic listening have demonstrated the negative impact of increased listening effort ('cognitive energy') on auditory task performance (Pichora-Fuller *et al.*, 2016; Gagné *et al.*, 2017) and cognitive load has been shown to increase audiometric thresholds (Heinrich *et al.*, 2020). Decreased cognitive flexibility is predictive of higher audiometric thresholds (Brännström *et al.*, 2020) and trajectories of recall memory are predictive of impending hearing impairment measured audiometrically (Maharani *et al.*, 2020). In a longitudinal study by Kiely *et al.*, faster rates of decline in audiometric scores were predicted by incident probable cognitive impairment (MMSE score); interestingly, while known correlates of hearing impairment such as low education, noise damage, diabetes and history of stroke were independently associated with baseline hearing levels, they were not predictive of change in hearing thresholds (Kiely *et al.*, 2012).

Dichotic listening tasks have been used extensively to test 'central auditory function' and are relevant here as they simultaneously leverage many of the domain-general cognitive functions (attention, working memory, cognitive flexibility) that are of interest in predicting hearing ability discussed above. In this sense, they are frequently conceptualised as tests of cognitive load (synonymous with 'cognitive effort' or 'cognitive energy', (Pichora-Fuller *et al.*, 2016; Gagné *et al.*, 2017)) but it should be noted that they also leverage domain-specific processes. Dichotic listening references the simultaneous presentation of different acoustic events to each ear (Cherry, 1953; Broadbent, 1954). Several clinical



tests have been developed such as dichotic digits (Musiek, 1983; Musiek *et al.*, 1991), dichotic consonant-vowel recognition (Berlin *et al.*, 1972), dichotic sentence identification (Fifer *et al.*, 1983) and others. The two most commonly used report conditions are i) free recall, where individuals are instructed to repeat stimuli directed to both ears and ii) a directed attention test, where the subject attends to one ear only (Musiek and Chermak, 2015). Dichotic listening paradigms have been shown to be sensitive to a number of 'central auditory processing disorders' (Musiek *et al.*, 1991, Gates *et al.*, 2008b; Hommet *et al.*, 2010; Musiek and Chermak, 2015) and scores decline with age (Fischer *et al.*, 2017). Performance on the dichotic digits test in particular has been shown to be significantly impaired in participants with AD compared with healthy older control participants (Utoomprurkporn *et al.*, 2020).

### **Neurodegeneration and hearing loss**

Whilst there is accumulating evidence for a correlation between hearing loss and cognitive impairment and dementia (most cases presumably being AD), the correlation between dementia and hearing thresholds is far less well established, with fewer studies, small group sizes and inconsistent methodological classification. The majority of studies have included participants diagnosed with MCI, AD or both, typically failing to demonstrate significant differences between MCI or AD and age-matched healthy control subjects (Strouse *et al.*, 1995; Idrizbegovic *et al.*, 2011; Rahman *et al.*, 2011, Goll *et al.*, 2012a, Golden *et al.*, 2015a, c, 2016), although this is not universal (Gates *et al.*, 1995, 2008a).

A very limited number of studies have explored audiometric thresholds in FTD and PPA. Hardy *et al.* recorded significant differences in audiometric thresholds in nvPPA patients compared with both AD and control participants (and no difference between AD and controls) as well as increased interaural asymmetry (worse ear – better ear difference score, (Hardy *et al.*, 2019)). In a study with seven lvPPA patients, audiometric thresholds were significantly different from controls (Goll *et al.*, 2011). No significant differences were demonstrated in a study of svPPA (Goll *et al.*, 2012b).

Dichotic listening tasks have been studied in the context of neurodegenerative disease, particularly AD, where they are consistently abnormal (Bouma and Gootjes, 2011; Häggström *et al.*, 2018, 2020) even when peripheral hearing function is controlled for (Gates *et al.*, 2010, 2011). Given that dichotic listening combines multiple cognitive processes that are of potential relevance to audiometric performance and that dichotic listening performance declines in the presence of neurodegenerative disease, a question of interest (that to my knowledge has not been previously explored), is to what extent dichotic listening ability might predict audiometric performance.

In this chapter, I assessed performance on pure tone audiometry in AD and the three major FTD syndromes (bvFTD, svPPA and nvPPA). Correlations between audiometric thresholds and various

cognitive measures were explored and the impact of dichotic listening performance on audiometric performance was also assessed. Based on previous work (Strouse *et al.*, 1995; Idrizbegovic *et al.*, 2011; Rahman *et al.*, 2011, Goll *et al.*, 2012a, Golden *et al.*, 2015a, c, 2016; Hardy *et al.*, 2019), I predicted that patients with AD, svPPA and bvFTD would not show significantly different audiometric thresholds when compared with controls, but that patients with nvPPA would show significantly elevated audiometric thresholds compared to controls, AD, svPPA and bvFTD.

### 3.3 Methods

#### 3.3.1 Participants

Ten patients with typical AD, fifteen patients with BvFTD, eight patients with svPPA and six patients with nvPPA were recruited along with their partners, with each group meeting the relevant syndromic diagnostic criteria for mild to moderate severity (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011; Dubois *et al.*, 2014). Fifteen healthy older individuals with no history of neurological or psychiatric disorders participated as control subjects.

A summary of the demographic, clinical and general neuropsychological characteristics of participants are listed in Table 3.1.

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

Characteristic	Healthy Control	AD	svPPA	nvPPA	bvFTD
<b>Demographic and Clinical</b>					
No. (M:F)	15 (9:6)	10 (7:3)	8 (5:3)	6 (6:0)	15 (11:4)
Age (years)	65.2 (6)	69.2 (10.7)	65.6 (7.3)	68.5 (7.5)	66.1 (5.7)
Handedness (R:L)	13:2	9:1	8:0	5:1	14:1
Symptom duration (years)	N/A	<b>4.0 (1.8)<sup>c**, e*</sup></b>	<b>6.4 (2.0)<sup>b**, d**</sup></b>	<b>3.0 (1.6)<sup>c**, e**</sup></b>	<b>5.5 (1.6)<sup>b*, d**</sup></b>
Education (years)	15.2 (3.0)	14.5 (4.1)	15.3 (2.1)	13.2 (2.2)	<b>12.9 (2.7)<sup>a*</sup></b>
MMSE (/30)	29.6 (0.6)	<b>22.4 (6.4)<sup>a**</sup></b>	<b>22.9 (5.1)<sup>a**</sup></b>	<b>22.7 (7.2)<sup>a**</sup></b>	<b>23.4 (3.5)<sup>a**</sup></b>
Hearing Threshold (dB)	17.7 (8.2)	<b>29.1 (11.2)<sup>a**, e**</sup></b>	23.8 (8.0)	<b>29.7 (3.5)<sup>a**, e*</sup></b>	<b>19.6 (7.4)<sup>a**, d*</sup></b>
SII (%)	83.6 (13.4)	<b>65.5 (22.9)<sup>a**, c*, e*</sup></b>	<b>82.0 (11.7)<sup>b*</sup></b>	69.5 (9.7)	<b>79.5 (11.5)<sup>b*</sup></b>
<b>Neuropsychology</b>					
<b>General Intellect</b>					
Performance IQ	118.1 (13.0)	<b>80.6 (11.1)<sup>a**, c**</sup></b>	<b>120.3 (12.6)<sup>b**, d**</sup></b>	<b>89.8 (25.3)<sup>a**, c**</sup></b>	<b>96.2 (23.2)<sup>a*, c*</sup></b>
Verbal IQ	122.6 (8.9)	<b>86.4 (20.9)<sup>a*</sup></b>	<b>73.1 (19.3)<sup>a**, e*</sup></b>	<b>79.3 (15.7)<sup>a**</sup></b>	<b>94.1 (20.2)<sup>a**, c*</sup></b>
NART	39.4 (6.7)	<b>35.9 (10.8)<sup>c**, d**</sup></b>	<b>18.5 (13.2)<sup>a**, b**, e**</sup></b>	<b>16.3 (18.0)<sup>a**, b**, e*</sup></b>	<b>32.5 (12.9)<sup>c**, d*</sup></b>
Predicted Premorbid IQ	119.2 (5.5)	<b>116.3 (8.9)<sup>c**, d**</sup></b>	<b>101.9 (10.9)<sup>a**, b**, e**</sup></b>	<b>99.9 (15.1)<sup>a**, b**, e*</sup></b>	<b>113.5 (10.7)<sup>c**, d*</sup></b>
<b>Executive Function</b>					
WASI Block Design (/71)	45.7 (13.1)	<b>11.9 (10.7)<sup>a**, c**, e*</sup></b>	<b>44.8 (14.6)<sup>b**, e**</sup></b>	<b>28.4 (23.9)<sup>a*</sup></b>	<b>26.3 (16.9)<sup>a**, b*, c**</sup></b>
WASI Matrices (/32)	26.2 (3.0)	<b>11.7 (7.8)<sup>a**, c**</sup></b>	<b>27.4 (3.2)<sup>b**, c**, d**</sup></b>	<b>16.7 (11.8)<sup>a**, c**</sup></b>	<b>15.7 (9.0)<sup>a**, c**</sup></b>
WMS-R Digit Span Reverse (max)	5.9 (1.1)	<b>3.3 (1.7)<sup>a**, c**</sup></b>	<b>5.6 (1.6)<sup>b**, e*</sup></b>	<b>4.0 (0)<sup>a*</sup></b>	<b>4.2 (1.6)<sup>a**, c*</sup></b>
Letter Fluency (F, 1 min)	17.9 (5.5)	<b>10.1 (4.3)<sup>a**</sup></b>	<b>7.8 (6.0)<sup>a**</sup></b>	10.5 (9.2)	<b>8.6 (6)<sup>a**</sup></b>
Category Fluency (Animals, 1 min)	24.2 (6.3)	<b>12.3 (6.9)<sup>a**, c*</sup></b>	<b>5.5 (5.0)<sup>a**, b*, e*</sup></b>	<b>13.0 (5.2)<sup>a**</sup></b>	<b>11.5 (5.3)<sup>a**, c*</sup></b>

Trails A (s)	33.4 (12.8) <sup>†</sup>	68.6 (34.9) <sup>a**, d*</sup>	45.6 (18.3)	37.3 (7.8) <sup>b*</sup>	60 (32.8) <sup>a*</sup>
Trails B (s)	59.9 (24.3) <sup>†</sup>	203.9 (81.2) <sup>a**, c*, e*</sup>	134.4 (95.4) <sup>a*, b*</sup>	113.3 (63.7)	119.8 (81.3) <sup>a**, b*</sup>
D-KEFS Stroop Colour Naming (s)	29.4 (5.1) <sup>†</sup>	56.0 (17.1) <sup>a**, d*</sup>	49.7 (11.4) <sup>a**, d*</sup>	73.3 (12.4) <sup>a**, b*, c*, e*</sup>	46.9 (17.2) <sup>a**, d*</sup>
D-KEFS Stroop Word Reading (s)	21.9 (4.3) <sup>†</sup>	34.0 (15.6) <sup>a**, d*</sup>	28.0 (5.6) <sup>a*, d**</sup>	66.8 (14.1) <sup>a**, b*, c**, e**</sup>	28.9 (13.1) <sup>d**</sup>
D-KEFS Stroop Interference (s)	55.8 (14.0) <sup>†</sup>	121.7 (38.7) <sup>a**, e*</sup>	89.9 (15.2) <sup>a**, d**</sup>	123.8 (11.3) <sup>a**, c**</sup>	85.3 (40.7) <sup>a*, b*</sup>
<b>Working Memory</b>					
WMS-R Digit Span Forward (max)	6.9 (1.1)	6.1 (1.1) <sup>d**</sup>	7.1 (1.1) <sup>d**</sup>	4.3 (1.0) <sup>a**, b**, c**, e**</sup>	6.3 (1.4) <sup>d**</sup>
<b>Episodic Memory</b>					
RMT Words (/50)	48.2 (4.0) <sup>†</sup>	33.4 (8.8) <sup>a**</sup>	35.0 (5.9) <sup>a**</sup>	40.0 (12.7) <sup>a**</sup>	37.8 (9.3) <sup>a**</sup>
RMT Faces (/50)	40.8 (3.6)	29.6 (5.6) <sup>a**</sup>	32.3 (4.1) <sup>a**</sup>	33.8 (3.9) <sup>a*</sup>	33.1 (6.3) <sup>a**</sup>
Camden PAL (/24)	20.3 (4.7) <sup>†</sup>	6.6 (5.8) <sup>a**, d*, e*</sup>	9.4 (8.1) <sup>a**</sup>	14.2 (6.2) <sup>a*, b*</sup>	14.1 (7.3) <sup>a**, b*</sup>
<b>Naming</b>					
Graded Naming Test (/30)	25.9 (2.4) <sup>†</sup>	14.8 (8.3) <sup>a**, c**</sup>	1.9 (5.3) <sup>a**, b**, d**, e**</sup>	10.2 (9.2) <sup>a**, c**</sup>	18 (13) <sup>a**, c**</sup>
Boston Naming Test (/30)	28.8 (1.3) <sup>†</sup>	N/A	6.1 (9.6) <sup>a**, d*</sup>	17.3 (8.0) <sup>a**, c*</sup>	N/A
<b>Comprehension</b>					
BPVS (/150)	147.3 (2.2) <sup>†</sup>	146.0 (3.5) <sup>c**</sup>	70.5 (47.1) <sup>a**, b**, d*, e**</sup>	125.8 (25.0) <sup>a*, c*</sup>	134.5 (20.4) <sup>a**, c**</sup>
Concrete Synonyms (/25)	23.9 (1.1) <sup>†</sup>	N/A	8.7 (9.2) <sup>a**</sup>	15.8 (10.0) <sup>a*</sup>	N/A
Abstract Synonyms (/25)	23.7 (1.9) <sup>†</sup>	N/A	8.8 (8.4) <sup>a**</sup>	14.2 (8.2) <sup>a**</sup>	N/A
WASI Vocabulary (/80)	72.5 (3.8) <sup>†</sup>	56.2 (15.1) <sup>a**, c*, d*</sup>	26.4 (24.7) <sup>a**, b*, e*</sup>	23.6 (19.4) <sup>a**, b*, e*</sup>	48.3 (20.4) <sup>a**, c*, d*</sup>
PALPA-55 (/24)	23.8 (0.4) <sup>†</sup>	N/A	15.7 (10.1) <sup>a**</sup>	13.8 (7.2) <sup>a**</sup>	N/A
<b>Speech Repetition</b>					
PALPA-55 (/24)	23.8 (0.4) <sup>†</sup>	N/A	15.7 (10.1) <sup>a**</sup>	13.8 (7.2) <sup>a**</sup>	N/A

Word (/45)	Repetition	44.6 (0.6)	N/A	<b>42.8 (2.9)<sup>a**</sup></b>	<b>26.5 (18.0)<sup>a**</sup></b>	N/A
Graded (/10)	Sentences	9.8 (0.5)	N/A	<b>7.7 (2.4)<sup>a*</sup></b>	<b>4.6 (3.4)<sup>a**</sup></b>	N/A
<b>Posterior Cortical Function</b>						
GDA Calculation (/24)		15.6 (5.2)	<b>6.1 (4.2)<sup>a**, c*</sup></b>	<b>14.1 (5.2)<sup>b*, d*</sup></b>	<b>6.0 (2.7)<sup>a**, c*</sup></b>	11.6 (8.4)
VOSP (/20)		18.7 (1.8)	<b>15.2 (2.3)<sup>a**</sup></b>	<b>16.9 (2.3)<sup>a*</sup></b>	15.2 (5.9)	<b>16.1 (2.7)<sup>a**</sup></b>

Mean (standard deviation) scores are shown unless otherwise indicated; maximum scores are shown after tests (in parentheses). Significant differences ( $p < 0.05$ ) between disease groups and healthy controls are indicated in bold; \* $p < 0.05$ ; \*\* $p < 0.01$ ; <sup>a</sup> significantly different from control; <sup>b</sup> significantly different from AD; <sup>c</sup> significantly different from SD; <sup>d</sup> significantly different from PNFA; <sup>e</sup> significantly different from BvFTD; † non-parametric measures used due to violation of assumptions for the GLM

### 3.3.2 Experimental design and stimuli

#### 3.3.2.1 Pure tone audiometry

We followed the British Society of Audiology (BSA), recommended procedure for pure-tone audiometry as per the 2018 guideline (BSA, 2018), using the dual-channel GSI Audiostar Pro (*GSI AUDIOSTAR PRO™ USER MANUAL*, 2013). All patients were tested in the same, quiet room, with average ambient sound-level of 37 dB as measured via a calibrated, RadioShack Digital Sound Level Meter (CAT.NO.: 3300099). BSA guidelines for PTA suggest an ambient noise cut-off of 35 dB or less (BSA, 2018); to neutralize the +2 dB above recommended testing threshold in our room, all testing was performed via the calibrated GSI Audiostar Pro headphones, with calibrated, noise-reducing ear-cups provided by the supplier. Testing was commenced at the better hearing ear (according to the subjects account) at 1000 Hz. Frequency testing proceeded as follows, 2000 Hz, 4000 Hz, 8000 Hz, 500 Hz and 250 Hz and for the first ear only, 1000 Hz was retested to ensure a 5 dB variation or less. Tone duration was between 1 and 3 seconds and the duration between tone presentations was varied between 1 and at least 3 seconds, avoiding predictability. Subjects were instructed to respond by pressing a clicker, for the whole duration of the sound presentation. As per guidelines, threshold was determined via the following method:

1. Following a satisfactory positive response, the level of the tone was reduced in 10 dB steps until no further response occurred
2. The level of the tone was increased in 5 dB steps until a response occurred
3. After the first response using an ascending approach, the level was decreased by 10 dB and another ascending 5 dB series was started until the subject responded again.
4. The level was decreased by 10 dB and increased by 5 dB until the subject responded at the same level on two out of two, three or four (i.e. 50 % or more) responses on the ascent. This was taken as the hearing threshold level. Threshold was defined as the lowest level at which responses occurred in at least half of a series of ascending trials with a minimum of two responses required at that level.
5. The next frequency was then tested, starting at a clearly audible level (e.g. 30 dB above the adjacent threshold) and used the 10-dB-down, 5-dB-up sequence described in Step 4 until the threshold criterion was satisfied.

### 3.3.2.2 Defining Hearing Loss

Hearing loss was defined according to recommendations by the Global Burden of Disease Expert Group on Hearing Loss, which are summarised in Table 3.2 (Olusanya *et al.*, 2019).

**Table 3.2 Grades of hearing impairment as recommended by the Global Burden of Disease Expert Group on Hearing Loss**

Category	Pure tone audiometry <sup>a,b</sup>	Hearing in quiet	Hearing in noise
Normal hearing	–10.0 to 4.9 dB hearing level	Excellent hearing	Good hearing
	5.0 to 19.9 dB hearing level	Good hearing	Rarely have difficulty in following/ taking part in a conversation
Mild hearing loss	20.0 to 34.9 dB hearing level	Does not have problems hearing what is said	May have real difficulty following/ taking part in a conversation
Moderate hearing loss	35.0 to 49.9 dB hearing level	May have difficulty hearing a normal voice	Has difficulty hearing and taking part in conversation
Moderately severe hearing loss	50.0 to 64.9 dB hearing level	Can hear loud speech	Has great difficulty hearing and taking part in conversation
Severe hearing loss	65.0 to 79.9 dB hearing level Profound	Can hear loud speech directly in one's ear	Has very great difficulty hearing and taking part in conversation
Profound hearing loss	80.0 to 94.9 dB hearing level	Has great difficult hearing	Cannot hear any speech
Complete or total hearing loss	95.0 dB hearing level or greater	Profoundly deaf, hears no speech or loud sounds	Cannot hear any speech or sound
Unilateral	< 20.0 dB hearing level in the better ear, 35.0 dB hearing level or greater in the worse ear	Does not have problems unless sound is near poorer hearing ear	May have real difficulty following/ taking part in a conversation

<sup>a</sup> In the better ear

<sup>b</sup> Average of 500, 1000, 2000 and 4000 Hz

### 3.3.2.3 Dichotic Digits Test

The dichotic digits test used was similar to the original test developed by Musiek et al (Musiek, 1983). It is composed of naturally spoken digits from 1 to 10, excluding the number 7 (the only polysyllabic number in English and therefore uniquely identifiable). Pairs of digits are presented separately to each ear and timed to coincide, preventing the use of timing cues or the introduction of lag bias. A total of 4 digits (2 pairs at each ear) are presented per trial, with an inter-digit interval of 500 ms. Intensity levels across the stimuli are matched. The test was administered using the free recall method, with the subject asked to repeat all 4 digits in any order for each trial, with a total of 20 digit-pairs (40 digits) presented to each ear, making a total of 80 test items. Responses could also be indicated with a number chart provided if desired or if vocalisation of responses was too difficult.

## 3.4 Statistical analysis

A full description of the analysis pipeline is given in general methods section 2.9. To test for a main effect of disease group on right ear, left ear, left ear – right ear difference, better ear, worse ear and worse ear – better ear difference mean threshold, a multiple-linear regression model was used. Where this omnibus test was significant, post-hoc between-group comparisons were explored using independent t-tests. Effect sizes were estimated in the regression model by calculating Eta-squared. Model diagnostics (described in general methods, section 2.9) were performed on each model to confirm that the assumptions of the GLM were met.

For pairwise, partial and semi-partial correlations, Spearman's rank correlation was used. This was chosen in preference to Pearson's correlation as the MMSE and WASI Matrices measures were not normally distributed and when comparing estimates between Pearson and Spearman correlations on the MMSE scores there was significant difference in correlation scores, implying that test assumptions had a significant impact on computation of results.

To assess the contribution of various cognitive measures to audiometric thresholds, exploratory correlational analyses were performed between better and worse ear threshold scores and age (as baseline), disease severity as measured by the MMSE and WASI Matrix reasoning, attention and working memory as measured by forward digit span and reverse digit span and cognitive load as measured by the dichotic digits test (noting, as discussed above that dichotic listening also has an auditory-specific component). It is important here to emphasise that the main purpose of this exploratory analysis was to summarise the main characteristics of the data and guide future hypothesis generation and experimental design as the small group sizes and large number of correlations explored increases the likelihood of false discovery.



To assess the individual contribution of cognitive measures, whilst accounting for the effects of age on better and worse ear thresholds, a series of partial and semi-partial correlational analysis between better and worse ear thresholds and the above cognitive measures were performed whilst keeping age fixed.

Correlation between cognitive measures were explored for three reasons: first, there are a priori reasons to anticipate that cognitive measures might be correlated, for example, due to similar task demands (e.g. forward and reverse digit span, spelling WORLD backwards in the MMSE); second, various cognitive measures correlated with better and worse ear scores; third, in the interest of dimension reduction to avoid over-fitting the model, particularly given the small group sizes. Dichotic digits test score was most significantly correlated with better and worse ear scores, whilst accounting for the effects of age, as well as being significantly correlated with all other cognitive measures. The effect of including dichotic digits test score as a proxy for the contribution of cognition to pure tone thresholds was explored using a multiple-linear regression model, with better and worse ears scores as the dependent variable, diagnostic group as the independent variable and both age and dichotic digits test score as covariates.

A threshold of  $p < 0.05$  was accepted as the criterion of statistical significance for all tests.

## 3.5 Results

### 3.5.1 General participant characteristics

General participant characteristics are summarised in Table 3.1. Patient groups did not differ significantly from healthy controls in gender distribution, age or handedness, ( $p > 0.05$ ). Mean symptom duration differed significantly between patient groups, with significantly longer disease duration in the svPPA and bvFTD groups compared to the AD and nvPPA groups, but overall severity of cognitive impairment did not (MMSE).

### 3.5.2 Performance on pure tone audiometry adjusting for age

Audiograms (figure 3.1, panels A and B) showed significantly elevated right ear thresholds across frequencies in the AD, nvPPA and bvFTD groups compared to the control group and significantly elevated left ear thresholds in the nvPPA group compared to the control group, but a similar overall frequency sensitivity profile in all groups.

Mean audiometric thresholds (average of 250, 500, 1000, 2000, 4000 and 8000 Hz) differed significantly between groups for right ear ( $F(5,48) = 5.091$ ,  $p < 0.001$ ); left ear ( $F(5,48) = 4.823$ ,  $p = 0.0012$ ); better ear ( $F(5,48) = 4.863$ ,  $p = 0.0011$ ) and worse ear scores ( $F(5,48) = 5.164$ ,  $p < 0.001$ ), while adjusting for

the effect of age. There were no significant interaural differences between groups measured as either left ear minus right ear ( $F(5,48) = 0.889, p = 0.496$ ) or worse ear minus better ear difference scores ( $F(5,48) = 1.255, p = 0.299$ ). Group mean scores and interaural difference scores (0.25 – 8 KHz) are summarised in Table 3.3. Groupwise classifications of hearing impairment according to recommendations by the Global Burden of Disease Expert Group on Hearing Loss are summarised in Table 3.4 (Olusanya *et al.*, 2019).

Post-hoc between group comparisons for right ear scores revealed that this was driven by the AD ( $t = 2.47, p = 0.017$  [95% CI: 1.65 – 16.14]), nvPPA ( $t = 2.29, p = 0.026$  [95% CI: 1.194 – 18.18]) and bvFTD ( $t = 2.16, p = 0.036$  [95% CI: 0.464 – 13.207]) groups performing significantly worse than the healthy control group). No other group differences were significant. Effect size estimation through calculation of eta-squared revealed that approximately 34.7% ([95% CI: 0.082 – 0.469]) of performance results were explained by the model. Disease group contributed approximately 15.9% ([95% CI: 0 – 0.291]) of the effect in the model, with age contributing approximately 19.6% ([0.034 – 0.375]) (see Table 3.5).

Post-hoc between group comparisons for left ear scores revealed that this was driven by the nvPPA group ( $t = 2.85, p = 0.006$  [95% CI: 4.65 – 26.98]) performing significantly worse than the healthy control group (see Table 3.6). No other group differences were significant. Effect size estimation through calculation of eta-squared revealed that approximately 33.4% ([95% CI: 0.072 – 0.457]) of performance results were explained by the model (see table 3.5). Disease group contributed approximately 15.4% ([95% CI: 0 – 0.284]) of the effect in the model, with age contributing approximately 19.5% ([95% CI: 0.034 – 0.375]) of the effect (see Table 3.5).

Post-hoc between group comparisons for better ear scores revealed that this was driven by the AD ( $t = 2.31, p = 0.025$  [95% CI: 1.035 – 14.99]) and nvPPA groups ( $t = 2.54, p = 0.014$  [95% CI: 0.147 – 18.51]) performing significantly worse than the healthy control group. No other group differences were significant. Effect size estimation through calculation of eta-squared revealed that approximately 33.6% ([95% CI: 0.073 – 0.459]) of performance results were explained by the model. Disease group contributed approximately 15.9% ([95% CI: 0 – 0.291]) of the effect in the model, with age contributing approximately 18% of the effect ([95% CI: 0.028 – 0.363]) (see Table 3.5).

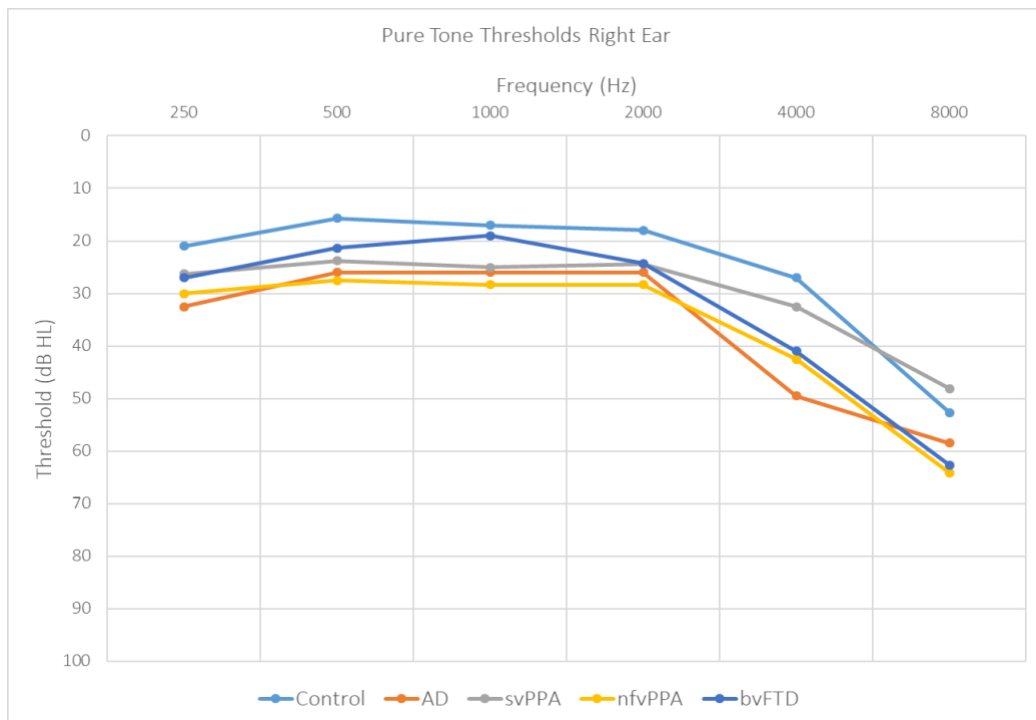
Post-hoc between group comparisons for worse ear scores revealed that this was driven by the nvPPA group ( $t = 2.42, p = 0.019$  [95% CI: 2.203 – 23.674]) performing significantly worse than the healthy control group. No other group differences were significant. Effect size estimation through calculation of eta-squared revealed that approximately 35% ([95% CI: 0.085 – 0.472]) of performance results were explained by the model. Disease group contributed approximately 13.6% ([95% CI: 0 – 0.262]) of the

effect in the model, with age contributing approximately 22.9% ([0.052 – 0.407]) of the effect (see table 3.5).

Inspecting individual scores (figure 3.2), there was overlap of test scores in all conditions (right, left, better ear and worse ear) amongst all groups. The nvPPA group results showed both the worst scores and the most consistent results, with less variation compared to other groups and the largest interaural differences (both left minus right and worse ear minus better ear, see Table 3.3 and figure 3.2). All other groups showed substantial variation in test scores.

There was a significant effect of age on test performance across all conditions: right ear ( $t = 3.42$ ,  $p = 0.001$  [95% CI: 0.237 – 0.913]), left ear ( $t = 3.41$ ,  $p = 0.001$  [95% CI: 0.31 – 1.19]), better ear ( $t = 3.28$ ,  $p = 0.002$  [95% CI: 0.206 – 0.857]) and worse ear ( $t = 3.77$ ,  $p = < 0.001$  [95% CI: 0.374 – 1.229]).

A



B

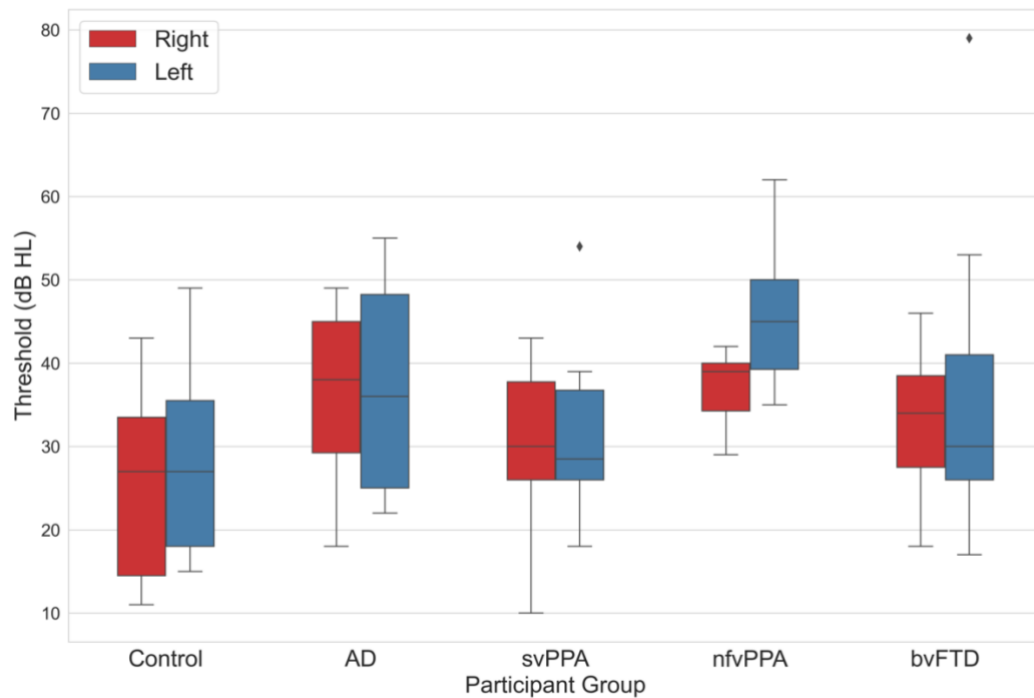


Figure 3.1 Audiometric frequency profiles (250, 500, 1000, 2000, 4000 and 8000 Hz) by group and ear, recorded in decibels hearing level (dB HL)

**A** Frequency specific audiometric profiles by participant group, right ear. **B** Frequency specific audiometric profiles by participant group, left ear. Coloured lines represent mean thresholds at each

frequency by participant group. Control (n = 15), AD (n = 10), svPPA (n = 8), nvPPA (n = 6), bvFTD (n = 15). AD, Alzheimer's disease; svPPA, semantic variant primary progressive aphasia; nvPPA, non-fluent variant primary progressive aphasia; bvFTD, behavioural variant frontotemporal dementia.

**A**



**B**

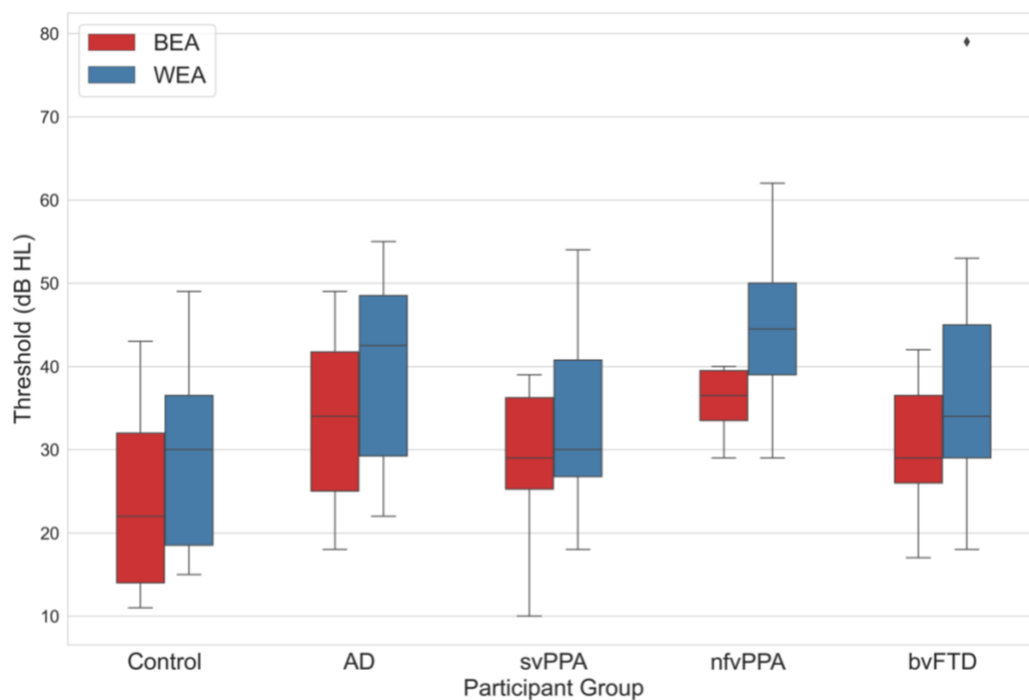


Figure 3.2 Mean audiometric thresholds (average of 250, 500, 1000, 2000, 4000 and 8000 Hz) by group and ear, recorded in decibels hearing level (dB HL)

**A** Mean audiometric threshold (250 – 8000 Hz) by participant group for the right (red) and left (blue) ears. **B** Mean audiometric threshold (250 – 8000 Hz) by participant group for the better (red) and worse (blue) ears.

(blue) ears. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. AD, Alzheimer's disease; SD, semantic dementia; PNFA, progressive non-fluent aphasia; BvFTD, behavioural variant frontotemporal dementia.

**Table 3.3 Summary statistics for audiometric thresholds (0.25 – 8 KHz) by ear and interaural difference scores, mean (SD)**

	Control	AD	svPPA	nfvPPA	bvFTD
Right ear	25.2 (11)	36.4 (4.9)	30.0 (10.6)	36.8 (4.9)	32.6 (8.4)
Left ear	27.4 (10.5)	36.9 (12.9)	31.9 (11.2)	45.7 (9.7)	35.3 (15.5)
Left ear – Right ear Difference	2.2 (6.2)	0.45 (7.3)	1.88 (7.6)	8.9 (12.3)	2.8 (12.3)
Better Ear	23.6 (10.5)	33.8 (10.7)	28.5 (9.4)	35.7 (4.3)	30.2 (7.7)
Worse Ear	29.0 (10.3)	39.5 (11.7)	33.4 (11.7)	44.6 (11.2)	37.7 (15.0)
Worse ear – Better ear Difference	5.4 (3.6)	5.8 (4.0)	4.9 (5.9)	8.9 (9.2)	7.5 (10.0)

This table summarises group scores (SD) for right ear, left ear, left ear minus right ear difference, better ear, worse ear and worse ear minus better ear difference. **AD**, Alzheimer's disease; **svPPA**, semantic variant primary progressive aphasia; **nfvPPA**, non-fluent variant primary progressive aphasia; **bvFTD**, behavioural variant frontotemporal dementia

**Table 3.4 Summary statistics for audiometric thresholds (0.5 – 4 KHz) at the better ear and classification of hearing loss, number : total (proportion)**

	Control	AD	svPPA	nfvPPA	bvFTD
Normal hearing	8:15 (0.53)	3:10 (0.3)	2:8 (0.25)	0:6 (0)	5:15 (0.33)
Mild hearing loss	6:15 (0.4)	2:10 (0.2)	6:8 (0.75)	6:6 (1.0)	9:15 (0.6)
Moderate hearing loss	1:15 (0.07)	5:10 (0.5)	0:8 (0)	0:6 (0)	1:15 (0.07)

This table summarises hearing loss classification by group with proportion in parentheses. **AD**, Alzheimer's disease; **svPPA**, semantic variant primary progressive aphasia; **nfvPPA**, non-fluent variant primary progressive aphasia; **bvFTD**, behavioural variant frontotemporal dementia

**Table 3.5 Estimation of effect sizes for right ear, left ear, better ear and worse ear mean thresholds, adjusting for age**

Effect sizes for linear models	Eta-Squared	df	[95%Conf. Interval]
<b>Right Ear</b>			
Model	0.347	5	0.082 0.469

Group	0.159	4	.	0.291
Age	0.196	1	0.034	0.375
<b>Left Ear</b>				
Model	0.334	5	0.072	0.457
Group	0.154	4	.	0.284
Age	0.195	1	0.034	0.375
<b>Better Ear</b>				
Model	0.336	5	0.073	0.459
Group	0.159	4	.	0.291
Age	0.183	1	0.028	0.363
<b>Worse Ear</b>				
Model	0.350	5	0.085	0.472
Group	0.136	4	.	0.262
Age	0.229	1	0.052	0.407

This table summarises group the effect sizes of the model for audiometric thresholds at the right, left, better and worse ears. The eta-squared number is expressed as a proportion ranging from 0 – 1.0

### 3.5.3 Correlations between hearing, age and cognitive measures

#### 3.5.3.1 Pure tone audiometry and age

There was significant correlation between both better ear thresholds (Spearman  $\rho = 0.482$ ,  $p = < 0.0001$ ) and worse ear thresholds (Spearman  $\rho = 0.531$ ,  $p = < 0.0001$ ) and age (see table 3.7).

#### 3.5.3.2 Pure tone audiometry and disease severity

There was a significant correlation between both better (Spearman  $\rho = -0.288$ ,  $p = 0.041$ ) and worse ear thresholds and MMSE score (Spearman  $\rho = -0.315$ ,  $p = 0.024$ , see table 3.7). Adjusting for age, there was significant partial correlation between MMSE score and better ear (Spearman  $\rho = -0.308$ ,  $p = 0.029$ ) and worse ear (Spearman  $\rho = -0.356$ ,  $p = 0.011$ ) thresholds (see tables 3.8 and 3.9).

There was significant correlation between worse ear thresholds and WASI Matrices score (Spearman  $\rho = -0.324$ ,  $p = 0.020$ , see table 3.7). Accounting for age, there was significant partial correlation between worse ear thresholds and WASI Matrices score (Spearman  $\rho = -0.301$ ,  $p = 0.034$ , see table 3.9).



### 3.5.3.3 Pure tone audiometry, attention and working memory

There was no significant correlation between better (Spearman  $\rho = -0.109$ ,  $p = 0.434$ ) or worse ear thresholds (Spearman  $\rho = -0.177$ ,  $p = 0.202$ ) and forward digit span (see table 3.7). Accounting for age, there was no significant partial correlation between better ear (Spearman  $\rho = -0.1269$ ,  $p = 0.3651$ ) or worse ear thresholds (Spearman  $\rho = -0.217$ ,  $p = 0.128$ ) and forward digit span (see tables 3.8 and 3.9).

There was no significant correlation between better ear (Spearman  $\rho = -0.070$ ,  $p = 0.631$ ) or worse ear (Spearman  $\rho = -0.115$ ,  $p = 0.431$ ) thresholds and reverse digit span (see table 3.7). Accounting for age, there was no significant partial correlation between reverse digit span and either better ear (Spearman  $\rho = -0.113$ ,  $p = 0.444$ ) or worse ear (Spearman  $\rho = -0.174$ ,  $p = 0.238$ ) thresholds (see tables 3.8 and 3.9).

### 3.5.3.4 Cognitive load and pure tone audiometry

There was a significant correlation between both better ear (Spearman  $\rho = -0.344$ ,  $p = 0.011$ ) and worse ear (Spearman  $\rho = -0.389$ ,  $p = 0.004$ ) thresholds and dichotic digits test score (see table 3.7). Accounting for age, there was a significant partial correlation between dichotic digits total score and better ear (Spearman  $\rho = -0.318$ ,  $p = 0.0004$ ) and worse ear (Spearman  $\rho = -0.374$ ,  $p = 0.006$ ) thresholds (see tables 3.8 and 3.9).

### 3.5.3.5 Correlation between cognitive measures

There were significant correlations between all combinations of cognitive measures, which are summarised in table 3.10. Overall, the dichotic digits test was most significantly correlated with better and worse ear thresholds whilst accounting for age, with results explored below.

**Table 3.6 Summary statistics of mean (SD) cognitive scores by group**

	Control	AD	svPPA	nfvPPA	bvFTD
Age	65.2 (6)	69.2 (10.7)	65.6 (7.3)	68.5 (7.5)	66.1 (5.7)
MMSE	29.6 (0.6)	22.4 (6.4)	22.9 (5.1)	22.7 (7.2)	23.4 (3.5)
WASI Matrices	26.2 (3.0)	11.7 (7.8)	27.4 (3.2)	16.7 (11.8)	15.7 (9.0)
Forward Digit Span	6.9 (1.1)	6.1 (1.1)	7.1 (1.1)	4.3 (1.0)	6.3 (1.4)
Reverse Digit Span	5.9 (1.1)	3.3 (1.7)	5.6 (1.6)	4.0 (0)	4.2 (1.6)
Dichotic Digits Test	71.1 (10.6)	54.9 (14.2)	63.8 (12.2)	36.5 (15.1)	58.3 (14.0)

This table summarises group scores, mean (SD), for the cognitive factors explored for correlation with pure tone audiometric thresholds. **AD**, Alzheimer's disease; **svPPA**, semantic variant primary progressive aphasia; **nfvPPA**, non-fluent variant primary progressive aphasia; **bvFTD**, behavioural variant frontotemporal dementia

**Table 3.7 Spearman's rho correlations between better and worse hearing ears with age, disease severity, working memory and cognitive load**

	Better Ear	p-value	Worse Ear	p-value
Age	0.482	< 0.001	0.531	< 0.001
<b>Disease Severity</b>				
MMSE	-0.288	0.041	-0.315	0.024
WASI Matrices	-0.266	0.059	-0.324	0.020
<b>Attention and Working Memory</b>				
Forward Digit Span	-0.109	0.434	-0.177	0.202
Reverse Digit Span	-0.070	0.631	-0.115	0.431
<b>Cognitive Load</b>				
Dichotic Digits Test	-0.344	0.011	-0.389	0.004

This table summarises Spearman's rho correlations by group between better and worse ears, with each cognitive measure

**Table 3.8 Spearman's rho partial and semi-partial correlations between better hearing ear and disease severity, working memory and cognitive load whilst accounting for age**

	Partial	Semi-partial	Partial <sup>2</sup>	Semi-partial <sup>2</sup>	p-value
<b>Disease Severity</b>					
Age	0.530	0.508	0.281	0.258	< 0.001

MMSE	-0.308	-0.264	0.095	0.070	0.029
Age	0.506	0.490	0.256	0.240	< 0.001
WASI Matrices	-0.209	-0.179	0.044	0.032	0.145
<b>Attention and Working Memory</b>					
Age	0.486	0.483	0.236	0.233	< 0.001
Forward Digit Span	-0.127	-0.111	0.016	0.012	0.365
Age	0.558	0.557	0.311	0.310	< 0.001
Reverse Digit Span	-0.113	-0.094	0.013	0.010	0.444
<b>Cognitive Load</b>					
Age	0.466	0.473	0.217	0.191	0.021
Dichotic Digits Test	-0.318	-0.278	0.101	0.077	< 0.001

This table summarises partial and semi-partial correlations for the better hearing ear and various cognitive measures, whilst accounting for the effect of age. **AD**, Alzheimer's disease; **svPPA**, semantic variant primary progressive aphasia; **nfvPPA**, non-fluent variant primary progressive aphasia; **bvFTD**, behavioural variant frontotemporal dementia

**Table 3.9 Spearman's rho partial and semi-partial correlations between worse hearing ear and disease severity, working memory and cognitive load whilst accounting for age**

	Partial	Semi-partial	Partial <sup>2</sup>	Semi-partial <sup>2</sup>	p-value
<b>Disease Severity</b>					
Age	0.585	0.555	0.342	0.308	< 0.001
MMSE	-0.357	-0.293	0.127	0.086	0.011
Age	0.544	0.515	0.296	0.265	< 0.001
WASI Matrices	-0.301	-0.250	0.091	0.063	0.034
<b>Attention and Working memory</b>					
Age	0.541	0.532	0.292	0.283	< 0.001
Forward Digit Span	-0.212	-0.179	0.045	0.032	0.128
Age	0.583	0.579	0.340	0.335	< 0.001
Reverse Digit Span	-0.174	-0.142	0.030	0.020	0.238
<b>Cognitive load</b>					
Age	0.522	0.481	0.272	0.231	< 0.001
Dichotic Digits Test	-0.374	-0.317	0.140	0.100	0.006

This table summarises partial and semi-partial correlations for the worse hearing ear and various cognitive measures, whilst accounting for the effect of age. **AD**, Alzheimer’s disease; **svPPA**, semantic variant primary progressive aphasia; **nfvPPA**, non-fluent variant primary progressive aphasia; **bvFTD**, behavioural variant frontotemporal dementia

**Table 3.10 Spearman’s rho (p-value) correlations between cognitive measures**

	MMSE	WASI Matrices	Forward Span	Digit Span	Reverse Span	Digit Span
MMSE	-	-	-	-	-	-
WASI Matrices	0.340 (0.005)	-	-	-	-	-
Forward Digit Span	0.254 (0.072)	0.405 (0.003)	-	-	-	-
Reverse Digit Span	0.457 (0.001)	0.631 (< 0.001)	0.737 (< 0.001)	-	-	-
Dichotic Digits Test	0.573 (< 0.001)	0.444 (0.001)	0.631 (< 0.001)	0.557 (< 0.001)	-	-

This table summarises Spearman’s rho correlations between various cognitive measures. **AD**, Alzheimer’s disease; **svPPA**, semantic variant primary progressive aphasia; **nfvPPA**, non-fluent variant primary progressive aphasia; **bvFTD**, behavioural variant frontotemporal dementia

### 3.5.4 Performance on dichotic listening

Dichotic Digits Test score results failed to satisfy two assumptions of the GLM when age and audiometric scores were included in the model: normality of distribution of residuals and homogeneity of variance. The Kruskal-Wallis rank sum test was used for comparison of means across groups and the Mann-Whitney U test was used for between group comparisons. Participant groups differed significantly in their performance on the dichotic digits test ( $\chi^2(4) = 19.65, p = 0.0006$ , with ties). Post-hoc comparisons between disease groups and healthy controls revealed that this was driven by the AD ( $z = 2.92, p = 0.0035$ ), nvPPA ( $z = 3.20, p = 0.0014$ ) and bvFTD ( $z = 2.68, p = 0.0074$ ) groups performing significantly worse than the healthy control group and the nvPPA group performing significantly worse than the AD ( $z = 2.01, p = 0.045$ ), svPPA ( $z = 2.714, p = 0.007$ ) and bvFTD ( $z = 2.61, p = 0.009$ ) groups. No other group differences were significant.

Inspecting individual scores (Figure 3.3), the nvPPA group showed no overlap with the control group. Performance amongst the healthy control group was the most consistent, with tightly clustered scores aside from one outlying result. Variation amongst the dementia groups was significantly greater than the healthy control group, including the svPPA group, even though this group was not statistically different from the healthy control group. Aside from the nvPPA group, which had minor overlap with the other dementia groups, all the other dementia groups showed significant overlap with one another.

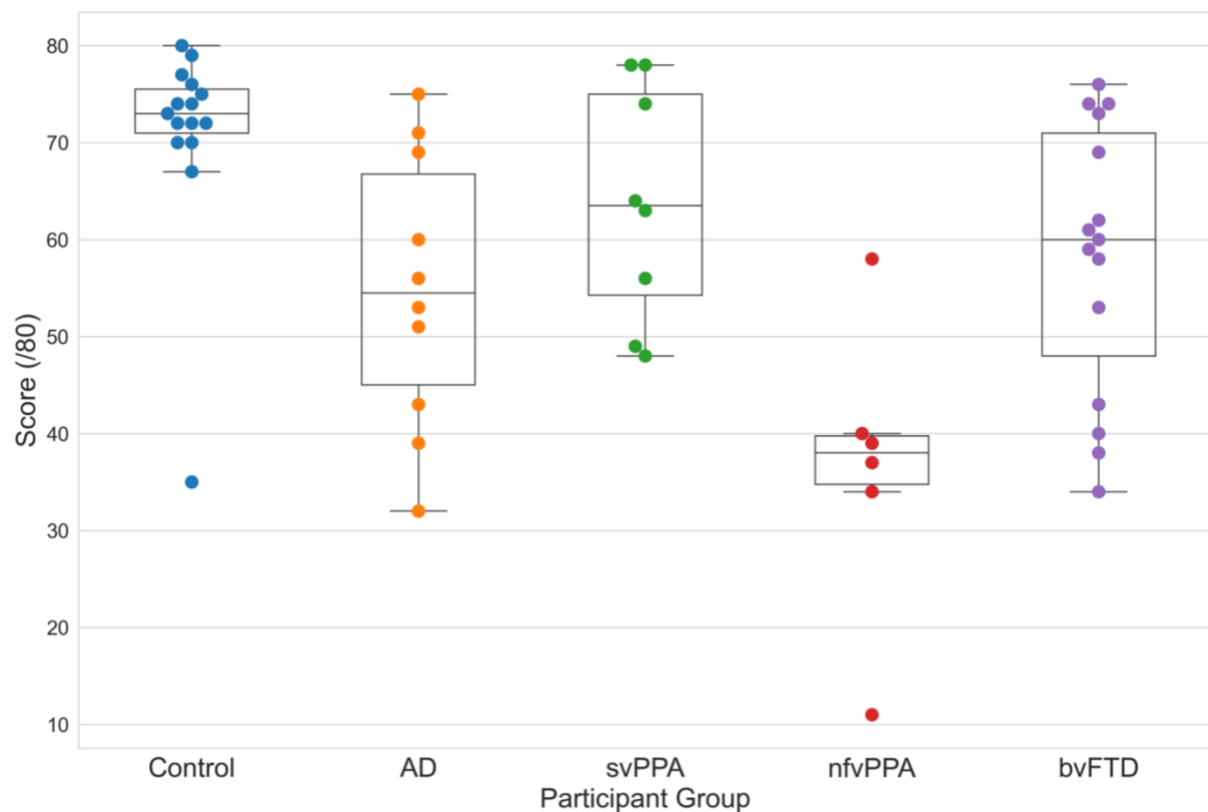


Figure 3.3 Mean score on the dichotic digits test by group

Profiles of participant group performance on the Dichotic Digits Test. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. Circles represent individual participant performance. **AD**, Alzheimer's disease; **svPPA**, semantic dementia; **nvfPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.

### 3.5.5 Performance on pure tone audiometry, age and cognition

With inclusion of the dichotic digits test as an additional predictor in the model, only right ear scores showed a significant difference between groups ( $F(5,48) = 4.217$ ,  $p = 0.002$ ).

Post-hoc between group comparisons for right ear scores revealed that this was driven by the AD group ( $t = 2.04$ ,  $p = 0.047$  [95% CI: 0.1 – 16.084]) performing significantly worse than the healthy control group. No other group differences were significant. Effect size estimation through calculation of eta-squared revealed that approximately 35% ([95% CI: 0.068 – 0.462]) of performance results were explained by the model (see table 3.11). Disease group contributed approximately 9.6% ([95% CI: 0 – 0.209]) of the effect in the model, age contributing approximately 19.9% ([95% CI: 0.035 – 0.380]) and dichotic digits test score approximately 0.5% ([95% CI: 0 – 0.108]) of the effect in the model (see table 3.11).

To look at whether this effect was purely the result of ‘general cognitive’ factors, the same model was examined with MMSE instead of dichotic digits. With this model, there was significant difference between groups for right ear ( $F(6,44) = 4.13, p = 0.0023$ ), left ear ( $F(6,44) = 4.18, p = 0.0021$ ) and better ear scores ( $F(6,44) = 4.14, p = 0.0022$ ).

Post-hoc between group comparisons for right ear scores revealed that this was driven by the AD ( $t = 2.14, p = 0.038, [95\% \text{ CI: } 0.54 \text{ to } 17.7]$ ) and nvPPA ( $t = 2.07, p = 0.044, [95\% \text{ CI: } 0.28 \text{ to } 19.5]$ ) groups performing significantly worse than the healthy control group. No other group differences were significant. Effect size estimation through calculation of eta-squared revealed that approximately 36% ([95% CI: 0.066 – 0.472]) of performance results were explained by the model, with disease group contributing approximately 12.1% ([95% CI: 0 – 0.246]) of the effect in the model, age contributing approximately 21.0% ([95% CI: 0.036 – 0.396]) and MMSE score approximately 0.1% ([95% CI: 0 – 0.065]) of the effect in the model (see table 3.12).

Post-hoc between group comparisons for left ear scores revealed that this was driven by the nvPPA ( $t = 2.07, p = 0.044, [95\% \text{ CI: } 0.28 \text{ to } 19.5]$ ) group performing significantly worse than the healthy control group. No other group differences were significant. Effect size estimation through calculation of eta-squared revealed that approximately 36.3% ([95% CI: 0.068 – 0.475]) of performance results were explained by the model, with disease group contributing approximately 11.9% ([95% CI: 0 – 0.244]) of the effect in the model, age contributing approximately 22.6.0% ([95% CI: 0.045 – 0.411]) and MMSE score approximately 0.4% ([95% CI: 0 – 0.106]) of the effect in the model (see table 3.12)

Post-hoc between group comparisons for better ear scores revealed that this was driven by the nvPPA ( $t = 2.30, p = 0.026, [95\% \text{ CI: } 1.29 \text{ to } 19.5]$ ) group performing significantly worse than the healthy control group. No other group differences were significant. Effect size estimation through calculation of eta-squared revealed that approximately 36.1% ([95% CI: 0.066 – 0.473]) of performance results were explained by the model, with disease group contributing approximately 12.7.9% ([95% CI: 0 – 0.255]) of the effect in the model, age contributing approximately 20.6% ([95% CI: 0.034 – 0.3911]) and MMSE score approximately 0.0% ([95% CI: 0 – 0.043]) of the effect in the model (see table 3.12)

**Table 3.11 Estimation of effect sizes for right ear mean threshold, adjusting for age and dichotic digits test score, AD**

Effect sizes for linear models	Eta-Squared	df	[95%Conf.	Interval]
Model	0.350	6	0.068	0.462
Group	0.096	4	.	0.209
Age	0.199	1	0.035	0.380

Dichotic Digit Test	0.005	1	.	0.108
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This table summarises effect sizes using eta-squared for the right ear in AD patients with age and dichotic digits score included in the model

**Table 3.12 Estimation of effect sizes for right ear mean threshold, adjusting for age and MMSE score**

Effect sizes for linear models	Eta-Squared	df	[95%Conf.	Interval]
<b>Right Ear, AD</b>				
Model	0.360	6	0.066	0.472
Group	0.121	4	.	0.246
Age	0.210	1	0.036	0.396
MMSE	0.001	1	.	0.065
<b>Left Ear, nfvPPA</b>				
Model	0.363	6	0.068	0.475
Group	0.119	4	.	0.244
Age	0.226	1	0.045	0.411
MMSE	0.004	1	.	0.106
<b>Better Ear, nfvPPA</b>				
Model	0.361	6	0.066	0.473
Group	0.127	4	.	0.255
Age	0.206	1	0.034	0.391
MMSE	0.000	1	.	0.043

This table summarises effect sizes using eta-squared for right, left and better hearing ears with age and dichotic digits score included in the model. **AD**, Alzheimer's disease; **nfvPPA**, nonfluent variant primary progressive aphasia.



### 3.6 Discussion

The findings presented in this chapter demonstrate that patients with AD, nvPPA and bvFTD have significantly elevated pure tone audiometric thresholds compared to healthy controls and patients with svPPA after adjusting for the effect of age, which remained the most significant predictor of audiometric thresholds. The most marked and consistent elevation of audiometric thresholds was seen in the nvPPA group, none of whom were classified as having normal hearing according to recommendations by the Global Burden of Disease Expert Group on Hearing Loss (tables 4.1 and 4.2 (Olusanya *et al.*, 2019)), which is consistent with previous results (Hardy *et al.*, 2019). The nvPPA group were also the only group with significantly elevated thresholds on all four significant contrasts (right ear, left ear, better ear and worse ear). In contrast to the majority of prior studies, the AD group showed the second most severely elevated audiometric thresholds, although this was only significant for right ear and better ear thresholds and the range of hearing scores was wide (Strouse *et al.*, 1995; Idrizbegovic *et al.*, 2011; Rahman *et al.*, 2011, Goll *et al.*, 2012a, Golden *et al.*, 2015a, c, 2016). The bvFTD group only demonstrated significantly raised audiometric thresholds for the right ear contrast, which, given the small group sizes must be interpreted cautiously. No other between group comparisons were significant and there was significant variation within all groups, demonstrated by wide confidence intervals. No significant interaural asymmetry (left vs right, worse ear vs better ear) was identified in this data set.

Dichotic digits test score and MMSE score both showed moderate and statistically significant partial correlations with better and worse ear audiometric thresholds when controlling for the effect of age, but the same was not true for forward digit span, reverse digit span and WASI Matrices score. When dichotic digits test score was included in the model, only right ear scores for participants with AD remained statistically significant, whereas with MMSE score included, significant scores were recorded for right, left and better ear scores.

#### **Candidate pathological substrates**

In the introduction to this chapter I noted that age-related hearing loss and AD share multiple risk factors that are typically regarded as proxies of vascular risk such as obesity, diabetes and hypertension, which might suggest a common pathological driver of cochlear and cortical degeneration (Swords *et al.*, 2018). In this study, age remained the most significant and consistent predictor of audiometric thresholds, which is consistent with previous data (Linssen *et al.*, 2014; Swords *et al.*, 2018) and the audiometric profiles across all syndromes were similar to the ‘typical’ high-frequency biased hearing loss associated with ageing. Notwithstanding the fact that the pure tone audiogram is a poor predictor of cochlear pathology (Landegger *et al.*, 2016), the effect of group remained significant when adjusting for age, suggesting that a common vascular pathology is unlikely or at least insufficient as a causal

explanation of the increased risk of dementia associated with peripheral hearing loss. Furthermore, all patients in this study underwent brain imaging with MRI and were screened for evidence of significant vascular disease on brain imaging as an inclusion criterion in the study. A common role for A $\beta$  pathology is rendered highly unlikely by the fact that neither bvFTD or nvPPA are associated with A $\beta$  pathology, yet their thresholds were significantly elevated, as well as the fact that previous research has not established a link between hearing loss and in vivo A $\beta$  pathology (Parker *et al.*, 2020).

FTD syndromes and AD both have brain tissue deposition of hyperphosphorylated tau, however, the pathological changes described in FTD show marked heterogeneity and tau is not present in all cases (Hodges and Patterson, 2007, Rohrer *et al.*, 2010a, 2011; Spinelli *et al.*, 2017; Convery *et al.*, 2019; Sivasathiseelan *et al.*, 2019). Additionally, the common pathologic finding in the auditory cortex of patients with AD and FTD is of dendritic spine loss, with marked decrease in spine density, which is consistent with a general toxic mechanism involving mitochondrial dysfunction and oxidative stress (Iqbal *et al.*, 2010, Baloyannis *et al.*, 2011a, b)). It therefore seems implausible that tau is a common pathologic substrate underlying the association between hearing loss and dementia. There is also no extant evidence of FTLD-tau deposition in the cochlea or subcortical structures.

### **General cognitive mechanism(s)**

The results presented here show that cognitive factors are significantly correlated with audiometric thresholds even when accounting for age, which is consistent with evidence that cognitive decline best predicts prospective changes in hearing threshold (Gates *et al.*, 2010; Kiely *et al.*, 2012; Maharani *et al.*, 2020). The effect was not universal, with only dichotic digits test score and MMSE score showing significant correlations for both ears when controlling for age, whereas measures of attention and auditory working memory (forward and reverse digit span) failed to show any significant correlation with audiometric thresholds. Performance on both the dichotic digits test and MMSE are dependent on a broad range of cognitive functions, with dual-task paradigms in particular felt to reflect the brain's ability to handle 'cognitive load', which is a multi-domain concept in itself (Pichora-Fuller *et al.*, 2016; Gagné *et al.*, 2017; Heinrich *et al.*, 2020). Additionally, including either dichotic digits test score or MMSE score in the model significantly reduced the effect of group on audiometric score, which was most marked for the dichotic digits test. These findings would appear to lend support to the idea that impoverished peripheral hearing taxes 'cognitive resources' in a general way.

There are several important challenges to the idea that the general taxation of cognitive resources is causally related to the development of dementia. First, such wide-ranging cognitive effects would be expected to affect neurodegenerative syndromes fairly indiscriminately because the implied range of impaired cognitive functions is broad, but this is not the case. The svPPA group did not exhibit

significantly elevated audiometric thresholds compared to control participants, despite the fact that they performed significantly worse than controls on the MMSE and MMSE score was correlated with audiometric performance. Further, the effect of including dichotic digits test score or MMSE score in the model was not equivalent; the effect of dichotic digits test score was near universal and significantly, produced the most pronounced effect in the nvPPA group. In contrast the effect of MMSE score was more modest, with AD performance being more sensitive to the effect of including MMSE score than in the nvPPA group. Second, while some recent evidence shows that audiometric thresholds are modulated by cognitive load, the effect is modest (approximately 2dB HL, (Heinrich *et al.*, 2020)). Third, there is no explanation for how such a general mechanism induces the diverse, but specific pathological changes found across neurodegenerative diseases. Finally, performance on the dichotic digits test is at least partially dependent on binaural integration at brainstem level and significant AD-related pathological changes have been previously demonstrated in the inferior colliculus (Parvizi *et al.*, 2001; Baloyannis *et al.*, 2009); this may go some way to explaining the correlation between audiometric and dichotic digit test performance in this group.

### **Interaction between pathology, sensory loss and cognition**

Central to our current understanding of neurodegenerative diseases is the fact that disease-specific pathogenic proteins target segregated, large-scale brain networks that give rise to distinct profiles of cognitive dysfunction (Seeley *et al.*, 2009; Warren *et al.*, 2013, Johnson *et al.*, 2021a; Vogel *et al.*, 2021). This implies that the effect of impoverished sensory encoding at the auditory periphery would not be expected to have an equal effect across neurodegenerative diseases due to differential involvement of domain-specific auditory cognitive processes as well as unequal compromise of domain-general cognitive processes depending on task demands. In such a model, peripheral hearing loss modulates the individual effects of neurodegeneration. Conversely, how the specific degenerative network phenotypes caused by AD and FTD pathology might mediate elevation of audiometric thresholds remains an open question, which I consider below.

### **Alzheimer's disease**

As discussed in the introduction to this chapter, in contrast to the sizeable (9%) attributable risk of incident dementia associated with mid-life hearing loss (Livingston *et al.*, 2017)), studies looking at the age-matched hearing thresholds of patients diagnosed with AD and healthy control subjects have tended to show no significant differences in audiometric thresholds (Strouse *et al.*, 1995; Idrizbegovic *et al.*, 2011; Rahman *et al.*, 2011, Goll *et al.*, 2012a, Golden *et al.*, 2015a, c, 2016). In the few studies where significant differences have been demonstrated, the reported mean threshold elevation at the better and worse ears was a modest 5-7 dB HL (Gates *et al.*, 1995, 2008a). In this study, AD was

associated with significantly elevated mean thresholds at the right ear and better ear only whilst controlling for the effects of age, with a mean difference of approximately 8 dB HL, which is consistent with the findings reported by Gates *et al.* (Gates *et al.*, 2008a). Of note is the significant variability of the effect, with 95% confidence intervals of approximately 1 – 16 dB HL; while this effect may simply reflect continuous variation that is more apparent due to small group size, another possibility is that this reflects the increasingly recognised sub-syndromic differences in regional tau deposition within AD, which have correspondingly distinct clinical phenotypes (Vogel *et al.*, 2021). Answering this question would likely require a much larger sample size.

Following the discussion above on the lack of AD-specific pathological change in the primary auditory cortex, one would not expect the changes in stimulus sensitivity to reside in auditory cortex (Esiri *et al.*, 1986). At the same time, the persistent difference in threshold sensitivity in the AD group even when accounting for the ‘general’ effect of ‘cognitive load’ (in this case, dichotic digits test score) also militates against this simply being a ‘generic’ cognitive effect. As discussed above, the correlation between dichotic digit score and audiometric performance may reflect auditory brainstem involvement by AD pathology, however, the correlation is only partial. An interesting possibility is whether the central cholinergic depletion that is characteristic of AD modulates downstream synaptic sensitivity, which is known to be positively cholinergically mediated (i.e. the presence of acetylcholine increases stimulus sensitivity (Ayala and Malmierca, 2015; Kuchibhotla *et al.*, 2017; Hampel *et al.*, 2018; Yakunina *et al.*, 2019)). This study is not equipped to answer this question directly, but it should be explored in future research.

### **Frontotemporal dementias**

The most striking alterations in audiometric thresholds were observed in the nvPPA group, which replicates previous findings (Hardy *et al.*, 2019); notably, this group of patients is also most commonly described as developing ‘pure word deafness’ and there is a general pattern of deficits in ‘early’ auditory processing in this disorder (Goll *et al.*, 2010a; Grube *et al.*, 2016; Utianski *et al.*, 2019). Several potential mechanisms may be involved, none of which are mutually exclusive. Thalamic atrophy in nvPPA is significant, which is likely to affect both feedforward or ‘bottom-up’ sensory inputs from the inferior colliculus to cortex, as well as ‘top-down’ modulation of tuning and sensory gating via cortico-thalamic and cortico-fugal circuitry (Seeley *et al.*, 2008; Whitwell *et al.*, 2009; Rohrer *et al.*, 2011; Suga, 2012; Bocchetta *et al.*, 2018; Cash *et al.*, 2018). Presumably this is not the entire explanation as thalamic atrophy is even more prominent in patients with bvFTD (Bocchetta *et al.*, 2018) but audiometric thresholds in this group were only statistically significantly different for the right ear contrast. Perhaps this is partly explained by the specific compromise of inferior-frontal regions in nvPPA in contrast to

bvFTD, that may modulate stimulus sensitivity via a more general compromise of top-down predictive mechanisms that cascade down the auditory hierarchy. Additionally, task performance may be altered through the compromise of various domain-general cognitive functions such as attention, working memory and cognitive flexibility that are underpinned by activity in fronto-parietal networks (Fritz *et al.*, 2007; Huang *et al.*, 2013, 2016; Lakatos *et al.*, 2013, Kaya and Elhilali, 2017b; Baddeley and Hitch, 2019; Luo and Maunsell, 2019; Manohar *et al.*, 2019; Utoomprurkporn *et al.*, 2020) – regions that are core targets in nvPPA (Rohrer *et al.*, 2009; Seeley *et al.*, 2009; Cope *et al.*, 2017; Spinelli *et al.*, 2017; Henry *et al.*, 2018; Lombardi *et al.*, 2021).

Some support for the idea of a particular vulnerability to the interaction between both ‘bottom-up’ and ‘top-down’ effects in nvPPA is provided by dichotic digits performance in this group, which was profoundly impaired. Furthermore, the effect of adjusting for dichotic digits score was especially striking, rendering all significant contrasts (right, left, better and worse ears) non-significant. The dependence of dichotic digit performance on both brainstem and cortical processes discussed above is consistent with this. Additional support for this notion comes from two sources: first, MMSE score, which is far less auditory specific, and is more tailored to detect the impairments found in AD than nvPPA had a significantly more limited effect on the nvPPA group; second, the svPPA group did not show any significant audiometric differences compared with controls, despite significant cognitive impairment, consistent with the fact that svPPA is typically a disease of the anterior-temporal lobes (with later involvement of orbito-frontal areas (Rohrer *et al.*, 2008, 2009; Seeley *et al.*, 2009; Fletcher and Warren, 2011; Lam *et al.*, 2014; Collins *et al.*, 2017; Spinelli *et al.*, 2017; Cope *et al.*, 2020)), regions that are not strongly implicated in the above processes. These ideas remain speculative, but could inform future work.

Overall, I suggest that the findings discussed in this chapter, combined with previous work and theoretical considerations imply that the primary driver of auditory cognitive changes in dementia is through the direct pathogenic changes that target specific brain networks. Seen in this way, the effect of peripheral hearing loss is to ‘unmask’ incipient dementia through its interaction with neurodegenerative pathology. It is important to note that this idea remains compatible with a direct, synergistic role for peripheral hearing loss in augmenting the neural effects of neurodegenerative pathology, although this is beyond the scope of this thesis. Additional insight might be gained by more direct measures of cochlear performance by measurement of otoacoustic emissions, as well as cochlear responses to efferent modulation by examining otoacoustic suppression through contralateral stimulation. The idea that auditory changes in dementia primarily driven by alterations in cognitive abilities might be borne out more readily by examining auditory performance across neurodegenerative diseases under difficult listening conditions, which is explored in the next chapter (chapter 4).



## 4 Speech perception tests in dementia

### 4.1 Chapter Summary

#### 4.1.1 Aims

- Measure performance on degraded speech tests across canonical dementia syndromes
- Compare performance between novel and pre-existing degraded speech tests
- Make a preliminary assessment of the potential of degraded speech tests as sensitive and specific physiological biomarkers of neurodegenerative diseases

#### 4.1.2 Methods

- A total of 37 patients with FTD (svPPA, nvPPA and bvFTD) and AD were assessed with 15 healthy older patients acting as a control group
- The gaps-in-noise test was used as a test of absolute temporal acuity
- Three, novel degraded speech tests were created and compared with a pre-existing speech-in-babble task
- To account for the possible confounding effect of peripheral hearing status on test performance a speech specific audiometrically derived measure (speech intelligibility index) was included as a covariate in the statistical models

#### 4.1.3 Results

- There was no statistically significant difference in temporal absolute threshold across syndromes
- Performance on the three novel degraded speech tests was significantly impaired across the FTD syndromes, but not AD, with the nvPPA group consistently performing poorest
- There were no significant differences between groups on the pre-existing speech-in-babble test

#### 4.1.4 Conclusion

- Degraded speech tests show promise as potential ‘stress tests’ of auditory cognitive function
- This effect is not generic, with variation in the sensitivity of individual tests to detect group differences in performance that are likely due to syndrome specific network involvement

- Certain tests were able to stratify syndromic groups, suggesting a degree of specificity that may inform future work on the design of syndrome specific tests
- Overall, degraded speech tests may prove useful as physiological biomarkers of neurodegenerative disease



## 4.2 Introduction

A core goal of the work in this PhD is to investigate the potential utility of auditory cognitive tests as diagnostic tools in dementia, based on the demands they place on the auditory brain. Degraded speech refers to speech that has been altered in some way as to reduce the intelligibility of this signal (Jiang *et al.*, 2021). Several key observations have motivated interest in and the development of degraded speech tests: first, difficulty listening in degraded conditions (e.g. noise or reverb) is both the commonest complaint of older listeners (whom are at greatest risk of developing dementia); second, speech-in-noise perception (SiN) is highly variable even in listeners with ‘normal’ audiograms; third, cortical mechanisms are likely to contribute significantly to SiN perception. In general terms, due to the variety of cognitive demands imposed by degraded speech processing, degraded speech offers significant potential as a cognitive ‘stress test’. More specifically, as neurodegenerative diseases target discrete, large-scale brain networks (Seeley *et al.*, 2009; Warren *et al.*, 2013, Johnson *et al.*, 2021a; Vogel *et al.*, 2021), tests of degraded speech perception could be useful in examining how the brain recruits the resources required to resolve the specific challenges posed by any type of degraded speech, giving greater insight into brain function and symptomatology as well as being potential functional biomarkers of disease.

### Degraded speech perception

The importance of cortical processing in degraded speech is underscored by the fact that hearing in noise ability widely varies, despite similarities in audiogram or speech understanding in quiet, with composite measures of cognition and access to spectrotemporal fine structure ((TFS) i.e. cochlear performance) best predicting performance across a range of SiN tasks (Füllgrabe *et al.*, 2015; Billings and Madsen, 2018; Holmes and Griffiths, 2019; Yeend *et al.*, 2019; Lad *et al.*, 2020). Acoustically, speech perception is most affected by degradation of information in the temporal domain, with neural decoding of speech depending primarily on activity patterns in the left AC (Albouy *et al.*, 2020). This is demonstrated by the fact that when speech is time-compressed, phase locking to speech envelope predicts successful detection of a target word (Ahissar *et al.*, 2001). Of course, any impoverishment of sensory encoding in the periphery and/or subcortical structures may have negative perceptual consequences at a cortical level (Bidelman *et al.*, 2019b). During speech processing the brain is especially sensitive to acoustic onsets, which may be particularly useful in noisy environments as it promotes segmentation cues, such as phonetic or word boundaries and measurement of grouping thresholds (where segmentation is through cross-correlation of temporally coherent and harmonically related events) better characterises SiN performance than absolute audiometric thresholds alone (Daube *et al.*, 2019; Holmes and Griffiths, 2019; Sohoglu, 2019). Cortically, speech specific acoustic sensitivity or ‘form-dependence’ is greatest in areas peri-AC, with increasingly ‘form-independent’ (i.e.

acoustically insensitive) areas posteriorly, inferolaterally and in frontal speech-related areas such as IFG and PMC (Davis and Johnsrude, 2003).

Converging evidence from behavioural, pupillometric and neuroimaging measures supports the idea that resolving degraded speech is a cognitively demanding challenge that scales with the complexity of the listening task (Wagner *et al.*, 2016). Current computational/theoretical models of degraded speech processing posit the importance of the reciprocal interplay of “bottom-up” auditory sensory information, with integrative “top-down” predictions based on prior knowledge and contextual information (Jiang *et al.*, 2021). A unifying framework for this dynamic is provided by the theory of predictive coding, whereby ‘active listening’ supposes one universal imperative: to maximise the evidence for our generative models of the world and describes how discrete lexical, prosodic and speaker attributes give rise to continuous acoustic signals and conversely, how continuous acoustic signals are recognised as words (Friston *et al.*, 2020; Jiang *et al.*, 2021). Dynamics consistent with the predictive coding model have been demonstrated in fronto-temporal circuits that form the core speech network (Kumar *et al.*, 2011; Cope *et al.*, 2017; Chao *et al.*, 2018; Benhamou *et al.*, 2020). Domain-specific speech processing regions involve a core speech network of ventral (STG, MTG, ITG, ATL and IFG), with evidence supporting a ‘dual-stream’ of hierarchical and reciprocal information flow from primary auditory cortex in Heschl’s gyrus ventrally (STG, MTG, ITG and ATL) and dorsally (TPJ, IPL and IFG) (Hickok and Poeppel, 2007; Alain *et al.*, 2018; Di Liberto *et al.*, 2018). Additional involvement of domain-general resources such as performance monitoring (cingulo-opercular network), verbal memory (PMC), semantic processing, attention and inhibitory control, are recruited depending on task-demands (fronto-parietal network including the dlPFC and the IPC, (Hoenig and Scheef, 2009; Evans *et al.*, 2016; Ralph *et al.*, 2016; Wagner *et al.*, 2016; Peelle, 2018)).

Neuroimaging studies of degraded speech perception consistently identify broadly similar regions, suggesting a symmetric but left-weighted network with additional contributions from the pre-SMA, left hippocampus and bilateral anterior insulae (Davis and Johnsrude, 2003; Adank, 2012; Jiang *et al.*, 2021). Importantly, higher listening effort in degraded speech processing is associated with more extensive recruitment of both the domain-specific and domain-general regions involved in resolving degraded speech described above, which is both task specific and adaptive. Listeners who are more resistant to the detrimental effects of noise in degraded speech perception show greater flexibility in allocation of these neural resources to task (Obleser *et al.*, 2007; Alain *et al.*, 2018; Price *et al.*, 2019; Schiavo and Froemke, 2019; Rysop *et al.*, 2021).

### **Temporal processing and neurodegenerative disease**

Given the fundamental time dependence of auditory processing and the sensitivity of speech perception to timing cues described above, investigating basic temporal processing acuity across neurodegenerative diseases may give additional insights into difficulties with degraded speech perception. Previous evidence of deficits in rhythm processing have been demonstrated in participants with nvPPA, with the authors favouring a unifying deficit of temporal processing as being responsible for several features of this syndrome (Grube *et al.*, 2016). Additionally, basal ganglia structures have been shown to play a role in both absolute and relative timing judgements (Cope *et al.*, 2012, 2014; Merchant *et al.*, 2013; Paton and Buonomano, 2018), with basal ganglia atrophy having been demonstrated in bvFTD (Seeley *et al.*, 2008; Whitwell *et al.*, 2009; Rohrer *et al.*, 2011; Bocchetta *et al.*, 2018; Cash *et al.*, 2018). There is also evidence that frontal regions appear to play a role in temporal processing judgements (Grondin, 2010), which might lead to common difficulties in temporal processing across FTD generally.

One of the commonest methods for measuring temporal resolution is gap detection, where participants are required to identify silent intervals of varying duration, which is typically 2-3ms (Phillips, 1999). The Gaps-in-Noise (GIN) test included here uses a broadband stimulus that is less likely to lead to variation in performance due to peripheral hearing status and has been used extensively in participants without dementia (Musiek *et al.*, 2005). The task is affected by lesions in both the brainstem and 'cerebrum' (in the original experiment this included six patients with 'left hemisphere lesions', two with 'right hemisphere lesions' and one with a 'diffuse lesion' affecting both hemispheres), although appears to be more sensitive to 'cortical lesions' (Musiek *et al.*, 2005; Musiek and Chermak, 2015).

### **Degraded speech tests and neurodegenerative disease**

Multiple degraded speech tests have been developed over the years to probe 'central auditory function'. 'Low-redundancy' tests are ones where the speech signal has been degraded in some way as to reduce the amount of redundancy built into the speech sample, thereby reducing the information available for analysis. Broadly speaking, low-redundancy tests can be grouped into three classes: i) tests that alter the spectral content of speech (such as low-pass filtered speech, or noise-vocoded speech), ii) speech-in-noise or speech-in-competition tests and iii) time-compressed speech tests (Musiek and Chermak, 2015). In addition to some degree of sensitivity to central auditory dysfunction, they provide insights regarding an individual's 'auditory closure' abilities, i.e. the ability of the brain to resolve the auditory signal with reduced information (Musiek and Chermak, 2015). Given the extensive cortical processing of degraded speech, this ability is eroded by central auditory dysfunction, which limits the brain's ability to deploy the wide range of cognitive resources that assist in resolving the degraded signal. All low-redundancy tests are potentially sensitive to the effects of peripheral hearing loss, but

nonetheless, spectrally filtered (low-pass) and time-compressed speech tests have been shown to be sensitive to cortical and subcortical pathology (Karlsson and Rosenhall, 1995).

There are a priori reasons to believe that low-redundancy tests are likely to be impaired across neurodegenerative syndromes (Hardy *et al.*, 2016; Johnson *et al.*, 2020, 2021a). Most obviously, the three PPA syndromes share a common primary degeneration of language function via differential involvement of brain regions involved in speech processing (Seeley *et al.*, 2009, Hardy *et al.*, 2017b, a; Marshall *et al.*, 2018). Additionally, differential involvement of domain-general frontal and temporal lobe regions recruited during effortful listening are likely to be compromised across FTD syndromes (Seeley *et al.*, 2009; Whitwell *et al.*, 2012; Rohrer *et al.*, 2015; Cash *et al.*, 2018). AD and lvPPA share common involvement of posterior speech areas involving the tempo-parietal junction that are important for phonological processing as well as precuneus, IPL and hippocampus that I described above in the context of semantic control, working memory and attention (Seeley *et al.*, 2009; Warren *et al.*, 2012; Vogel *et al.*, 2021).

There is limited existing data on the use of the tests described above in dementia, but individuals with AD have been shown to perform significantly worse than healthy control participants on speech-in-competition tasks (Gates *et al.*, 2010, 2011, Golden *et al.*, 2015a) and AD participants who were administered a low-pass filter test performed significantly worse than healthy controls (Krishnamurti *et al.*, 2011). In a test of phonemic structure using ‘spectrally rotated speech’ (the energy spectrum remains constant but is inverted), svPPA and nvPPA showed equivalent, significantly inferior performance when compared to controls (Hardy *et al.*, 2017a). The same stimuli were used to assess activation patterns using fMRI, demonstrating bilateral activation of lateral posterior to mid STG and STS as well as dorsal motor areas (Hardy *et al.*, 2017b). To my knowledge, no time-compressed speech tests have been explored explicitly in the context of dementia, but monosyllable time-compressed speech tests used in patients with non-degenerative diffuse cortical lesions have shown significant deterioration compared to controls at compression rates of 60% (Kurdziel *et al.*, 1976; Bornstein *et al.*, 1994; Wilson *et al.*, 1994; Karlsson and Rosenhall, 1995).

In summary, the complexity of processing degraded speech places increased demands on cognitive processes that are proportional to the difficulty of the task. Under non-challenging conditions responses are dominated by domain-specific auditory areas, but as listening becomes more difficult, domain-general brain regions are increasingly recruited. The cognitive ‘effort’ imposed by the computational complexity of resolving degraded speech makes them potentially ideal “stress tests” in dementia. Both the domain-specific and domain-general regions involved in degraded speech processing are also likely to be differentially involved across dementia syndromes, which may enable some specificity in stratifying syndromic groupings. On the temporal acuity task, I predict performance

across the FTD groups to be worse than both healthy control and AD participants, with the bvFTD group likely to be the most severely affected due to basal ganglia involvement. For the degraded speech tests, I predict worst performance in the nvPPA group due to a combination of bottom-up sensory processing deficits as well as abnormal frontal top-down prediction mechanisms, followed by significant deficits in the bvFTD group through domain-general frontal compromise and the AD group via involvement of inferior parietal regions. I predict an intermediate deficit in the svPPA group through compromise of semantic lexical access.

## 4.3 Methods

### 4.3.1 Participants

Ten patients with typical AD, fifteen patients with BvFTD, eight patients with svPPA and six patients with nvPPA were recruited along with their partners, with each group meeting the relevant syndromic diagnostic criteria for mild to moderate severity (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011; Dubois *et al.*, 2014). Fifteen healthy older individuals with no history of neurological or psychiatric disorders participated as control subjects.

A summary of the demographic, clinical and general neuropsychological characteristics of participants are listed in Table 3.1.

### 4.3.2 Experimental design and stimuli

The general setup for each experiment in this thesis is described in general methods section 2.6. All speech tests included in this chapter were designed to record the performance threshold of the subject on that test, using the same ‘1up-1down’ staircase paradigm, whereby a correct response prompts the program to increase the difficulty level by one step and an incorrect response causes a step down in difficulty. The procedure automatically terminates once performance reaches a statistical threshold accuracy of 50% (averaged over the preceding 8 trials), i.e. the average success rate has dropped to chance levels. Each test delivers a single target word which the subject is asked to repeat back to the examiner. Subjects with aphasia were permitted to write the word they heard if they were unable to repeat it. Words were presented in random order and responses were inputted by me into the experimental program as either correct or incorrect. The program automatically stored responses in a text file for later analysis offline.

Speech production is highly variable, with phonetic makeup, manner of articulation, prosodic tendencies of the speaker and other suprasegmental cues having a significant influence on the intelligibility of individual words (Eggebraaten and Bae, 2017; Spyridakou *et al.*, 2020). The time-compressed speech (monosyllable) and speech-in-babble (SiB) test both used the same pre-recorded, phonemically and phonetically balanced consonant-vowel-consonant word lists previously recorded on compact disc and supplied to the Dementia Research Centre (DRC), by Professor Doris-Eva Bamiou, UCL (Bamiou *et al.*, 2015; Spyridakou *et al.*, 2020). This list was retained for the time-compressed speech (monosyllable) test as the list has been previously validated in a UK population in the SiB test (Spyridakou *et al.*, 2020).

Previous evidence shows that monosyllabic words tend to be acoustically less uniform and have shallower articulation functions (i.e. are less discriminatory) than spondee words (disyllable words with equal stress on both syllables, such as “cowboy” (HUDGINS *et al.*, 1947; Eggebraaten and Bae, 2017)). To examine whether or not using a spondee word list is superior to a monosyllable word list, both the Spectrally Filtered Speech and Time-Compressed Speech (Spondee) tests utilised the C.I.D. W-1 list of 36 spondee words originally developed by Hudgins *et al.* (HUDGINS *et al.*, 1947; Eggebraaten and Bae, 2017) and adopted as the standard list prescribed by the American Speech-Language-Hearing Association ((ASHA), table 4.1). A small number of ‘American-English’ words were replaced with a ‘British-English’ spondee to reduce familiarity bias (e.g., “sidewalk” was replaced with “pavement”). For the same reason, the word list was recorded by a male with a native Standard Southern English accent, using neutral intonation to reduce variance from prosodic cues. The words were recorded at the UCL Language and Cognition Department in a sound-proof booth, using a condensing microphone with a

pop-shield to reduce sibilant artefact. Samples were recorded using the audio software platform Audacity®, Version 2.2.3.



**Table 4.1 C.I.D W-1 spondee word list**

Airport (Airplane)	Farewell	Iceberg	Playground
Armchair	Football (Baseball)	Inkwell	Railroad
Birthday	Grandson	Mousetrap	Schoolboy
Cowboy	Greenhouse (Hothouse)	Mushroom	Stairway
Daybreak	Greyhound	Northwest	Sunset
Doormat	Hardware	Oatmeal	Toothbrush
Drawbridge	Headlight	Padlock	Whitewash
Duckpond	Horseshoe	Pancake	Woodwork
Eardrum	Hotdog	Pavement (Sidewalk)	Workshop

The C.I.D W-1 spondee word list comprising 36 spondee words. ‘American-English’ words that were replaced with ‘British-English’ equivalents are indicated in brackets.

#### 4.3.2.1 Gaps-In-Noise Test

The Gaps-In-Noise Test (GIN) was adapted from Musiek et al (Musiek *et al.*, 2005). The GIN is composed of a series of 6-sec segments of computer-generated broadband noise containing 0 to 3 silent intervals or ‘gaps’ per noise segment. Each gap contains a tone pip. The inter-stimulus interval between successive noise tokens (segments) is 5 secs and the gap durations presented are 2, 3, 4, 5, 6, 8, 10, 12, 15 and 20 msec. Both gap duration and the location of gaps within the noise segments are pseudorandomised with regard to when they occur. The number of gaps per noise segment is also varied. The minimum duration between consecutive gaps is 500 msec. Participants were familiarised with the task and were told that in each segment the maximum number of pips was 3 and the minimum number was 0. 4 practice trials were played to familiarise participants with the test. Experimental evaluation followed with 36 trials, with each gap duration presented a total of 6 times. Participants were asked to indicate their responses either by stating the number of gaps explicitly, using a clicker, or finger-counting according to preference and respective deficits.

Test score was evaluated as both mean score (%) and the approximate threshold (ms), which was determined by calculating the lowest threshold where the participant scored 4/6 correct and score on all thresholds above was maintained at a minimum of 4/6. If a participant scored less than 4/6 on a higher threshold, the next threshold score of 4/6 was used as the approximate threshold.

The original test was designed to be administered monaurally to each ear in an effort to lateralise central auditory dysfunction, however, this requires 17 minutes of test time, which I found to be excessive for our participant groups and was concerned that variation in test performance would predominantly reflect fatigue or loss of attention, rather than true gap duration performance. Early testing revealed performance between ears to be equivalent and therefore testing was administered binaurally to halve the test time. This sacrifices the lateralisation afforded by monaural testing, however, with strong a priori assumptions about lateralisation, I felt this compromise was justified.

#### 4.3.2.2 Spectrally Filtered Speech

The stimuli manipulated for this test were the spondee words as described above in section 4.3.2 and listed in Table 4.1. Stimuli were manipulated to progressively narrow the spectral bandwidth in the speech signal to simulate degraded listening conditions similar to a telephone line. The non-manipulated condition was labelled 8000 Hz to approximate the range of frequencies included in the raw speech signal. All subsequent stimuli were high-pass filtered at 350 Hz to remove all fundamental frequencies from the speech waveform and were simultaneously low-pass filtered using a 48dB roll-off

from the centre-frequency of a specified Bark scale critical band. A roll-off is used instead of sharp cut-off to avoid introducing acoustic artefacts into the speech signal.

Critical bands describe the frequency bandwidth of an auditory filter in the cochlea and are roughly equivalent to the more commonly used 1/3 octave bands. 1/3 octave bands are more mathematically convenient, but less 'physiological' than the Bark scale, which was derived directly from measurements in humans and is why I used it here. The Bark scale was derived by Zwicker in 1961 (see table 8.4 in the appendix, (Zwicker, 1961)). This gave a total of fourteen filter levels, with the corresponding peak centre-frequencies: 8000, 3400, 2900, 2500, 2150, 1850, 1600, 1370, 1170, 1000, 840, 700, 570, 450 Hz. Example spectrograms for the word "cowboy" at 8000, 3400, 1850 and 450 Hz are shown in figure 4.2. Because filter bandwidth increases with increasing frequency, the test was scored by filter number, rather than centre frequency to avoid introducing non-linearities in the data and biasing towards extreme data points.

Figure 4.2 Spectrogram of the word “cowboy” at 8000 Hz, 3400 Hz, 1850 Hz and 450Hz peak frequencies

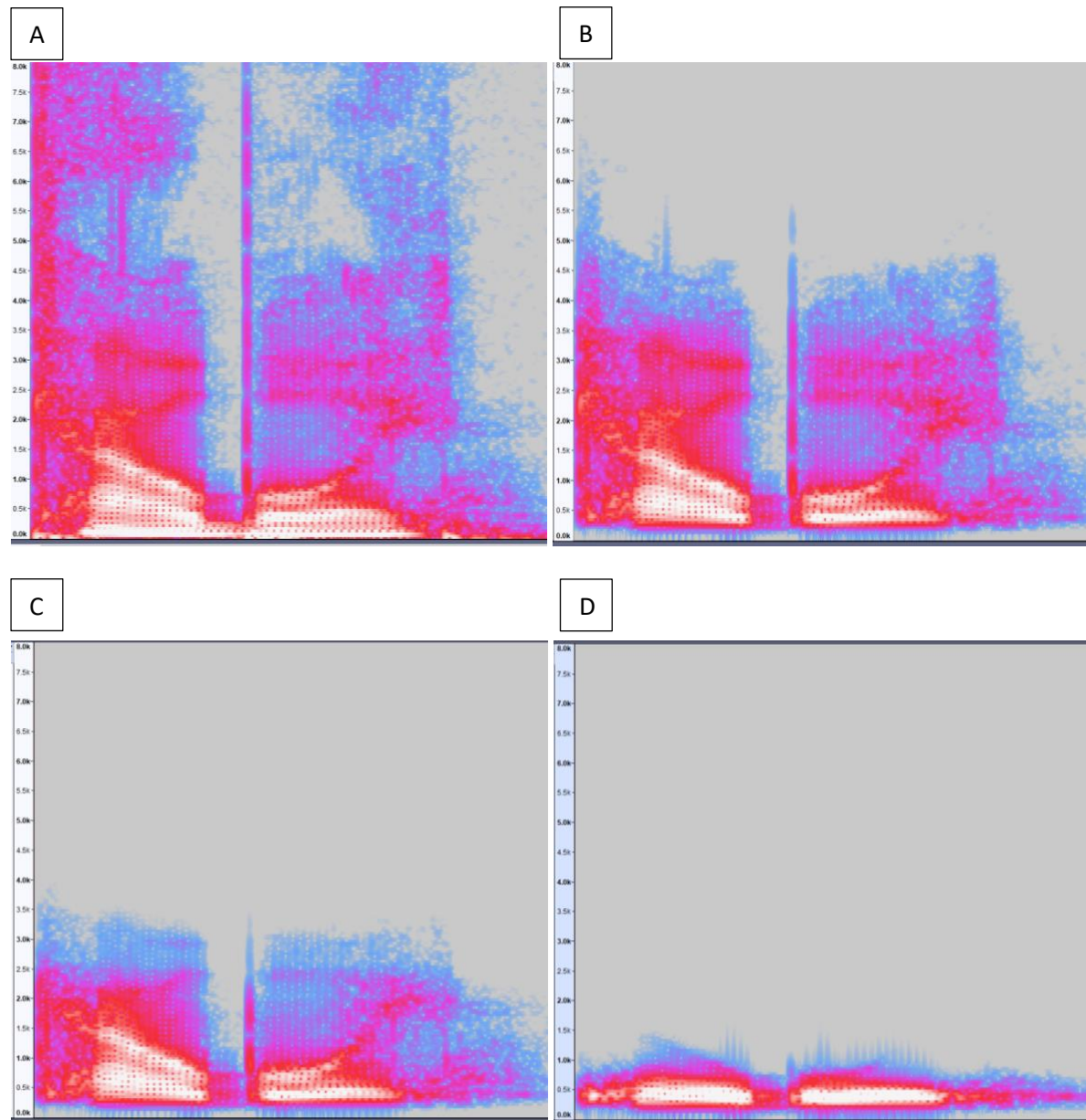


Figure 4.1 Spectrogram of the word “cowboy” at 8000 Hz, 3400 Hz, 1850 Hz and 450Hz peak frequencies

Colour intensity represents energy across frequencies from blue (low energy) to red (high energy). **A** Unfiltered speech with a spectral bandwidth of approximately 0 – 8000 Hz, representing 22 auditory filters. **B** 350 – 3400 Hz band-pass filtered speech, excluding frequencies below 350 Hz and above 3400 Hz, representing 14 auditory filters. **C** 350 – 1850 Hz band-pass filtered speech, representing 10 auditory filters. **D** 350 – 450 Hz band-pass filtered speech, representing 2 auditory filters.

#### 4.3.2.3 Time-Compressed Speech (Monosyllable)

Using the phonemically and phonetically balanced word list described in section 4.3.2, stimuli were manipulated to progressively time-compress each word as a percentage of the original word length, i.e. 100% compression would correspond to the word being presented twice as fast as the original word. Compression was achieved digitally using a time-compression algorithm in Audacity®, Version 2.2.3 which manipulates the rate of speech without altering the power spectrum or pitch of the speech. Compression rates were between 0 and 260% in steps of 20%. Stimuli were presented in a randomised order using the 1up-1down staircase paradigm described in section 4.3.2.

#### 4.3.2.4 Time-Compressed Speech (Spondee)

Using the C.I.D W-1 spondee word shown in table 4.1, the same time compression procedure described above in section 4.3.2.3 was used for this test. Compression rates were between 0 and 300% in steps of 20%. Stimuli were presented in a randomised order using the 1up-1down staircase paradigm described in section 4.3.2.

#### 4.3.2.5 Speech-In-Babble

A similar procedure was used to that described by Bamiou and Spyridakou (Bamiou *et al.*, 2015; Spyridakou *et al.*, 2020). In brief, 25 randomly selected monosyllabic consonant-vowel-consonant words from a phonemically and phonetically balanced list recorded by a female, native Standard Southern English' speaker presented on a background of multi-talker babble. The multi-talker babble is a mixed recording of 20 different talkers at approximately equal levels and was taken from the UCH/Middlesex Hospital Video LaserDisc 1993: IHR babble.wff (.wav) sampled May 23, 1996: 22.05 kHz, 16-bit file (66 dB(A) root-mean-square sample values): 15 sec. The babble was presented at a constant level and the level of the target word was varied to alter the SNR. Each trial was 6s long, with the target presented at 3s. The SNR values used in my experiment ranged from 16 dB to 0dB SNR in steps of 4 dB SNR.

### 4.4 Statistical Analysis

A full description of the analysis pipeline used in this thesis is given in general methods section 2.9. For each experiment included in this chapter a main effect of disease group on test score was tested, followed by post-hoc between-group comparisons if the omnibus test was significant. Effect sizes were estimated in the regression model by calculating Eta-squared.

All experiments included in this chapter used the same covariates of speech intelligibility (SII) index to control for effects of peripheral hearing status on test performance and WASI Matrices score as a

marker of both disease severity and executive function. The SII was derived from each participant's pure tone audiogram using the in-built software in the GSI Audiostar Pro audiometer and is described in detail in section 2.5.2 in chapter 2. I chose to use the SII to adjust for the effect of peripheral hearing status over the pure tone average as it is a more specific (and nuanced) measure of the impact of an individual's pattern of peripheral hearing loss on their ability to recognise speech because it is weighted towards speech specific frequencies.

A threshold of  $p < 0.05$  was accepted as the criterion of statistical significance for all tests.

## 4.5 Results

### 4.5.1 General participant characteristics

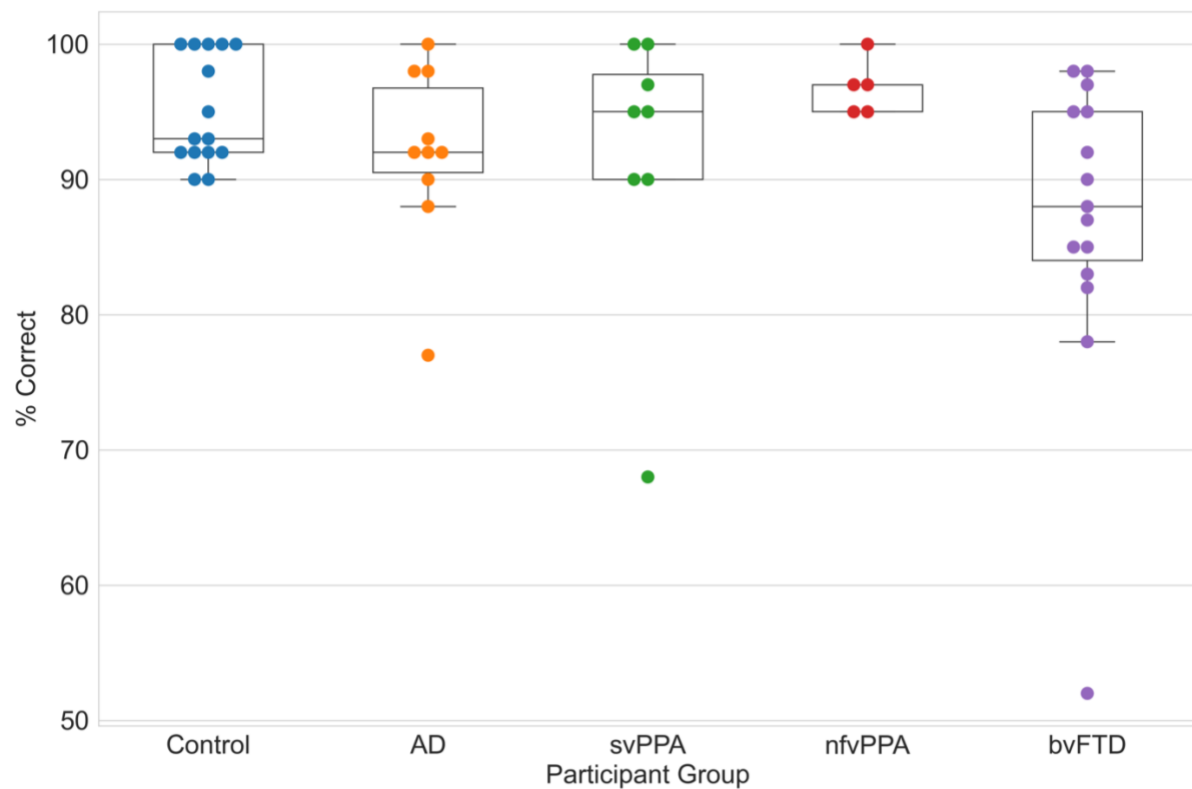
General participant characteristics are summarised in table 3.1 in chapter 3. Patient groups did not differ significantly from healthy controls in gender distribution, age or handedness, ( $p > 0.05$ ). Mean symptom duration differed significantly between patient groups, with significantly longer disease duration in the svPPA and bvFTD groups compared to the AD and nvPPA groups, but overall severity of cognitive impairment did not (MMSE). Hearing threshold and SII both differed significantly between groups.

### 4.5.2 Performance on Gaps-In-Noise

GIN average score results failed to satisfy two assumptions of the GLM: normality of distribution of residuals and homogeneity of variance. The Kruskal-Wallis rank sum test was used for comparison of means across groups and the Mann-Whitney U test was used for between group comparisons. Participant groups differed significantly in their performance on the GIN task ( $(\chi^2(4) = 9.592, p = 0.0479, \text{with ties})$ ). Post-hoc comparisons between disease groups and healthy controls revealed that this was driven by the bvFTD group performing significantly worse than the healthy control group ( $z = 2.608, p = 0.0091$ ). No other group differences were significant.

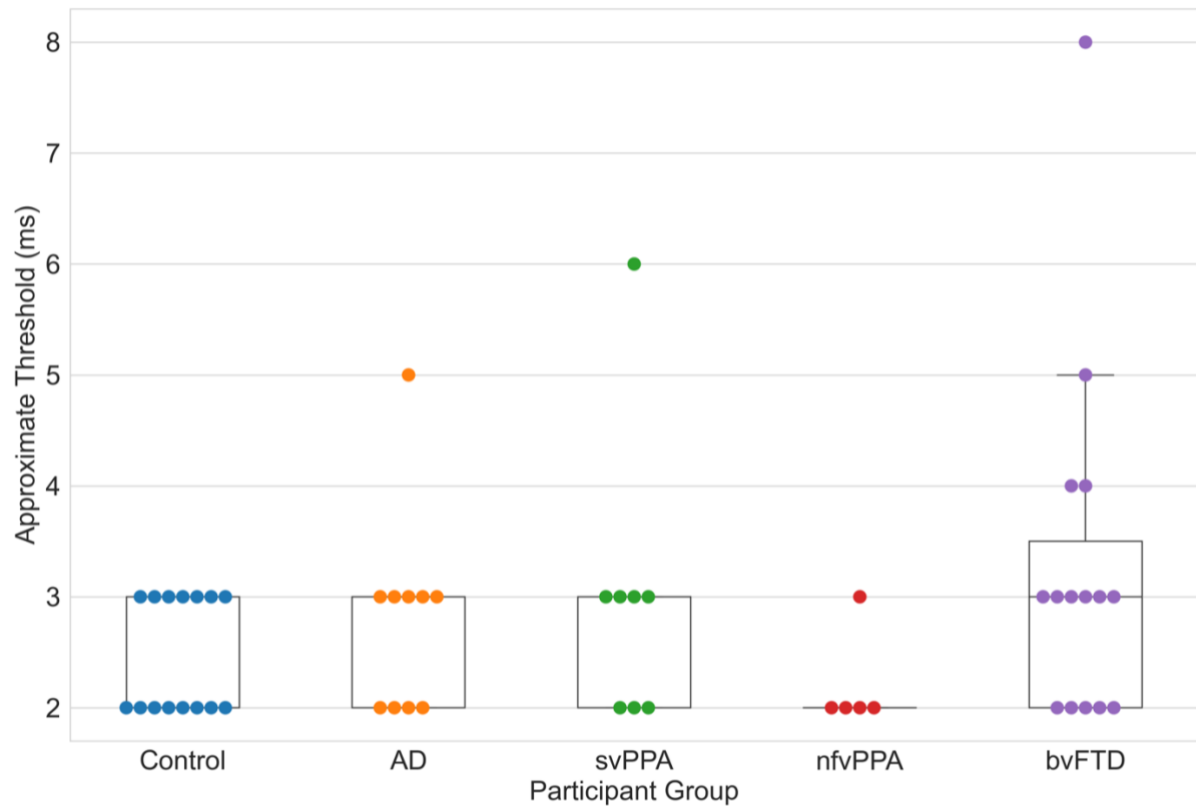
Inspecting individual scores (Figure 4.3), aside from the bvFTD group, most participants scored more than 90%, with many individuals performing at ceiling, particularly in the healthy control group. Only the BvFTD group had individuals with mean scores of less than 90%, with approximately 53% (8/15) of the group scoring less than 90%. All groups showed significant overlap with one another; the bvFTD group showed the widest variation in scores, but overall, scores within the other groups were relatively tightly correlated.

GIN approximate threshold violated the same assumptions of the GLM as the GIN average score. Participant groups did not show significant differences in approximate threshold ( $\chi^2(4) = 5.536$ ,  $p = 0.2402$ , with ties), see Table 6.5.2.3, Figure 6.5.2.2)).



**Figure 4.2 Percentage of correctly identified gaps on the Gaps-In-Noise (GIN) test**

Profiles of participant group performance on the Gaps-In-Noise task. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. Circles represent individual participant performance. **AD**, Alzheimer's disease; **svPPA**, semantic dementia; **nfvPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.



**Figure 4.3 Approximate gap-detection threshold in milliseconds (ms)**

Profiles of participant group approximate thresholds on the Gaps-In-Noise task. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. Circles represent individual participant performance. **AD**, Alzheimer's disease; **svPPA**, semantic dementia; **nvPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.



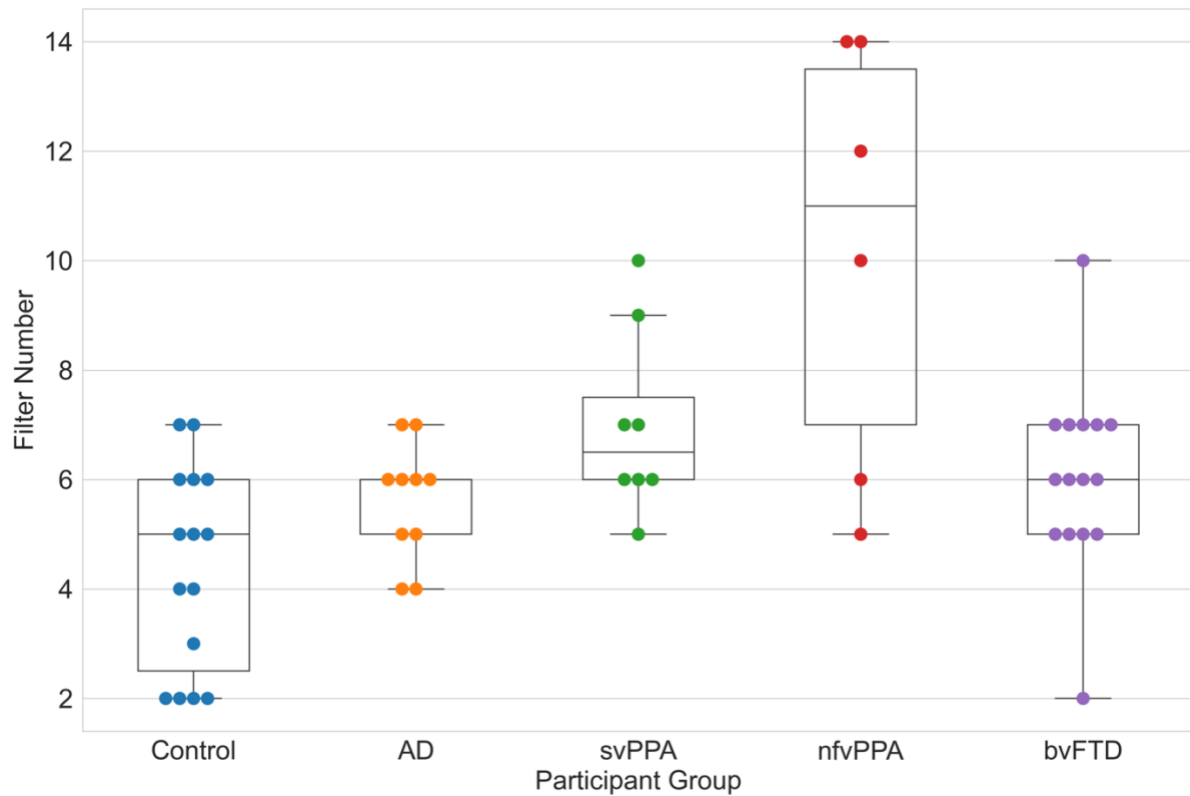
### 4.5.3 Performance on Spectrally Filtered Speech

Participant groups differed significantly in their performance on the spectrally filtered speech task ( $F(6,44) = 7.393$ ,  $p < 0.001$ ). Post-hoc between group comparisons revealed that this was driven by the nvPPA group performing significantly worse than the AD ( $t = -4.13$ ,  $p < 0.001$ , 95% CI: [-6.387 to -2.197]), svPPA ( $t = -3.18$ ,  $p < 0.001$ , 95% CI: [-6.016 to -1.344]), bvFTD ( $t = -4.34$ ,  $p < 0.001$ , 95% CI: [-6.221 to -2.272]) and healthy control ( $t = -5.88$ ,  $p < 0.001$ , 95% CI: [-8.296 to -4.061]) groups; the svPPA group performing significantly worse than the healthy control group ( $t = -2.94$ ;  $p < 0.005$ , 95% CI: [-4.21 to -.787]); and the bvFTD group performing significantly worse than the healthy control group ( $t = -2.28$ ,  $p = 0.028$ , 95% CI: [3.642 to -.222]). No other group differences were significant.

Inspecting individual scores (Figure 4.5), 67% (4/6), participants in the nvPPA group scored below the healthy control range, compared to 25% (2/8) in the svPPA group, and 6.7% (1/15) in the BvFTD group. All scores in the AD group overlapped with the healthy control group. While the most severe individual performance deficits were exhibited by patients with nvPPA, there was wide variation in performance within groups.

There was no significant effect of SII ( $t = -0.76$ ,  $p > 0.05$ , 95% CI: [-0.56 to 0.025]) or WASI matrices score ( $t = 1.65$ ,  $p > 0.05$ , 95% CI: [-0.15 to 0.146]) on test performance.

Effect size estimation through calculation of eta-squared statistics revealed that approximately 50.2% (95% CI: [21.1% to 59.9%]) of performance results were explained by the model. Disease group was the main driver of test performance, explaining approximately 47% (95% CI: [20.4% to 59%]) of the model, with SII contributing approximately 1.3% (95% CI: [0% to 13.9%]) and WASI matrices score 5.8% (95% CI: [0% to 22.2%], see Table 4.2).



**Figure 4.4 Spectrally Filtered Speech**

Profiles of participant group performance on the spectrally filtered speech task. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. Circles represent individual participant performance. **AD**, Alzheimer's disease; **svPPA**, semantic dementia; **nfvPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.

**Table 4.2 Estimation of Effect Sizes for perception of Spectrally Filtered Speech**

Effect sizes for linear models	Eta-Squared	Df	[95%Conf.	Interval]
Model	0.502	6	0.211	0.599
Group	0.472	4	0.204	0.590
SII	0.013	1	.	0.139
WASI Matrices	0.058	1	.	0.222

This table summarises effect sizes using eta-squared for the spectrally filtered speech test with SII and WASI Matrices score included in the model

#### 4.5.4 Performance on Time-Compressed Speech (Monosyllable)

Participant groups differed significantly in their performance on the time-compressed speech (single word) task ( $F(6,44) = 6.131$ ,  $p < 0.001$ ). Post-hoc between group comparisons revealed that this was driven by the nvPPA group performing significantly worse than the healthy control ( $t = -3.53$ ,  $p < 0.001$ , 95% CI: [-142.084 to -38.755]) and svPPA groups ( $t = -2.29$ ,  $p = 0.027$ , 95% CI: [-121.802 to -7.819]) and the bvFTD group performing significantly worse than the healthy control group ( $t = -3.11$ ,  $p < 0.001$ , 95% CI: [-106.193 to -22.753]). No other group differences were significant.

Inspecting individual scores (figure 4.5, panel A), there was overlap of test scores amongst all groups. The nvPPA group showed the most consistent results, with all scores clustered between 0 and 40 % compression. All other groups showed significant variation in test scores.

There was a significant effect of SII on test performance ( $t = 2.61$ ,  $p = 0.012$ , 95% CI: [0.289 to 2.254]). The effect of WASI matrices score was non-significant ( $t = 0.02$ ,  $p > 0.05$ , 95% CI: [-1.947 to 1.979]).

Effect size estimation through calculation of eta-squared revealed that approximately 45.5% (95% CI: [15.8% to 55.8%]) of performance results were explained by the model. Disease group was the main driver of test performance, although this only explained approximately 26% (95% CI: [25% to 40.7%]) of the effect in the model, with SII contributing approximately 13% (95% CI: [0.6% to 31.8%]) of the effect and WASI matrices 0% (see table 4.3).

#### 4.5.5 Performance on Time-Compressed Speech (Spondee)

Participant groups differed significantly in their performance on the time-compressed speech (spondee) task ( $F(6,44) = 15.385$ ,  $p < 0.001$ ). Post-hoc between group comparisons revealed that this was driven by the nvPPA group performing significantly worse than the healthy control ( $t = -6.16$ ,  $p < 0.001$ , 95% CI: [-171.52 to -86.9]), AD ( $t = -4.93$ ,  $p < 0.001$ , 95% CI: [-144.17 to -60.5]), svPPA ( $t = -2.56$ ,  $p = 0.014$ , 95% CI: [-105.96 to -12.7]) and bvFTD ( $t = -4.96$ ,  $p < 0.001$ , 95% CI: [-136.53 to -57.68]) groups and the svPPA group performing significantly worse than the healthy control group ( $t = -4.12$ ,  $p < 0.001$ , 95% CI: [-104.1 to -35.75]). No other group differences were significant.

Inspecting individual scores (figure 4.5, panel B), 83% (5/6) of patients in the nvPPA group scored below the healthy control range, compared to 37.5% (3/8) in the svPPA group, 26.7% (4/15) in the BvFTD group and 30% (3/10) in the AD group. While the most severe individual performance results were exhibited by participants in the nvPPA group, there was wide variation in performance within groups.

There was a significant effect of SII ( $t = 4.27$ ,  $p < 0.01$ , 95% CI: [0.898 to 2.506]) on test performance. The effect of WASI matrices score on test score was non-significant ( $t = 0.39$ ,  $p > 0.05$ , 95% CI: [-1.29 to 1.92]).

Effect size estimation through calculation of eta-squared revealed that approximately 67.7% (95% CI: [44.8% to 74.4%]) of performance results were explained by the model. Disease group was the main driver of test performance, explaining approximately 54.1% (95% CI: [28.5% to 64.6%]) of test performance, with SII contributing approximately 29.3% (95% CI: [8.7% to 47.1%]) and WASI matrices score 0.4% (95% CI: [0% to 10.3%], see table 4.3).

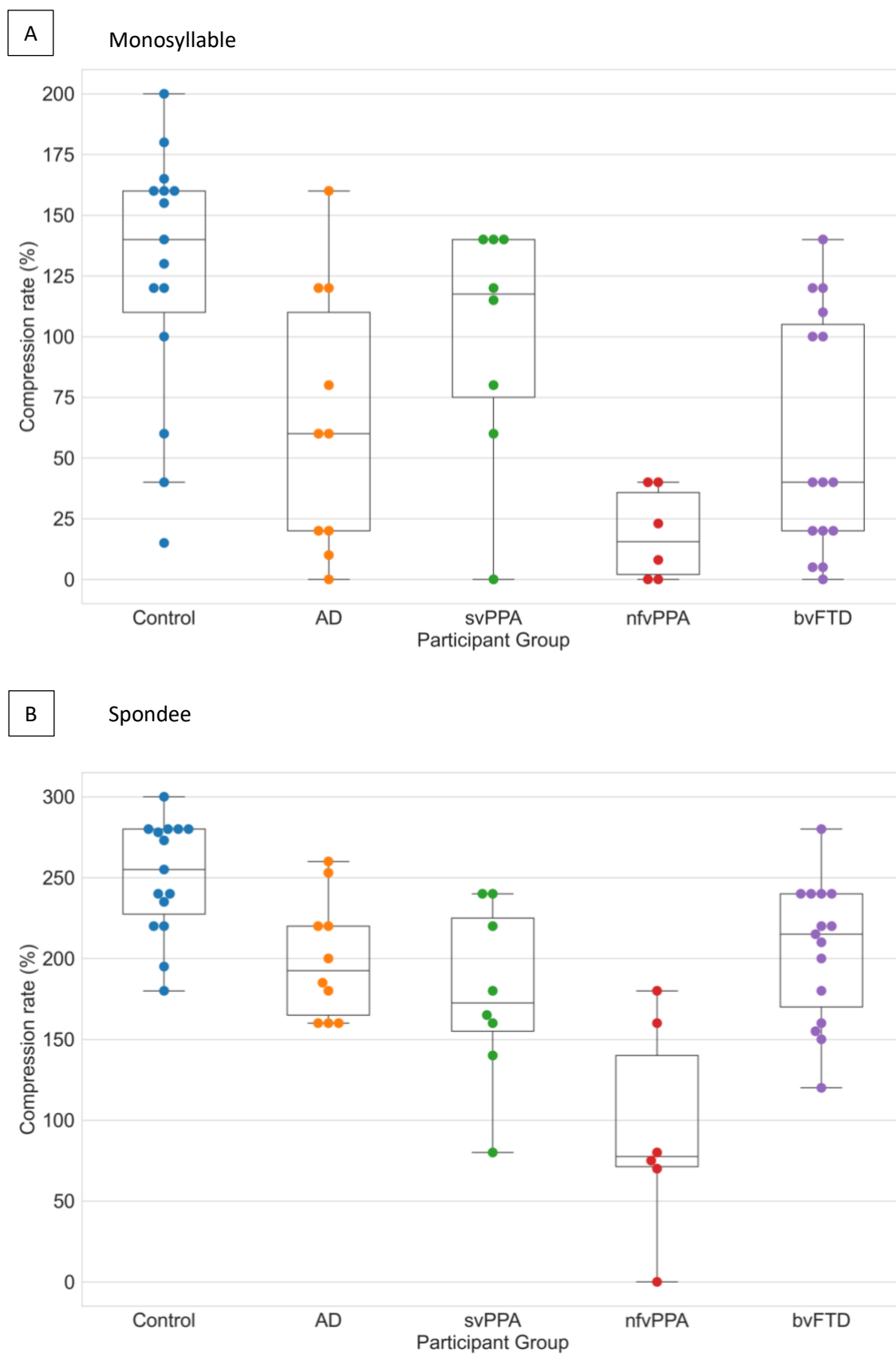


Figure 4.5 Time-compressed Speech Performance

**A** Profiles of participant group performance on the time-compressed (monosyllable) speech task. **B** Profiles of participant group performance on the time-compressed (spondee) speech task. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. Circles represent individual participant performance. **AD**, Alzheimer's disease; **svPPA**, semantic dementia; **nfvPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.

**Table 4.3 Estimation of Effect Sizes for perception of Time-compressed Speech**

Effect sizes for linear models	Eta-Squared	df	[95%Conf.	Interval]
<b>Time-compressed speech (monosyllable)</b>				
Model	0.455	6	0.158	0.558
Group	0.266	4	0.025	0.407
SII	0.134	1	0.006	0.318
WASI Matrices	0.000	1	.	.
<b>Time-compressed speech (spondee)</b>				
Model	0.677	6	0.448	0.744
Group	0.541	4	0.285	0.646
SII	0.293	1	0.087	0.471
WASI Matrices	0.004	1	.	0.103

This table summarises effect sizes using eta-squared for the time-compressed speech (monosyllable) and time-compressed speech (spondee) tests with SII and WASI Matrices score included in the model

#### 4.5.7 Performance on speech-in-babble

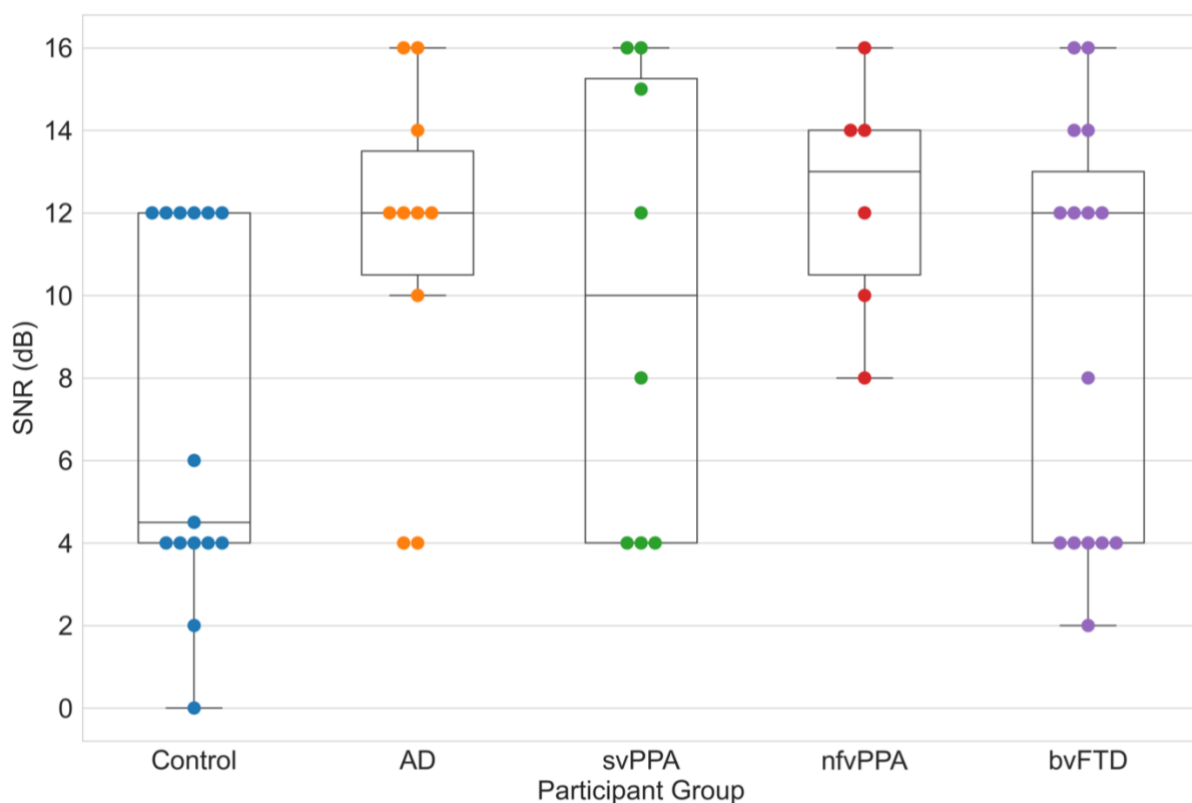
Participant groups differed did not differ significantly in their performance on the speech-in-babble task ( $F(6,44) = 2.943, p < 0.017$ ).

Inspecting individual scores (figure 4.4), there was significant overlap in performance across all groups, with wide variation in performance within groups.

There was a significant effect of SII ( $t = -2.87, p < 0.01, 95\% \text{ CI: } [-0.22 \text{ to } -0.039]$ ) on test performance. The effect of WASI matrices score on test score was non-significant ( $t = -0.27, p > 0.05, 95\% \text{ CI: } [-0.21 \text{ to } 0.158]$ ).

Effect size estimation through calculation of eta-squared revealed that approximately 28.6% (95% CI: [1.0% to 40%]) of performance results were explained by the model. SII was the main driver of test performance, explaining approximately 15.7% (95% CI: [1.4% to 34.3%]) of the model, with disease group explaining only 7% (95% CI: [0% to 17.2%]) of test performance and WASI matrices score 0.2% (95% CI: [0 to 8.8%], see table 4.4).





**Figure 4.6 Speech-in-Babble**

Profiles of participant group performance on the speech-in-babble task. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. Circles represent individual participant performance. AD, Alzheimer's disease; svPPA, semantic dementia; NFVPPA, progressive non-fluent aphasia; BvFTD, behavioural variant frontotemporal dementia. SNR (dB), signal-to-noise ratio in decibels.

**Table 4.4 Estimation of Effect Sizes for perception of Speech-in-Babble**

Effect sizes for linear models	Eta-Squared	df	[95%Conf.	Interval]
Model	0.286	6	0.010	0.401
Group	0.070	4	.	0.172
SII	0.157	1	0.014	0.343
WASI Matrices	0.002	1	.	0.088

This table summarises effect sizes using eta-squared for the speech-in-babble test with SII and WASI Matrices score included in the model

## 4.6 Discussion

The findings presented in this chapter demonstrate that patients with canonical syndromes of FTD perform significantly worse than patients with AD and healthy controls on three low-redundancy speech tests: spectrally filtered speech, time-compressed speech (monosyllable) and time-compressed speech (spondee). Within FTD, the nvPPA group performed worst on all three tests. These deficits persisted when a speech-weighted index of peripheral hearing status (speech intelligibility index) and a measure of disease severity were included in the statistical model as covariates. There was no significant difference in performance amongst any of the groups on a speech-in-competition test: speech-in-babble. On a test of temporal processing acuity (GIN), there was a significant difference in performance between bvFTD patients and controls in terms of mean percent correct, however, there was no significant difference between any group and controls when absolute gap detection threshold was measured.

### **Temporal acuity and neurodegenerative disease**

The neural basis of timing information is distributed and to some degree, task-specific (Paton and Buonomano, 2018). This is not surprising given the fact that time itself is continuous and therefore has the potential for infinite scale. Specific to speech, timing information is particularly relevant to segmentation of the speech signal by temporal onsets, with speech related timing activity predominantly served by neural activity patterns in the left primary AC (Albouy *et al.*, 2020). There is evidence that pathological changes related to AD and FTD pathology occur in the auditory cortex (Baloyannis *et al.*, 2011a, b), with limited data suggesting relative sparing of primary AC as compared to higher auditory areas in AD (Esiri *et al.*, 1986; Griffiths *et al.*, 2020). Results from the GIN test recorded here are internally inconsistent at face value, with bvFTD patients showing significantly poorer gap detection scores than controls when measured as percentage correct score, but no significant difference in absolute gap detection thresholds across groups. A true deficit in gap detection in bvFTD patients might be explained by compromise of fronto-striatal circuits in bvFTD, as basal ganglia structures have both a timing-specific role (Grondin, 2010; Merchant *et al.*, 2013; Cope *et al.*, 2014; Paton and Buonomano, 2018) and are involved in network activity subserving task monitoring, with evidence for gap detection success in healthy adults correlating with activation in primary auditory cortices and the cingulo-opercular network (Üstün *et al.*, 2017; Vaden *et al.*, 2017, 2020). Additionally, patients with FTD show significant thalamic atrophy compared to controls, with thalamic circuits being implicated in unified-time perception as well as a role in speech processing by top-down modulation (i.e. tuning) of thalamic responses to fast time-varying features (von Kriegstein *et al.*, 2008; Merchant *et al.*, 2013; Bocchetta *et al.*, 2018).

Whilst the above explanation for gap detection differences has some face validity, there are several reasons why the result may be specious. First, absolute threshold is almost certainly a more useful metric of temporal acuity than percent correct score, particularly in the context of patients with bvFTD, who are likely to have non-task related variability in performance, especially on a gap detection task which is lengthy and has low salience. This is reinforced by the fact that the bvFTD group showed the greatest variability, with the most extreme data points. Second, the gap detection task used here assesses temporal acuity in the millisecond range, whereas studies assessing basal ganglia involvement in temporal judgements suggest they are relevant in the hundreds of milliseconds to seconds range (Merchant *et al.*, 2013; Cope *et al.*, 2014; Paton and Buonomano, 2018) and frontal regions appear to play a role in the accumulation of temporal information over time (Grondin, 2010). Finally, whilst there are differences in the degree of thalamic degeneration in FTD across syndromes, it remains a common feature of all FTD sub-syndromes (FTD atrophy relative to controls: bvFTD 9%, nvPPA 8% and svPPA 5%) so one would expect each to suffer the same effect, which is clearly not the case in this data (Bocchetta *et al.*, 2018). Overall, I suggest that there is no evidence of significant differences in temporal acuity in the millisecond range between controls and patients with dementia, but this would be borne out better with larger group sizes.

### **Degraded speech and neurodegenerative disease**

The spectrally filtered speech test and the time-compressed speech tests showed highly concordant profiles of group performance, with the effect of group accounting for the majority of the variance in the statistical model. Of the three, the best performing model overall was for the time-compressed (spondee) test, followed by the spectrally filtered speech test and finally the time-compressed (monosyllable) test. The spectrally filtered speech and time-compressed speech tests presented here use the same fundamental structure and both degrade the spectro-temporal characteristics of the speech signal directly (although the mechanism and emphasis are different) and therefore are worth considering together. Acoustically, the spectrally filtered speech test primarily alters spectrotemporal fine structure (TFS) whilst the time-compressed speech tests primarily affect the temporal envelope (ENV). Speech recognition is dominated ENV cues, but is enhanced by access to TFS, particularly in complex listening conditions (Shannon *et al.*, 1995; Moon *et al.*, 2014). ‘Phonetic cues’ are acoustic dimensions that are used perceptually to identify speech sounds; there are a number of co-occurring phonetic cues for any particular speech contrast, which is why there is high redundancy (and therefore robust intelligibility) in the speech signal (Winn *et al.*, 2012). TFS can convey at least two types of segmental phonetic information: segmental cues to place of articulation and vowel quality and segmental cues to voicing and manner. ENV cues include manner of articulation, voicing, vowel identity

and prosody (Rosen, 1992). In reality, TFS and ENV cues are interdependent both acoustically and perceptually and therefore degradation of either has some degree of effect on the other.

The nvPPA group showed universally poorest performance on the spectrally filtered speech and time-compressed speech tests, in line with my predictions. ‘Pure’ nvPPA reportedly shows atrophy restricted to IFG and pre-SMA, however, the heterogeneity of nvPPA is increasingly recognised both syndromically and anatomically, with additional involvement of striatal and peri-Sylvian regions being demonstrated (Rohrer *et al.*, 2009; Seeley *et al.*, 2009; Cope *et al.*, 2017; Spinelli *et al.*, 2017; Henry *et al.*, 2018; Lombardi *et al.*, 2021). One would anticipate that compromise of these key speech processing regions results in a particularly detrimental interaction between impaired bottom-up sensory processing and overly precise, inflexible top-down prediction mechanisms between the IFG and temporal cortex (Rohrer *et al.*, 2009; Seeley *et al.*, 2009; Grube *et al.*, 2016; Cope *et al.*, 2017; Hardy *et al.*, 2017a; Spinelli *et al.*, 2017; Henry *et al.*, 2018; Lombardi *et al.*, 2021). Evidence for the effect of this inflexibility is indirectly supported by the fact that rapid perceptual learning bolsters performance on time-compressed speech tasks (Rotman *et al.*, 2020) and previous work on perceptual learning of degraded speech has shown that nvPPA patients were the most consistently impaired group when learning sine-wave speech compared to other dementia participants and healthy controls (Hardy *et al.*, 2018).

Both the bvFTD and svPPA groups showed significantly reduced performance on the spectrally filtered speech test. Atrophy in bvFTD is heterogeneous with early atrophy of frontal and fronto-limbic regions, as well as basal ganglia structures (Seeley *et al.*, 2008; Whitwell *et al.*, 2009; Rohrer *et al.*, 2011; Bocchetta *et al.*, 2018; Cash *et al.*, 2018). Orbito-frontal and anterior temporal white matter tracts degenerate and functionally there is fronto-limbic disconnection, with elevated local connectivity within prefrontal cortex (Farb *et al.*, 2013; Lam *et al.*, 2014). Cingulo-opercular activity increases as the speech signal progressively degrades and has been shown to positively correlate with word recognition in healthy adults, whilst fronto-opercular atrophy in both bvFTD and nvPPA negatively correlates with phonemic and semantic fluency (Vaden *et al.*, 2013, 2015, 2017; Suppa *et al.*, 2020). svPPA is dominated by initially asymmetric (left more than right) antero-inferior temporal lobe atrophy, with caudal extension to include structures in the mesial, inferior and lateral temporal lobes, with later disease including inferior frontal regions and fronto-temporal white-matter tracts (Rohrer *et al.*, 2008, 2009; Seeley *et al.*, 2009; Fletcher and Warren, 2011; Lam *et al.*, 2014; Collins *et al.*, 2017; Spinelli *et al.*, 2017; Cope *et al.*, 2020). Functionally, svPPA demonstrates decreased ATL connectivity to left MTG and IFG, with MTG-ATL connectivity correlating specifically with naming and word comprehension (Friederici, 2015; Bonilha *et al.*, 2017; Bonakdarpour *et al.*, 2019). Additionally, left ATL atrophy increases activity

in homologous right hemisphere structures, demonstrating a loss of left-laterality. This combination of temporal lobe atrophy in anterior temporal lobe areas and loss of laterality suggests that semantic compromise forces increased reliance on acoustic cues as processing is 'pushed' posteriorly in the temporal lobe, but that non-speech optimised areas in the right temporal lobe are recruited maladaptively to compensate (Cope *et al.*, 2020). This would be concordant with the svPPA group performing relatively worse than the bvFTD group on the spectrally filtered speech task but being less severely affected than the nvPPA group who sustain a 'double-hit' to both peri-Sylvian speech regions and key frontal speech regions.

In the bvFTD group, time-compressed speech performance was only significantly impaired on the monosyllable task. Monosyllable words tend to be acoustically less uniform and have shallower articulation functions (i.e. are less discriminatory) than spondee words (HUDGINS *et al.*, 1947); this effect was reflected in the greater within group variance on the time-compressed (monosyllable) test across all groups compared to the two spondaic word tests. In light of the small group sizes, giving a specific interpretation to this result may therefore be specious. In contrast to the bvFTD group, on the time-compressed speech tests, the svPPA group only showed significantly reduced performance on the spondee version of the test, which was concordant with svPPA group performance on the spectrally filtered speech test being worse than the bvFTD group. This might be explained by the greater influence of contextual information on the recognition of spondee words compared to monosyllable words (Moulin and Richard, 2015); as the acoustic properties of the word degrade, semantic impairment in participants with svPPA limits their ability to use semantic cues to aid spondaic word recognition. Another factor may be a word frequency effect, which would disproportionately impact patients with svPPA, however, this seems less likely as the C.I.D spondee list comprises high-frequency words in everyday use (HUDGINS *et al.*, 1947; Eggebraaten and Bae, 2017).

Perhaps surprisingly, performance on the degraded speech tasks was not statistically significantly different between AD participants and healthy control participants. This is surprising because one might suspect that core regions involved in typical AD such as the precuneus, temporal and inferior-parietal cortices have been shown to contribute significantly to speech processing in both ideal and degraded conditions (Davis and Johnsrude, 2003; Hoenig and Scheef, 2009; Seeley *et al.*, 2009; Adank, 2012; Whitwell *et al.*, 2012; Evans *et al.*, 2016; Ralph *et al.*, 2016; Wagner *et al.*, 2016; Alain *et al.*, 2018; Peelle, 2018; Jiang *et al.*, 2021). Additionally, only the nvPPA group had worse pure tone audiometry thresholds than the AD group and a significant degree of task performance on the time-compressed speech tests was attributable to peripheral hearing status. Finally there is evidence that brain regions involved in semantic control are altered in mild AD, although this did not correlate with performance

on linguistic tests (Mascali *et al.*, 2018). This last point is easiest to explain away as the study by Mascali *et al.* demonstrated that altered connectivity did not correlate with naming or phonological word fluency tasks (Mascali *et al.*, 2018), which is perhaps unsurprising as anterior temporal lobe regions (the semantic hub) are typically spared in AD (Seeley *et al.*, 2009; Warren *et al.*, 2012; Vogel *et al.*, 2021). The seeming lack of an effect of peripheral hearing status, despite the fact that only the nvPPA group had worse audiometric thresholds than the AD group and the significant peripheral loading of the time-compressed speech tests on audiometric thresholds is likely due to the fact that the audiometric changes in nvPPA are likely to reflect top-down effects than a primary deficit of peripheral hearing (discussed in chapter 3, (Cope *et al.*, 2017; Hardy *et al.*, 2019)). A fact supported by the nvPPA groups uniquely poor performance on the spectrally filtered speech test which showed much less significant loading on peripheral hearing status. It may be the case that there is sufficient preservation of domain-specific and domain-general frontal regions to allow adequate compensation for the degraded speech tests used here, despite changes elsewhere. Finally, visual inspection of scores showed a trend to worse scores on the time-compressed speech tests in the AD group which might have proven significant with sufficient group size.

### **Speech-in-babble and neurodegenerative disease**

The SiB task did not elicit any significant group differences on task performance and within group variance was high amongst all groups. Whilst some effect of small group sizes might be anticipated, performance was poorly explained by the model, with the majority of the model's explanatory power being driven by peripheral hearing score. Overall then, the SiB task employed here is a poor discriminator in neurodegenerative disease. At face value this may seem curious, as SiN tests are a universally used measure that are often shorthand for 'central hearing ability', therefore providing *prima facie* evidence for inclusion in the degraded speech test battery. Clearly, the increased cognitive demands of processing degraded speech are important across dementia syndromes as evidenced by the data presented above. Additionally, ample previous evidence demonstrates the importance of 'cognitive factors' in SiN perception (Füllgrabe *et al.*, 2015; Billings and Madsen, 2018; Holmes and Griffiths, 2019; Yeend *et al.*, 2019; Lad *et al.*, 2020), but specific aspects of this SiB test (and similarly constructed SiN) may limit its applicability as a test of 'central hearing', by which we really mean auditory cognition.

The addition of any type of noise to a speech test is with the intention of masking, which broadly can be conceptualised as either *energetic masking*, where masker energy is in the same frequency region(s) as the energy in the target signal, which reduces audibility and *informational masking*, where the masker itself is audible but 'competes' for cognitive resources (Rosen *et al.*, 2013). The importance of

this distinction is that *energetic masking* places significant demands on cochlear filtering, whereas *informational masking* taxes cognitive resource. This is supported by the fact that ageing without hearing loss or cognitive impairment (but ‘normal’ age-related cognitive decline) causes a decrease in speech intelligibility in informational maskers but not pure energetic maskers (Rajan and Cainer, 2008). Furthermore, the masking effect of speech *decreases* as more talkers are added (even from only 3 talkers upwards), i.e. pure *energetic masking* poses less cognitive demand (Rosen *et al.*, 2013). The SiB test used here used a 20-talker babble, which is spectrally approaching a broadband noise signal and therefore would be predicted to produce predominantly energetic masking. One would therefore expect performance to be most dependent on peripheral hearing status, which is consistent with the results obtained.

Evidence in this chapter suggests that participants with FTD have particular difficulty processing certain types of degraded speech. This is unlikely to be attributable to differences in absolute temporal acuity or differences in cochlear function. Degraded speech processing is task-dependent, being supported by a wide network of both domain-specific and domain-general cognitive mechanisms that is distributed across the brain. Extending these findings, performance on degraded speech tasks will be underwritten by the unique pathological involvement of large-scale brain networks across dementia syndromes. A unifying framework for the neural basis of these difficulties might be provided by predictive coding, a theory that posits the brain as a ‘Bayesian inference engine’, i.e. one that generates a predictive model of the current state of the world which is updated based on the sensory evidence it receives and how this compares to the model itself (Friston, 2005; Friston and Kiebel, 2009; Parr *et al.*, 2018). In this sense listening is an active process, that is instantiated in the brain (Friston *et al.*, 2020; Jiang *et al.*, 2021). Importantly, predictive coding is reciprocal and hierarchical, mediated by ‘feed-forward’ and ‘feed-back’ connections across cortical layers, with errors cascading from any given level throughout the system. The severe difficulties in the nvPPA cohort support this view as this disease has the most clear evidence of damage to pre-frontal regions implicated in ‘top-down’ auditory signal processing, as well as compromise of ‘lower-level’, ‘bottom-up’ sensory regions, with support from prior findings and the work in chapter 3 of this thesis (Grube *et al.*, 2016; Cope *et al.*, 2017; Friston *et al.*, 2020). Whilst this is theoretically plausible, the small group numbers, particularly in the nvPPA group should mean the results in this chapter, should be treated as preliminary and that proposed mechanisms remain speculative.

In contrast to the relatively general approach of exploiting computational complexity through degraded speech tasks in this chapter, in the next chapter I explore the specific ‘auditory signature’ of degenerative changes in a discrete ‘higher-order’ auditory processing brain region.





## 5 Phonological processing in dementia

### 5.1 Chapter Summary

#### 5.1.1 Aims

- Assessment of phonological processing across the primary progressive aphasias and AD
- Explore the syndromic specificity of a test of phonological processing as an auditory diagnostic tool in dementia

#### 5.1.2 Methods

- A total of 81 patients: 20 with lvPPA, 24 with nfvPPA, 22 with svPPA and 15 with typical AD were recruited from a larger longitudinal research cohort, with 73 age-matched healthy individuals who participated as control subjects
- Phonemic discrimination was assessed by using a subset of the PALPA-3 minimal pair task
- The neuroanatomical basis of task performance was assessed using voxel-based morphometry

#### 5.1.3 Results

- Phonemic discrimination was significantly impaired in patients with lvPPA and AD compared to patients with nfvPPA and svPPA as well as healthy control participants, with the lvPPA group being the most severely impaired
- Phonological working memory and audiometric threshold were correlated with task performance, but the effect of group remained significant when adjusted for phonological working memory and audiometric thresholds
- Performance was correlated with grey matter volume in the left angular gyrus

#### 5.1.4 Conclusion

- Phonemic discrimination ability is correlated with grey matter volume in the left angular gyrus, a region that has been consistently reported in studies of phonological processing
- Temporo-parietal regions including the angular gyrus are an early and specific target of lvPPA, the group with the poorest performance on the phonemic discrimination task
- Phonemic discrimination offers promise as a syndromic specific functional biomarker in lvPPA

## 5.2 Introduction

Chapter 4 (Speech Perception Tests in Dementia) of this thesis demonstrated the cross-syndromic utility of speech tests that manipulated the basic acoustic features of the speech signal in distinct ways (TFS or ENV predominant). The combination of ‘low-level’ acoustic changes, with the ‘high-level’ challenges of effortful listening leveraged both domain specific speech and language functions as well as domain general cognitive functions in a non-specific and implicit way (i.e. there was no way to understand explicitly which cognitive mechanisms were involved or the neuroanatomical substrate(s) of the perceptual compromise). To explore the potential use of speech tests as syndrome specific disease markers, I designed an experiment that investigated the effect of explicitly manipulating a ‘higher-order’ perceptual phenomenon (phonemic processing) that has strong prior evidence for neuroanatomical localisation in the IPL, a site which is a specific early target in lvPPA.

### Acoustic to phonetic mapping

Phonology is the linguistic framework that describes the units and structures of speech sounds that make up language, which includes phonemes, the perceptual particles of speech sounds that combine to form words (for example, the combination of /ʃ/, /ɒ/ and /p/ to make “shop” (Rosen, 1992; Yi *et al.*, 2019)). Phonological information is processed hierarchically, with basic acoustic-phonetic mapping and segmentation of phonetic boundaries (“acoustic edges”) subserved by regions in the STG bilaterally, with a left hemisphere bias that appears to be specifically sensitive to temporal structure and acoustic onsets (Overath *et al.*, 2015; Hamilton *et al.*, 2018; Daube *et al.*, 2019; Oganian and Chang, 2019; Yi *et al.*, 2019). There is evidence of selectivity to distinct phonetic features within STG, with acoustic properties encoded in a distributed population response that demonstrates activity suggestive of multi-dimensional integration of cues (Mesgarani *et al.*, 2014). More posteriorly, higher-order, ‘invariant’ representations of speech sounds consistent with phonetic categories are observed, which are more in keeping with ‘auditory object’ representation (Griffiths and Warren, 2004; Chang *et al.*, 2010, Goll *et al.*, 2010b; Okada *et al.*, 2010). PT has been implicated as a generic integration hub for complex sound processing (Griffiths and Warren, 2002), as well as a sensorimotor integration area with highly correlated activity in the pars opercularis (posterior Broca’s, (Warren *et al.*, 2005; Hickok *et al.*, 2009)). Evidence for the idea that the dorsal stream supports ‘form to articulation’ (i.e., uses phonological information to inform articulatory targets) has been furnished using a data driven, lesion based approach in stroke patients (Hickok and Poeppel, 2015; Fridriksson *et al.*, 2016).

### Phonological processing

Beyond the acoustic-phonetic mapping described in the STG, multiple brain regions have been implicated in various aspects of phonological processing. Processing of syllable order or discriminating

sounds on the basis of subtle temporal acoustic features typical of phoneme categories has been associated with activation in the left posterior part of the IFG and IPL regions, which might be explained by prior association of these areas with auditory working-memory (Price, 2012). Specifically, IPL appears to be involved in the detection of differences between phonemic categories (Turkeltaub and Branch Coslett, 2010). Both the SMG and the AG (subregions within the IPL) have been implied as ‘phonological stores’, although evidence for their specific roles is inconsistent (Rauschecker and Scott, 2009; Price, 2012). This may be related to task specific differences, for example, TMS during a semantic similarity task (word-comparison) and a phonological similarity task (homophone judgement) showed that stimulation to left AG slowed semantic but not phonological judgements, whereas stimulation to left SMG selectively affected responses in phonological but not semantic task (Sliwinska *et al.*, 2015).

There is accumulating evidence to suggest that phonological processing of speech sounds arises from the functional integration of acoustic processing in temporal lobe regions and articulatory processing in premotor and frontoparietal regions (Rauschecker and Scott, 2009; Price, 2012). Sensorimotor integration has been implicated in task-dependent working memory processes that maintain sound representations for temporal ordering judgements, clustering around the temporo-parietal junction (Andreatta *et al.*, 2010; Baddeley and Hitch, 2019). This is supported by the finding that covert articulation supports working memory encoding and that covert articulation of speech specifically activates areas in the temporo-parietal junction (Andreatta *et al.*, 2010; Baddeley and Hitch, 2019). As noted in the previous chapter on degraded speech processing, AG may be of additional importance in temporal ordering judgements, or possibly (following the TMS findings above) due to a semantic role in decision making in ambiguous circumstances (Noonan *et al.*, 2013; Ralph *et al.*, 2016; Rysop *et al.*, 2021), although its precise role in semantic cognition remains unclear (Jackson, 2021).

### **Phonological processing in PPA**

Whereas current diagnostic criteria for PPA emphasise impaired language output and linguistic processing (Gorno-Tempini *et al.*, 2011), deficits of auditory analysis are increasingly recognised in both lvPPA and nvPPA, with phonological processing deficits such as impaired accent processing, phonological dyslexia and reduced phonological working memory (Hailstone *et al.*, 2011, Hardy *et al.*, 2017b, 2018, 2019; Ruksenaite *et al.*, 2021). These deficits remain poorly defined but may be particularly relevant to the representation of phonemes as ‘auditory objects’ in lvPPA (Leyton *et al.*, 2014, 2017; Henry *et al.*, 2016; Giannini *et al.*, 2017, Hardy *et al.*, 2017b; Lukic *et al.*, 2019). Atrophy in lvPPA initially targets posterior temporal and inferior parietal cortices (Gorno-Tempini *et al.*, 2008, Rohrer *et al.*, 2010b; Lukic *et al.*, 2019; Tee and Gorno-Tempini, 2019), with significant evidence (discussed above) for the IPL as a core phonological processing region. There are therefore strong a

priori reasons to anticipate particular deficits in receptive phonological processing in lvPPA. Here, I assessed phonemic discrimination and its neuroanatomical correlates in patients representing all major PPA variants, patients with typical Alzheimer's disease (AD) and healthy age-matched individuals. Based on previous work (Dehaene-Lambertz *et al.*, 2005; Gorno-Tempini *et al.*, 2011; Henry *et al.*, 2016), I predicted that phonemic discrimination would be most markedly affected in lvPPA, with a regional grey matter correlate in left temporo-parietal cortex.

## 5.3 Methods

### 5.3.1 Participants

A total of 81 patients: 20 with lvPPA, 24 with nvPPA, 22 with svPPA and 15 with typical AD were recruited from a larger longitudinal research cohort, with each group meeting the relevant consensus diagnostic criteria for mild to moderate severity (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011; Dubois *et al.*, 2014). No participant had a clinical history of primary otological disease, and hearing aid users were excluded. None had radiological evidence of significant co-morbid cerebrovascular disease. All participants were native English speakers. Successful completion of the main experimental task requires the participant to be able to read monosyllabic words successfully, so participants either had to score >14 on the difficult National Adult Reading Test or >18 on the Schonell Graded Word Reading Test (selected as a cut-off because the Schonell test contains 19 monosyllabic words) (Schonell and Schonell, 1974; Nelson, 1982). These were converted using formulae listed in the NART Second Edition test manual into a standard score that is intended to give an indication of premorbid IQ; I used these scores as indicators of general reading ability ('reading IQ'). A total of 54 potential participants were excluded for not meeting the study-specific criteria (see Table 7.2). 73 age-matched healthy individuals with no history of neurological or psychiatric disorders participated as control subjects. Syndromic diagnoses were corroborated by a general neuropsychological assessment including measures of auditory verbal working memory (reverse digit span). Participant characteristics are summarised in Table 5.1.

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

Characteristic	Healthy Control	AD	svPPA	nfvPPA	lvPPA	Omnibus Comparison
<b>Demographic and Clinical</b>						
No. (M:F)	73 (41:32)	15 (3:12)	22 (5:17)	24 (16:8)	20 (6:14)	<b>p = 0.001</b>
Age (years)	65.77 (7.28)	68.98 (5.92)	65.82 (6.85)	67.61 (8.89)	66.57 (7.73)	F(4,149)=0.77 , p=0.545
Handedness (R:L)	43:8 <sup>c</sup>	14:1	20:2	19:5	18:2	p=0.736
Disease duration (years)	N/A	5.91 (2.43)	6.14 (3.47)	4.28 (1.59)	4.77 (2.02)	<b><math>\chi^2(3)=9.73</math>, p=0.021</b>
Education (years)	15.49 (2.78) <sup>d</sup>	15.40 (3.22)	14.91 (3.29)	13.83 (2.65)	15.15 (2.37)	$\chi^2(4)=7.59$ , p=0.108
Hearing Threshold (dB)	25.18 (4.48)	-	29.17 (9.89)	31.11 (9.99)	30.88 (8.14)	$\chi^2(3)=5.90$ , p=0.114
<b>Neuropsychology</b>						
<b>General Intellect</b>						
NART (Reading IQ)	120.29 (5.18)	109.19 (10.76)	100.56 (15.06)	92.01 (20.48)	94.23 (19.10)	<b><math>\chi^2(4)=78.86</math>, p&lt; 0.001</b>
<b>Executive Function</b>						
WASI Matrices (/32)	25.36 (6.62) <sup>b</sup>	14.33 (8.88)	23.09 (7.28)	18.58 (7.17)	12.45 (7.34)	<b><math>\chi^2(4)=55.13</math>, p&lt;0.001</b>
<b>Working Memory</b>						
WMS-R Digit Span Forward (max)	6.86 (1.03)	5.80 (1.08)	7.14 (0.94)	5.08 (1.28)	3.90 (1.29)	<b><math>\chi^2(4)=66.05</math>, p&lt;0.001</b>
WMS-R Digit Span Reverse (max)	5.19 (1.22)	3.87 (1.36)	5.27 (1.35)	3.35 (1.53)	2.70 (1.22)	<b><math>\chi^2(4)=56.65</math>, p&lt;0.001</b>
<b>Comprehension</b>						
PALPA-3 (/36)	35.64 (0.71)	33.53 (1.68) <sup>e</sup>	35.32 (1.17)	34.67 (1.71)	31.80 (4.10) <sup>e</sup>	<b>F(4,146)=8.70 , p&lt;0.001</b>

Mean (standard deviation) values are shown for continuous variables; distributions are shown for categorical variables. The right-hand column gives results of relevant statistical omnibus tests (details in Methods); significant between-group comparisons (p<0.05) are in bold. <sup>a</sup> Hearing composite scores based on pure tone audiometry performance were available for a subset of each participant group (lvPPA n = 10; nfvPPA n = 9; svPPA n = 12; Control n = 28); no hearing data were available for AD patients. <sup>b</sup> Datum was missing for one control participant. <sup>c</sup> Handedness data were not available for 22 healthy control participants. <sup>d</sup> Years of education were not recorded for eight healthy control participants. <sup>e</sup>

Significantly worse performance vs healthy control group in model adjusting for auditory verbal working memory (reverse digit span), reading ability (reading IQ) and gender ( $p < 0.05$ ). Fifty-four potential participants failing to meet study-specific inclusion criteria (the majority with a diagnosis of nvPPA) were excluded from the study. Control, healthy control participant group; F, female; L, left; lvPPA, patient group with logopenic variant primary progressive aphasia; M, male; N, number; nvPPA, patient group with nonfluent/agrammatic variant primary progressive aphasia; PALPA-3, Psycholinguistic Assessments of Language Processing in Aphasia - Test 3 (see text for details); R, right; svPPA, patient group with semantic variant primary progressive aphasia; WASI, Wechsler Abbreviated Scale of Intelligence.

Table 5.2 Subset of items from original 72-item PALPA-3 test used in experiment

No.	No. in original test	Target	Foil	Freq	Location	Type
8	8	Fall	Fawn	High	Final	Manner
11	11	Pain	Pail	High	Final	Manner
24	29	Cup	Cut	High	Final	Place
26	32	Run	Rung	High	Final	Place
20	23	Pig	Pick	High	Final	Voice
28	38	Code	Coat	High	Final	Voice
4	4	Bone	Moan	High	Initial	Manner
23	28	Sack	Tack	High	Initial	Manner
7	7	Deed	Bead	High	Initial	Place
15	16	Fail	Veil	High	Initial	Voice
17	19	Cut	Gut	High	Initial	Voice
29	43	Meat	Neat	High	Initial	Voice
16	18	Nod	Don	High	Metathetic	Manner
34	57	Lean	Kneel	High	Metathetic	Manner
9	9	Tape	Pate	High	Metathetic	Place
12	12	Moan	Gnome	High	Metathetic	Place
14	15	Toad	Dote	High	Metathetic	Voice
36	72	Debt	Ted	High	Metathetic	Voice
5	5	Rice	Write	Low	Final	Manner
22	26	Hen	Head	Low	Final	Manner
32	50	Robe	Road	Low	Final	Place
2	2	Leave	Leaf	Low	Final	Voice
18	20	Live	Life	Low	Final	Voice
30	47	Fang	Fan	Low	Final	Voice
10	10	Nip	Lip	Low	Initial	Manner
25	31	Mat	Bat	Low	Initial	Manner
13	13	Feed	Seed	Low	Initial	Place
19	22	Down	Gown	Low	Initial	Place
1	1	Pill	Bill	Low	Initial	Voice
27	34	Dale	Tale	Low	Initial	Voice
6	6	Mob	Bomb	Low	Metathetic	Manner
31	48	Nail	Lane	Low	Metathetic	Manner
3	3	Pat	Tap	Low	Metathetic	Place
21	24	Dab	Bad	Low	Metathetic	Place
33	54	Tuck	Cut	Low	Metathetic	Place
35	66	Mane	Name	Low	Metathetic	Place

The table gives the 36 pairs that were used in the present study. *Frequency* of the target (compared with the distractor) was manipulated in the original PALPA-3: for half of the items. The target has a higher frequency than the distractor; for the other half the target is lower or equivalent in frequency to the distractor. *Location* refers to the fact that pairs differ either in the initial or final positions of pairs, or in pairs that are metathetically related (i.e. the order of sounds is reversed). *Type* indicates whether the foil minimally deviates from the target in terms of voice, manner, or place of articulation.

### 5.3.2 Experimental design and stimuli

The general setup for each experiment in this thesis is described in general methods section 3.6. Stimuli were selected from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) battery ‘minimal pairs’ Test 3 (PALPA-3, (Kay *et al.*, 1992)) which assesses discrimination of phonemes differing on a single acoustic characteristic. On each trial, participants must underline which of two written words matches a spoken monosyllabic word (e.g., spoken ‘leave’ – written *leave/leaf*). I adopted a subset of 36 trials from the full PALPA-3 test to reduce the total test time and avoid fatigue effects (Table 7.3). Pure tone audiometry data, available for 59 participants, were used to generate a composite measure of peripheral hearing function.

The data used in this experiment were collected prior to the acquisition of the dual-channel GSI Audiostar Pro (*GSI AUDIOSTAR PRO™ USER MANUAL*, 2013) audiometer used in the dataset explored in chapters 4, 5 and 6 and therefore the pure tone audiometry procedure differed slightly to the one previously described. Pure tone audiometry was performed using an Otovation Roto audiometer ([www.otovation.com](http://www.otovation.com)) in a quiet room using the standard clinical audiometry protocol described in the general methods (chapter 3, (BSA, 2018)). Four frequency levels were tested (500, 1000, 2000, 4000 Hz), as opposed to 5 (8000 Hz excluded) due to equipment limitations. 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. The mean average across the four frequencies was calculated for each ear separately, and the lowest of these (i.e. reflecting the better ear) was used as a ‘peripheral hearing composite’ in analyses.

### 5.3.3 Brain MRI acquisition and analysis

#### 5.3.3.1 Structural Brain Imaging

For each subject visit, a sagittal 3-D magnetization-prepared rapid-gradient echo (MPRAGE) T1-weighted volumetric brain MR sequence (TE/TR/TI 2.9/2200/900 ms, dimensions 256 x 256 x 208, voxel volume of 1.1 x 1.1 x 1.1 mm) was acquired on a Siemens Prisma 3T MRI scanner using a 32-channel phased array head-coil. Structural scans were used for voxel-based morphometry analysis to assess the relationship between grey matter atrophy and performance on specific experimental tasks and to exclude any participants with significant vascular disease.



### 5.3.3.2 Structural image pre-processing

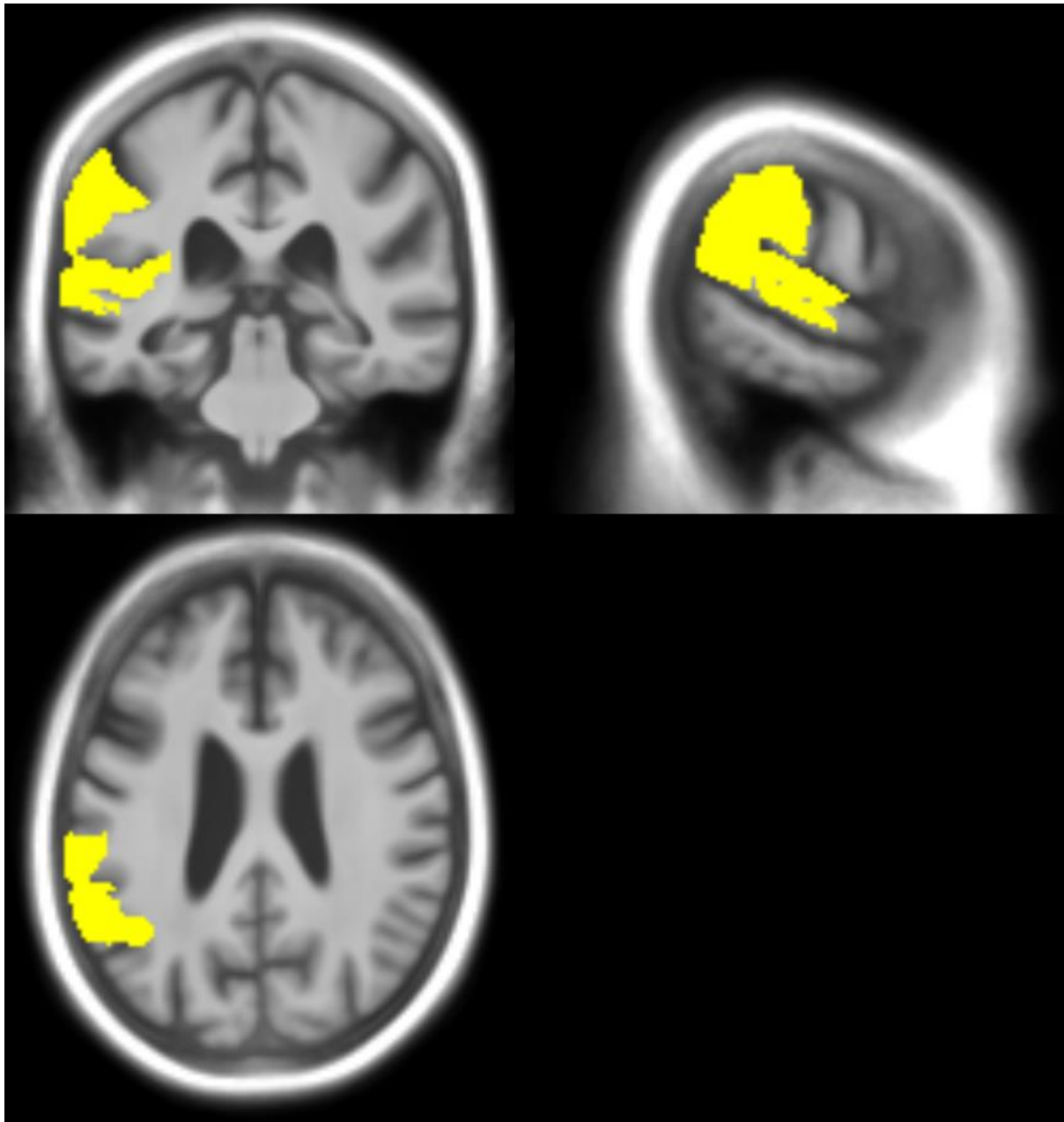
Pre-processing of brain images was performed in MATLAB R2020b™ using SPM12 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)); specifically, toolboxes for segmentation (Weiskopf *et al.*, 2011) and DARTEL (Ashburner, 2007) were applied following an optimised protocol (Ridgway *et al.*, 2008). Segmentation, normalisation and modulation of grey and white matter images were performed with default parameter settings and grey matter images were smoothed using a 6 mm full width-at-half-maximum Gaussian kernel (Worsley *et al.*, 1992). Following segmentation and smoothing, individual images were spatially registered to a group mean DARTEL template and then normalised to Montreal Neurological Institute (MNI) standard stereotactic space. SPM results were overlaid on a study-specific template mean structural brain image template created by warping all bias-corrected native-space T1 brain images to match the final DARTEL template and calculating the average of the warped brain images. An explicit mask was created using an automated strategy in SPM to ensure that only appropriate voxels were included in the analysis (Ridgway *et al.*, 2009). Total intracranial volume (TIV) was calculated for each patient by summing grey matter, white matter and cerebrospinal fluid volumes after automatic segmentation of tissue classes (Malone *et al.*, 2015).

### 5.3.3.3 Voxel based morphometry

Pre-processed structural images were entered into VBM analyses to assess neuroanatomical associations of experimental parameters of interest. Only patient cohorts were included in the VBM analysis to reduce the risk of reproducing anatomical associations representing grey matter atrophy maps of each syndrome, rather than identifying regional brain volume differences associated with the experimental parameter of interest. A multiple regression model was used to assess associations between voxel-wise grey matter volume and PALPA-3 score, adjusting for diagnosis, age, reverse digit span and total intracranial volume (TIV). TIV was used as a proxy for gender as it has been shown that gross morphological differences account for most univariate sex differences in grey matter volume (Ridgway *et al.*, 2009).

Statistical parametric maps were generated using an initial cluster-forming threshold ( $p < 0.001$ ) and assessed at peak statistical significance level  $p < 0.05$  after family-wise error (FWE) correction for multiple voxel-wise comparisons within a pre-specified anatomical region of interest (Figure 5.1). In general, FWE corrections over the whole brain are particularly stringent given the large number of voxels being compared that are unlikely to be relevant to the experimental question being explored. Small volume correction, where analysis is restricted to a specific region of interest (ROI), is an appropriate way of reducing Type I error while still preserving power to detect real effects if the ROI is

defined a priori on neuroanatomical grounds informed by previous literature. The pre-specified anatomical ROI used in this study was based on previous work (Dehaene-Lambertz *et al.*, 2005, Hardy *et al.*, 2017b), comprising left posterior superior temporal, supramarginal and angular gyri and planum temporale (STG, SMG, AG and PT respectively).



**Figure 5.1 Neuroanatomical region of interest specified for VBM analysis**

Representative brain MRI sections showing the neuroanatomical region (delineated in yellow) used to correct for multiple voxel-wise comparisons, based on prior anatomical hypotheses (see text). This region comprised posterior superior temporal gyrus, supramarginal gyrus, angular gyrus, and planum temporale, all in the left hemisphere.

#### 5.4 Statistical analysis

A full description of the analysis pipeline is given in general methods section 2.9. To test for a main effect of participant group on PALPA-3 discrimination score, a multiple linear regression model was

used, with pure tone audiometric score, IQ score, gender and reverse digit span included as covariates. Where this omnibus test was significant, post-hoc between-group comparisons were explored using independent t-tests. Model diagnostics (described in general methods, section 2.9) were performed on each model to confirm that the assumptions of the GLM were met. Where assumptions of the GLM were violated, the non-parametric Kruskal-Wallis test was used for between group comparisons.

Pearson's correlations were used to assess the relationship between phonemic discrimination score and peripheral hearing score, and phonemic discrimination score and active auditory verbal working memory (maximum reverse digit span) in the combined patient cohort.

A threshold of  $p < 0.05$  was accepted as the criterion for statistical significance throughout.

## 5.5 Results

### 5.5.1 General participant characteristics

Demographic, clinical and neuropsychological characteristics are summarised in Table 7.1. Participant groups differed significantly in gender distribution, Fisher exact  $p = 0.001$ , which was driven by the higher proportion of females to males in the nvPPA group than the other three participant groups (Table 1). The non-parametric Kruskal-Wallis test suggested a significant difference between patient groups in mean symptom duration,  $\chi^2(3) = 9.73$ ;  $p = 0.021$ , driven by a shorter duration in nvPPA relative to tAD ( $z = -2.51$ ,  $p = 0.012$ ) and svPPA ( $z = -2.35$ ,  $p = 0.019$ ). Disease severity as measured by WASI matrices score was significantly different between participant groups  $\chi^2(4) = 55.13$ ;  $p < 0.001$  with lvPPA worse than nvPPA,  $z = -2.56$ ,  $p = 0.014$ , lvPPA worse than svPPA,  $z = -3.94$ ,  $p < 0.001$ , no diff between lvPPA and tAD,  $z = -0.70$ ,  $p = 0.483$ , nvPPA worse than svPPA,  $z = -2.45$ ,  $p = 0.014$ , tAD worse than svPPA,  $z = -3.03$ ,  $p = 0.003$ , lvPPA worse than control,  $z = -5.73$ ,  $p < 0.001$ , nvPPA worse than control,  $z = -4.31$ ,  $p < 0.001$ , tAD worse than control,  $z = -4.65$ ,  $p < 0.001$ , no significant difference between svPPA and control,  $z = -1.28$ ,  $p = 0.201$ .

There was a significant difference across groups in reading ability,  $\chi^2(4) = 78.86$ ;  $p < 0.001$ , accounted for by the healthy control group performing better than all patient groups (all  $p < 0.001$ ) and the tAD group scoring higher than patients with lvPPA ( $z = 2.22$ ,  $p = 0.027$ ) and nvPPA ( $z = 2.56$ ,  $p = 0.011$ ). Forward digit span task performance also differed significantly across participant groups,  $\chi^2(4) = 78.86$ ;  $p < 0.001$ , with the lvPPA group performing worse than each other participant group (all  $p < 0.05$ ), patients with nvPPA performing worse than patients with svPPA ( $z = -4.66$ ,  $p < 0.001$ ) and Controls ( $z = -5.27$ ,  $p < 0.001$ ), and patients with tAD performing worse than patients with svPPA ( $z = -3.34$ ,  $p = 0.001$ ) and healthy controls ( $z = -3.21$ ,  $p = 0.001$ ). Similar patterns were seen for reverse digit span task

performance, with an overall significant difference across participant groups,  $\chi^2(4) = 56.65$ ;  $p < 0.001$  explained by the lvPPA group performing significantly worse than all other groups (all  $p < 0.05$ ), and the healthy control and svPPA groups both performing significantly better than the nvPPA and tAD participant groups ( $p < 0.05$ ).

There were no significant differences between groups in mean age [ $F(4,149) = 0.77$ ,  $p = 0.545$ ], handedness ( $p = 0.736$ ), years of education [ $\chi^2(4) = 7.59$ ;  $p = 0.108$ ], or hearing score [ $\chi^2(3) = 5.90$ ;  $p = 0.114$ ]; see Table 1.

### 5.5.2 Performance on phonemic discrimination

Participant groups differed significantly in their performance on the PALPA-3 task  $F(4,146)=8.79$ ,  $p<0.001$ ; see Table 1, Figure 1A). Post-hoc comparisons between groups revealed that this was driven by the lvPPA group performing significantly worse than the nvPPA ( $t=-5.03$ ,  $p<0.001$ ), svPPA ( $t=-4.64$ ,  $p<0.001$ ) and healthy control ( $t=-3.98$ ,  $p<0.001$ ) groups. The AD group also performed significantly worse than the nvPPA ( $t=-2.89$ ,  $p=0.004$ ), svPPA ( $t=-2.99$ ,  $p=0.003$ ) and healthy control ( $t=-2.48$ ,  $p=0.014$ ) groups. No other group differences were significant. Including hearing composite score as an additional covariate in the model revealed a similar performance profile of the lvPPA group versus other participant groups.

Inspecting individual scores (Figure 1A), 40% (8/20) of patients in the lvPPA group scored below the healthy control range, compared to 12.5% (3/24) in the nvPPA group, 4.5% (1/22) in the svPPA group, and 33.3% (5/15) in the AD group. While the most severe individual phonemic discrimination deficits were exhibited by patients with lvPPA, there was wide variation of performance within groups.

### 5.5.3 Correlations with working memory and audiometry

PALPA-3 score was significantly correlated both with reverse digit span across the entire cohort ( $r=0.47$ ,  $p<0.001$ ) and with hearing composite score in the subset of participants for whom hearing data were available ( $r=-0.278$ ,  $p=0.033$ ). To account for the possibility that auditory working memory was the major driver of my results, I ran a regression model including reverse digit span as a covariate in addition to reading IQ score, gender and hearing composite score. This model continued to show a significant difference between groups ( $F(7,51)=5.98$ ,  $p<0.001$ ) driven by the lvPPA group performing significantly worse than the other three participant groups (vs nvPPA  $t = 2.77$ ,  $p = 0.008$ ; vs svPPA  $t = 2.29$ ,  $p = 0.026$ ; vs Control  $t = 2.04$ ,  $p = 0.047$ ); no other between-group comparisons were significant. The AD group was not included in this analysis as audiometry data were not available for this group.

#### 5.5.4 Neuroanatomical associations

Across the PPA cohort, performance on the PALPA-3 task was significantly positively associated with grey matter volume in left angular gyrus ( $t=4.22$ ,  $p=0.031_{\text{FWE}}$ ). No other regional grey matter associations were identified in the pre-specified region of interest or across the whole brain.

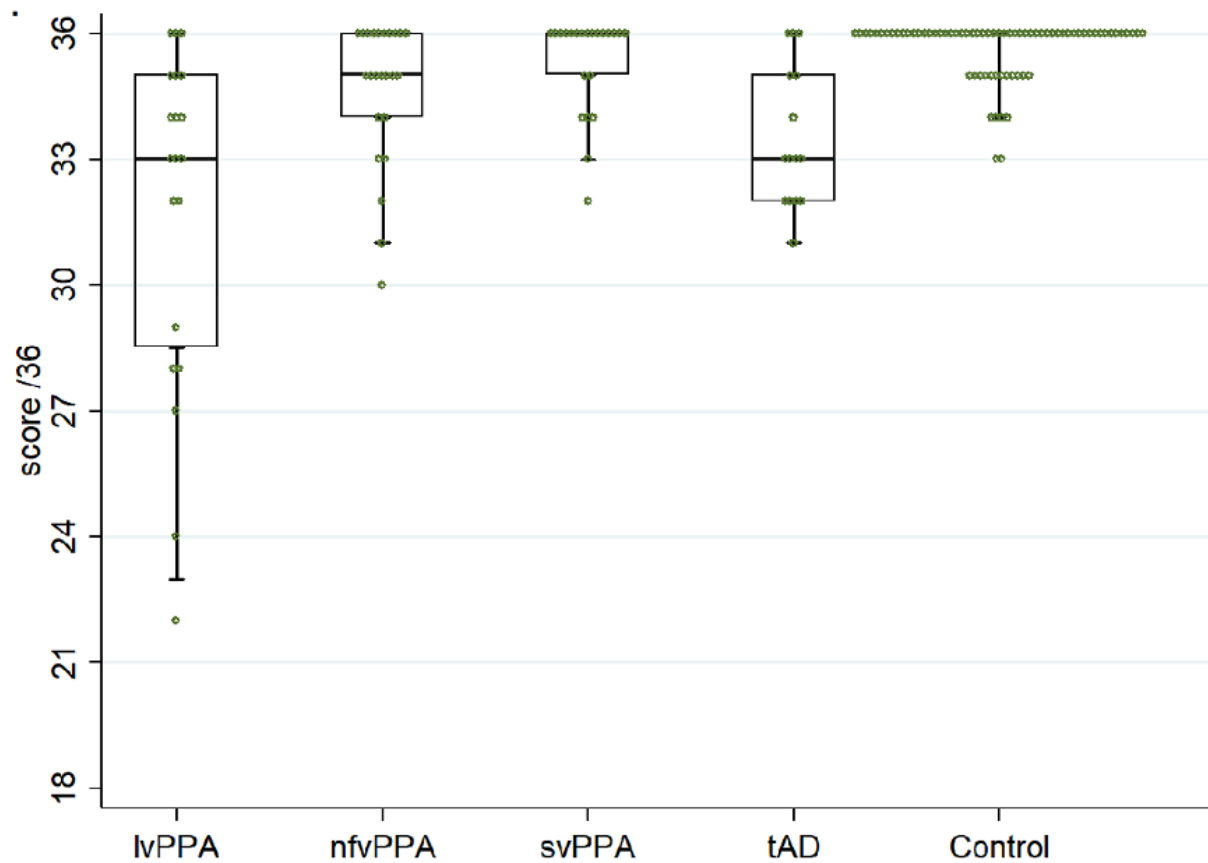
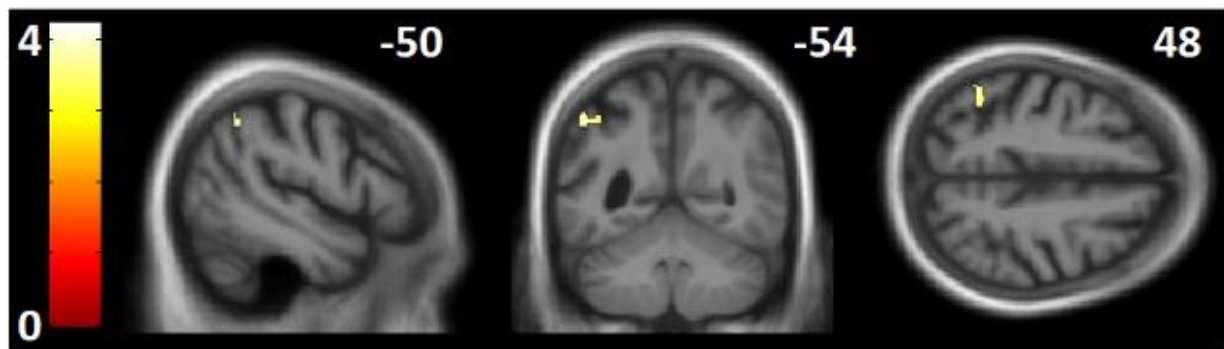


Figure 5.2 Profiles of participant group performance on the PALPA-3 minimal pairs task (see also table 5.1)

Circles show individual participant performance. For each group, horizontal lines indicate median score, oblongs code interquartile range and whiskers 95% confidence intervals; a score of 18 would correspond to chance performance. lvPPA, patient group with logopenic variant primary progressive aphasia; nfvPPA, patient group with nonfluent/agrammatic variant primary progressive aphasia; svPPA, patient group with semantic variant primary progressive aphasia; AD, patient group with typical Alzheimer's disease.



**Figure 5.3 Statistical parametric maps showing regional grey matter changes associated with behavioural performance**

Left angular gyrus positively associated with performance on the PALPA-3 minimal pair discrimination task in the combined PPA patient cohort ( $n=61$ ). Maps are rendered on sagittal (left), coronal (middle) and axial (right) sections of the group mean T1-weighted MR brain image in MNI space, thresholded at  $p < 0.001$  uncorrected for multiple voxel-wise comparisons over the whole brain for display purposes (the area indicated is significant at  $p = 0.031_{\text{FWE}}$  within the prespecified neuroanatomical region of interest (see Supplementary Material online). The colour bar indicates voxel-wise  $t$ -values, and the plane of each section is indicated using the corresponding MNI coordinate.



## 5.7 Discussion

The findings presented in this chapter demonstrate that patients with lvPPA (and to a lesser extent, AD) perform worse on phonemic discrimination than both healthy older individuals and patients with other major variants of PPA. This deficit was not attributable to reduced auditory verbal working memory capacity or peripheral hearing status. Phonemic discrimination performance across the PPA cohort was positively correlated with grey matter volume in left angular gyrus, a region that is likely to be core to the pathophysiology of lvPPA (Rohrer *et al.*, 2010b; Leyton *et al.*, 2014; Henry *et al.*, 2016; Giannini *et al.*, 2017, Hardy *et al.*, 2017b).

These findings corroborate previous work showing that patients with lvPPA perform poorly on tasks requiring manipulation of phonemic representations (e.g. phoneme deletion tasks (Henry *et al.*, 2016)) or decoding of phonemic spectrotemporal features (Hardy *et al.*, 2017b) and that PPA syndromes have specific profiles of auditory cognitive dysfunction (Hardy *et al.*, 2017b, 2019). Phonemic discrimination relies on fine-grained analysis of the ‘boundaries’ that define phonemes as auditory objects: it could therefore be considered to probe the auditory and linguistic processing interface, an earlier processing stage than is conventionally assessed in the linguistic evaluation of PPA. Phase entrainment of cortical oscillations has a specific, causal influence on neural responses to intelligible speech (Zoefel *et al.*, 2018). Sharp fluctuations in the temporal envelope of speech that are characteristic of phonetic boundaries have been shown to drive delta-theta rhythms, allowing the stimulus to be entrained at its syllabic rate, facilitating segmentation; entrainment fidelity correlates with intelligibility of the stimulus (Doelling *et al.*, 2014; Di Liberto *et al.*, 2015; Zoefel *et al.*, 2018). Categorical representations of phonemes that are normally sharply defined (Liberman *et al.*, 1957) might plausibly become ‘blurred’ therefore in lvPPA, making fine-grained phonemic discriminations more difficult. Supporting this notion comes from recent work in patients with lvPPA, showing increased tracking of the speech envelope in the theta band (which represents acoustic features, e.g. phonemes), but not delta oscillations (‘object-level’ representations such as words, phrases, (Dial *et al.*, 2021)). This suggests that poorer representation of phonemes in ‘higher-order’ areas that are more invariant (i.e., categorical, ‘object-like’ representations) forces patients with lvPPA to rely more heavily on the basic acoustic features of the speech signal (in keeping with the findings presented in the degraded speech chapter). Presumably, errors are more likely to occur with such ‘form-dependent’ phonological processing in the presence of words that are acoustically similar and therefore ambiguous, such as those used in the minimal pair discrimination task in this study. This work does not provide direct evidence for this idea, but it should be explored in future work.

The TPJ and IPL in the dominant hemisphere are targeted in lvPPA (Rohrer *et al.*, 2010b; Giannini *et al.*, 2017), with AG having been previously implicated in disambiguating degraded speech signals in PPA and AD (Hardy *et al.*, 2018), as well as in categorical phoneme discrimination in healthy participants (Turkeltaub and Branch Coslett, 2010). This region is affected in different variants of AD (Rohrer *et al.*, 2010b; Giannini *et al.*, 2017), providing a candidate neural substrate for the similar profiles of impaired phonemic discrimination in the lvPPA and AD groups (Leyton *et al.*, 2017), although neuroanatomical associations were only assessed in the PPA cohort here (due to insufficient availability of MRI scans for this cohort). Individual patients with lvPPA were not all impaired on this task, consistent with previous evidence that phonologic errors are not produced by every patient with lvPPA (Leyton *et al.*, 2014). This suggests that phonemic processing deficits may stratify sub-syndromes within lvPPA and raises the further possibility that deficits of phonemic perception and production may be coupled via fronto-parietal processing streams (Hickok *et al.*, 2011; Leonard *et al.*, 2016; Broderick *et al.*, 2018).

As discussed in the introduction to this chapter, sensorimotor integration has been implicated in task-dependent working memory processes that maintain sound representations for temporal ordering judgements, clustering around the temporo-parietal junction (Andreatta *et al.*, 2010; Baddeley and Hitch, 2019). Manipulation of letters in a working memory paradigm showed activation in left IFG, PMC, anterior insula, bilateral parietal lobes and cerebellum (Marvel and Desmond, 2012). Additionally, phonological assembly (grapheme reading), a process which participants are forced to undertake in the PALPA-3 minimal pair discrimination task if they are to be successful, was associated with activation in the left PG, IFG and SMG (Mei *et al.*, 2014). Activity appears to be correlated with task difficulty, with the same areas (left pars opercularis, SMG and PG) showing increasing activation as phonological demands increased (Twomey *et al.*, 2015). SMG is very closely related to AG anatomically and functional involvement of this area secondary to temporo-parietal atrophy is plausible. Although the present findings do not speak to this issue directly, the correlation between phoneme discrimination and reverse digit span (which requires repetition of a heard phoneme string) could potentially indicate a linkage between the accuracy of phonological input processing and speech output that could be explored in future work.

This work was preliminary: in particular, its clinical relevance needs to be further substantiated. However, our findings foreground several key points of potential clinical relevance while suggesting opportunities for future work. PPA syndromes are often challenging to differentiate, even for experts; phoneme discrimination may further this differentiation and select phonological tasks have been shown to predict diagnostic group membership (Henry *et al.*, 2016). This requires replication in larger

patient cohorts. A key issue is individual variation and heterogeneity within PPA syndromes (Figure 1A), particularly nvPPA (moreover, here I excluded those nvPPA patients with the most severe speech production deficits). Speech perception deficits may go undetected unless objectively assessed, contributing significant concealed morbidity; on the other hand, patients who complain of poor speech perception may be offered inappropriate hearing amplification interventions, delaying potential benefit from speech and language therapy.

How phonemic discrimination relates both to phonological production during speech and to other aspects of nonverbal auditory perception in lvPPA should be clarified, both behaviourally and with neuroimaging techniques that can assess the structural and functional integrity of language networks. An exciting avenue would be to investigate whether phoneme discrimination can be ameliorated or maintained. Previous work has shown retained capacity for perceptual learning of degraded speech in lvPPA (Hardy *et al.*, 2018), and minimal pair discrimination training has been shown to improve auditory discrimination in the context of stroke aphasia (Morris *et al.*, 1996). Minimal pair discrimination training in healthy second-language learners benefits not only phonologic perception but also speech production (Bradlow *et al.*, 1997), suggesting a novel, physiologically-motivated strategy for 're-tuning' phonological output in lvPPA.

## 6 Auditory symptoms, disability and handicap in dementia

### 6.1 Chapter Summary

#### 6.1.1 Aims

- Assess real-world auditory function, disability and handicap across canonical dementia syndromes using an auditory symptom questionnaire
- Correlate real-world auditory symptoms with pure tone audiometric thresholds and the various degraded speech measures explored in chapter 4
- Assess carer burden as frequent communication partners of people with dementia using a quality-of-life questionnaire
- Measure the prevalence of hyperacusis across dementia syndromes using a hyperacusis questionnaire

#### 6.1.2 Methods

- A total of 37 patients with FTD (svPPA, nvPPA and bvFTD) and AD were assessed with 15 healthy older patients acting as a control group
- Auditory symptoms, disability and handicap were assessed using the modified Amsterdam Inventory for Disability and Handicap (mAIAD)
- Carer burden and quality of life was measured using the Hearing Impairment Impact – Significant Other scale (HII:SOP)
- Symptoms of hyperacusis were explored using the Hyperacusis Questionnaire (HQ)

#### 6.1.3 Results

- Participants with dementia demonstrated significantly poorer real-world hearing ability and significantly increased auditory disability and handicap compared with healthy older control participants
- Correlations between audiometric thresholds and items on the mAIAD were weak, whilst correlations with various degraded speech measures were moderate, with strongest correlations between questionnaire items and the time-compressed (spondee) test

- Carer burden was significantly increased across dementia syndromes and in more so in FTD compared with AD
- Carer burden was concordant with auditory disability and handicap scores
- Scores on the hyperacusis questionnaire were generally higher in participants with dementia than healthy older control participants, particularly in the svPPA group, however, these were not statistically significant

#### 6.1.4 Conclusion

- Auditory symptoms questionnaires are a useful measure of real-world auditory function and correlate moderately with degraded speech tests, but poorly with audiometric thresholds
- Carer burden is significantly increased in frequent communication partners of people with dementia and are parallel auditory disability and handicap
- Hyperacusis was not shown to be significantly increased in participants with dementia compared with healthy older control participants, but this may be related to statistical power

## 6.2 Introduction

Auditory symptoms in dementia are typically poorly recognized by both patients and clinicians although they are present in many dementia syndromes (Hardy *et al.*, 2016, Johnson *et al.*, 2021a) and cognitive impairment itself makes diagnosing hearing loss more challenging (Dawes *et al.*, 2015). It has also been repeatedly demonstrated that the pure tone audiogram alone is a poor predictor of real-world auditory function, with the greatest evidence for this disparity coming from studies of speech-in-noise performance, which consistently demonstrate the importance of cognitive factors during SiN perception (Akeroyd, 2008; Füllgrabe *et al.*, 2015; Wayne and Johnsrude, 2015; Musiek *et al.*, 2017; Billings and Madsen, 2018; Holmes and Griffiths, 2019; Yeend *et al.*, 2019; Lad *et al.*, 2020). Combined, these features suggest that real-world auditory function should be proactively explored in patients with dementia and militates against reliance on the pure tone audiogram as a reliable index of auditory disability in daily life. Additionally, improved profiling of auditory disability across dementia syndromes may play a role in predicting what benefit, if any, is likely to be gained by auditory amplification as well as informing a more holistic approach to the mitigation of auditory disability (Bamiou *et al.*, 2015).

### **Measuring hearing disability and handicap in dementia**

Capturing real-world auditory function is vital for improving understanding of an individual's auditory performance across the broad range of complex listening environments encountered on a daily basis. Multiple auditory symptom questionnaires have been developed over the years to this end, but these have typically focused on what degree of auditory handicap can be explained by audiometric thresholds (Weinstein and Ventry, 1983; Brainerd and Frankel, 1985; Lutman *et al.*, 1987; Meijer *et al.*, 2003, 2004). This is generally problematic not only because results have shown generally poor correlation between audiometric thresholds and self-reported hearing disability and handicap, but specifically in the case of dementia as auditory disability and handicap are likely to predominantly reflect changes in 'central auditory processing' and its attendant variety of symptoms, over and beyond cochlear hearing loss (explored in chapters 3, 4 and 5). Recognising the shortfalls of an audiometrically focused approach, more recent efforts have tried to broaden the scope of disability measurement beyond the simple detection of sound to encompass communication (quiet and noise), discrimination of sounds and spatial sound processing (Meijer *et al.*, 2003, 2004; Gatehouse and Noble, 2004; Banh *et al.*, 2012; Bamiou *et al.*, 2015).

To my knowledge, no study to date has used auditory symptom questionnaires to measure auditory disability and handicap in participants with dementia. The modified Amsterdam Inventory of Auditory Disability and Handicap (mAID) was originally developed for hearing-impaired adults, to assess several

domains of auditory function including detection of sounds, auditory localisation, discrimination of sounds and the ability to understand speech in quiet and noise (Kramer *et al.*, 1995; Meijer *et al.*, 2003). The modified version includes only part A from the original questionnaire (which has three parts A, B and C; part B deals with former hearing performance and part C is self-assessed perception of handicap) and omits two statistically redundant items from the original 30 item questionnaire (Kramer *et al.*, 1995; Meijer *et al.*, 2003). The mAIAD has been successfully used to characterise auditory disability and handicap in patients suffering injury of central auditory pathways following non-aphasic stroke (Bamiou *et al.*, 2012). Based on first principles, this provides some face validity for its potential application in participants with dementia, who similarly acquire brain injury that involves important auditory brain regions albeit in a chronic and progressive, rather than acute way (Johnson *et al.*, 2021a).

### **Caregiver burden secondary to auditory impairment in dementia**

Previous observers have made note of the fact that because communication is a shared experience, any auditory disability and handicap experienced by an individual is likely to have a significant impact on their communication partners (Scarinci *et al.*, 2012). Multiple studies lend support to this view and several measures have been developed to assess carer burden secondary to frequent communication with hearing impaired individuals (Scarinci *et al.*, 2009, 2012; Preminger and Meeks, 2012). Several factors make direct measurement of carer burden desirable: first, as discussed above, the pure tone audiogram is a poor predictor of real-world auditory ability including communication and therefore risks significant underestimation of carer burden if relied upon alone; second, the range of auditory disability across dementia syndromes is broad and therefore its impact on regular communication partners is likely to be diverse; finally, a better understanding of how auditory disability and handicap correlates with carer burden will inform strategies for improving quality of life amongst both patients and carers.

### **Hyperacusis in dementia**

Hyperacusis describes the subjective experience of everyday sounds being perceived as intense and overwhelming and is closely related to, but not synonymous with tinnitus, which is the illusory perception of sound (Baguley, 2003; Baguley and Hoare, 2018). Despite problems with a consistent definition of what constitutes ‘hyperacusis’, the frequent failure to differentiate between hyperacusis and tinnitus as well as methodological research issues, a dominant theory of hyperacusis posits GABAergic and cholinergic alterations in central gain control as a potential mechanism for increased sound sensitivity (Auerbach *et al.*, 2014; Sedley *et al.*, 2015; Sedley, 2019). Whilst a core aspect of this theory is that central gain changes are maladaptive responses to impoverished sensory secondary to

peripheral hearing loss (cochlear and/or VIIIth nerve), multiple brain regions beyond dedicated auditory pathways have been implicated as playing a role in hyperacusis and tinnitus (Sedley, 2019) and therefore a pertinent question to ask is whether ‘primary’ changes in central gain as a result of neurodegenerative disease might provoke hyperacusis. Supportive evidence for this idea comes from findings of increased sensitivity to sound and increased tinnitus frequency in svPPA patients (who have not been shown to differ significantly from healthy controls audiometrically (Goll *et al.*, 2012b)) compared with healthy controls (Mahoney *et al.*, 2011). Moreover, loss of GABAergic inhibition of network hubs in the antero-mesial temporal lobes and emergent, aberrant excitatory projections from orbitofrontal to temporal polar cortex appear to be crucial in generating key cognitive and behavioural features of svPPA (Benhamou *et al.*, 2020). Extending this concept further, one might speculate that the cholinergic deficit that is typical of AD might render this group more sensitive to sound, either through changes in central gain, or more generic, cholinergically mediated attentional changes that may also have a prominent role in the modulation of auditory sensitivity (Hampel *et al.*, 2018; Sedley, 2019).

While central gain changes may play a core role in generating hyperacusis, the experience of hyperacusis is at least in part an emotional one (Baguley and Hoare, 2018) and therefore one might speculate that changes in emotional reactivity driven by neurodegenerative changes in non-auditory brain regions might increase the frequency of ‘hyperacusis’. Altered emotional responses to sounds, including acquired aversion to environmental sounds have been demonstrated with significantly increased frequency in svPPA, AD and bvFTD but infrequently in nvPPA (Fletcher *et al.*, 2015). Together then, whether or not hyperacusis is generated by changes in neural sensitivity such as in the central gain theory of hyperacusis, or is secondary to altered emotional responses, hyperacusis in dementia appears a worthwhile topic of investigation. The assessment of hyperacusis is problematic due to definitional and methodological issues (Baguley and Hoare, 2018). The most commonly used measure is the Hyperacusis Questionnaire (HG), which was designed to assess hypersensitivity to sound (Khalifa *et al.*, 2002); it has been validated in the general population, but not in a hyperacusis population and questions have been raised about the original construct validity (Fackrell *et al.*, 2015), however, it remains the most extensively used tool with limited options elsewhere (Baguley, 2003; Baguley and Hoare, 2018).

Three main aims were addressed in the study described in this chapter. First, to better characterize and attempt to quantify auditory symptoms in participants with dementia, I administered the Modified Amsterdam Inventory for Auditory Disability and Handicap (Kramer *et al.*, 1995; Meijer *et al.*, 2003;



Bamiou *et al.*, 2015). Second, to assess caregiver burden and how this correlated with participant auditory disability and handicap I used the Hearing Impairment Impact: Significant Other Profile (HII:SOP) questionnaire (Preminger and Meeks, 2012). Third, to assess the relative prevalence of hyperacusis across dementia syndromes, I used the Hyperacusis Questionnaire (HQ) (Khalifa *et al.*, 2002). I predicted that auditory disability and handicap would be significantly increased in participants with dementia compared to healthy controls and that this would be correlated with caregiver burden. I also predicted that participants with dementia would show increased sensitivity to sound demonstrated by higher scores on the HQ, with the svPPA group most severely affected, followed by the AD group.

## 6.3 Methods

### 6.3.1 Participants

Ten patients with typical AD, fifteen patients with BvFTD, eight patients with svPPA and six patients with nvPPA were recruited along with their partners, with each group meeting the relevant syndromic diagnostic criteria for mild to moderate severity (Gorno-Tempini *et al.*, 2011; Rascovsky *et al.*, 2011; Dubois *et al.*, 2014). Fifteen healthy older individuals with no history of neurological or psychiatric disorders participated as control subjects.

A summary of the demographic, clinical and general neuropsychological characteristics of participants are listed in Table 3.1.

### 6.3.2 Experimental design and stimuli

At each participant visit, I administered three previously validated questionnaires, the mAIAD, HII:SOP and HQ; their characteristics are summarised in table 6.1 (Khalifa *et al.*, 2002; Meijer *et al.*, 2003; Preminger and Meeks, 2012). Healthy older control participants completed the questionnaires themselves; for participants with dementia, questionnaires were completed by the primary carer on their behalf, to minimise the potential confound of disease associated non-auditory cognitive change biasing responses. Completed questionnaires were reviewed by me together with respondents to ensure that all items had been completed correctly and to address any confusion or queries regarding specific items within the questionnaires. Scoring for each questionnaire was completed by me following review. Control participants did not complete the HII:SOP as this was considered redundant in this group and study partners were not recruited for control participants either.

**Table 6.1 Administration of auditory symptom questionnaires**

Questionnaire	Format	No. of items	Item Scoring	Max Score	Threshold	Groups
Modified Amsterdam Inventory for Auditory Disability and Handicap (mAID)	Graded response: Almost never; Occasionally; Frequently; Almost always	28	1-4 Score negatively correlates with disability	112	None	All
Hearing Impact Significant Other Profile (HII:SOP)	Yes; Sometimes; No	20	5, 2.5, 0 Score positively correlates with carer burden	100	< 20*	Controls excluded
Modified Khalfa Hyperacusis Questionnaire (HQ)	Yes; Sometimes; No	20	5, 2.5, 0 Score positively correlates with sensitivity to sound	100	> 66**	All

\* Scores below this threshold are considered to indicate no carer burden

\*\* Scores above this threshold are considered to demonstrate hyperacusis

## 6.4 Statistical analysis

A full description of the analysis pipeline is given in general methods section 2.9. To test for a main effect of disease group on questionnaire score, a multiple-linear regression model was used, with pure tone mean threshold of both ears (0.25 – 8 KHz) used as a covariate following the original validation procedures for each questionnaire (Khalfa *et al.*, 2002; Meijer *et al.*, 2003; Preminger and Meeks, 2012). Where this omnibus test was significant, post-hoc between-group comparisons were explored using independent t-tests. Effect sizes for significant results were estimated in the regression model by calculating Eta-squared. Model diagnostics (described in general methods, section 3.9) were performed on each model to confirm that the assumptions of the GLM were met.

A core theme in this thesis is the importance of auditory cognitive processes to real-world hearing function, as well as the insensitivity of the pure tone audiogram to ‘centrally’ mediated auditory dysfunction. This is most obvious in the case of speech processing, which is the most fundamental aspect of daily life communication and social engagement. Understanding if and how various speech tests correlate with real-world auditory function is therefore a crucial step towards improving how we

measure auditory disability and handicap. To test for correlations between hearing test score and item response on the mAIAD across the patient cohort, Spearman correlations were computed for each of the following tests which were presented in chapters 3 and 4: pure tone audiometry (better ear average), speech-in-babble, spectrally filtered speech, time-compressed speech (monosyllable) and time-compressed speech (spondee). Spearman coefficients were then used to create a heatmap to aid visualisation of the relative performance of each hearing measure in relation to individual test items (see figure 6.1).

A threshold of  $p < 0.05$  was accepted as the criterion of statistical significance for all tests.

## 6.5 Results

### 6.5.1 General participant characteristics

General participant characteristics are summarised in Table 6.1. Patient groups did not differ significantly from healthy controls in gender distribution, age or handedness, ( $p > 0.05$ ). Mean symptom duration differed significantly between patient groups, with significantly longer disease duration in the svPPA and bvFTD groups compared to the AD and nvPPA groups, but overall severity of cognitive impairment did not (MMSE).

### 6.5.2 Measuring hearing disability and handicap

Summary statistics for performance on the mAIAD are shown in table 6.2. Mean scores on the mAIAD differed significantly between groups ( $F(5,48) = 9.821$ ,  $p = < 0.001$ ), after adjusting for the effect of audiometric thresholds (table 6.3). Post-hoc between group comparisons revealed that this was driven by the svPPA ( $t = -4.67$ ,  $p = < 0.001$ , 95% CI: [-37.159 to -14.772], nvPPA ( $t = -4.87$ ,  $p = < 0.001$ , 95% CI: [-45.016 to -18.672] and bvFTD ( $t = -3.67$ ,  $p = 0.001$ , 95% CI: [-27.718 to -8.078]) groups performing significantly worse than the healthy control group (see table 6.2); the svPPA ( $t = -3.16$ ,  $p = 0.003$ , 95% CI: [-32.169 to -7.113] and the bvFTD ( $t = -2.14$ ,  $p = 0.038$ , 95% CI: [-22.449 to -6.97]) groups performing significantly worse than the AD group (table 6.4); the nvPPA group performing significantly worse than the AD ( $t = -3.85$ ,  $p = < 0.001$ , 95% CI: [-38.867 to -12.171]) and bvFTD group ( $t = -2.24$ ,  $p = 0.03$ , 95% CI: [-26.455 to -1.437]) (tables 6.4 and 6.5). No other group differences were significant.

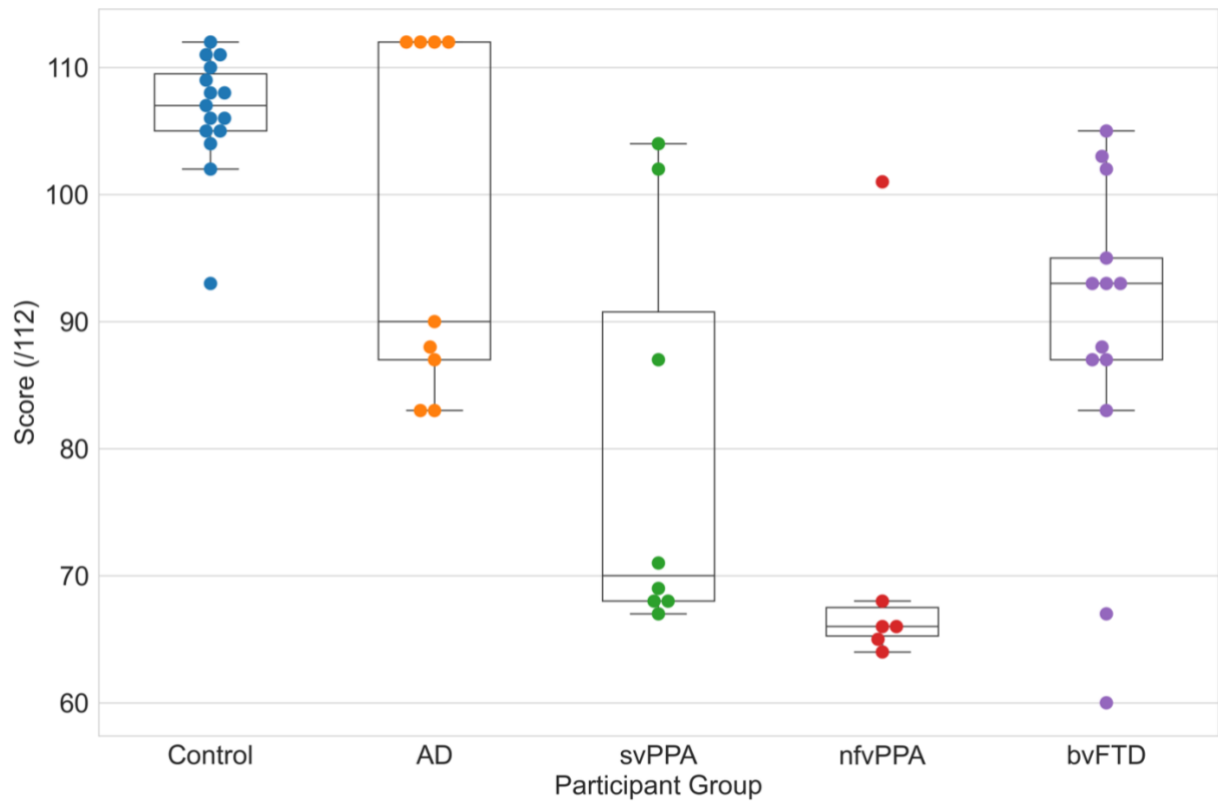
Effect size estimation through calculation of eta-squared revealed that approximately 51.6% ([95% 95% CI: 25% – 61.8%]) of performance results were explained by the model (see table 6.5). Disease group contributed approximately 46.3% (95% CI: [28.3% – 58.2%]) of the effect in the model, with pure tone audiometry contributing approximately 3.1% (95% CI: [0% – 17.3%]) of the effect (see table 6.5).

Spearman correlations between mAIAD item clusters (Discrimination, localisation, speech understanding in noise, speech understanding in quiet and auditory detection) and pure tone audiometry, speech-in-babble, spectrally filtered speech, time-compressed speech (monosyllable) and time-compressed speech (spondee) are demonstrated as a heatmap in figure 6.1. Questionnaire item correlations with audiometric score were almost universally weakest. Conversely, correlations with time-compressed speech (spondee) were almost universally strongest. A similar pattern of weakest correlations between questionnaire items and audiometric score, and the reverse pattern of strongest correlations and time-compressed speech (spondee) was repeated. Spectrally filtered speech showed the most specific profile, with generally weak correlations with detection of sounds and auditory localisation but strong correlations with intelligibility in quiet and noise and moderate correlations with sound discrimination.

**Table 6.2 Summary statistics for performance on the mAIAD, HII:SOP and HQ**

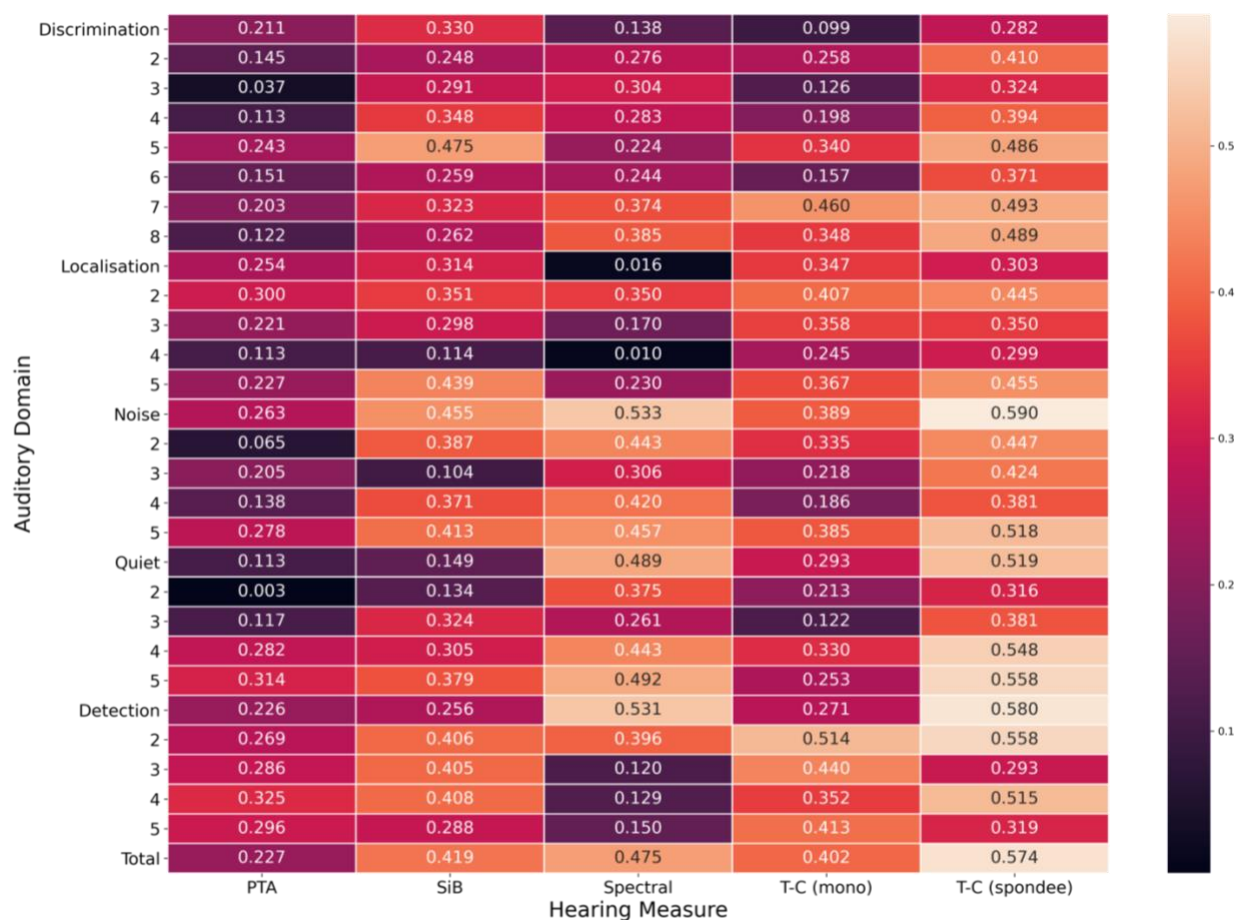
Group	n	mAIAD	HII:SOP	HQ
		Mean (SD)	Mean (SD)	Mean (SD)
Control	15	106.5 (4.7)	.	21.7 (16.6)
AD	9	97.7 (13.8)	25.8 (19.8)	35 (22.3)
svPPA	8	79.5 (15.9)	44.0 (29.5)	41.9 (23.4)
nfvPPA	6	71.7 (14.4)	54.2 (26.8)	30 (20.7)
bvFTD	14	86.9 (14.8)	41.5 (26.1)	35.8 (22.8)

Summary of scores by patient group, showing the mean score and (standard deviation) on the mAIAD, HII:SOP and HQ. **mAIAD**, modified Amsterdam Inventory for Disability and Handicap; **HII:SOP**, Hearing impairment impact – significant other; **HQ**, Hyperacusis Questionnaire; **AD**, Alzheimer’s disease; **svPPA**, semantic dementia; **nfvPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.



**Figure 6.1 Auditory disability and handicap in dementia**

Scores on the mAIAD by group. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. **AD**, Alzheimer's disease; **svPPA**, semantic dementia; **nfvPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.

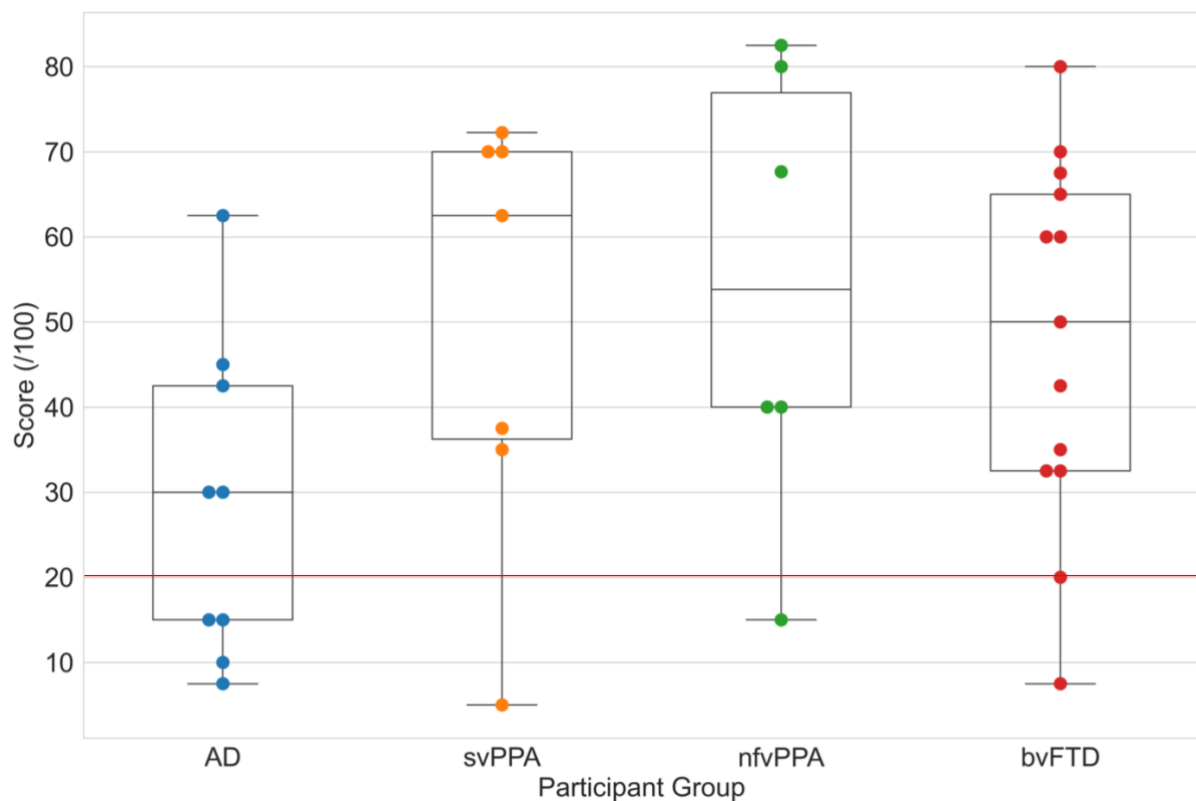


**Figure 6.2 Correlations between real-world auditory function and hearing measures**

Heatmap of correlations between questions on the Modified Amsterdam Inventory for Auditory Disability and Handicap (mAID) across the patient cohort. Each cell shows the Spearman correlation coefficient for various hearing measures with each item on the mAID; items are clustered by the auditory domain they are meant to probe. Warmer colour intensity represents increased correlation between the hearing measure score and the item on the mAID. **Discrimination**, items exploring auditory discrimination; **Localisation**, items exploring auditory localisation; **Noise**, items exploring speech understanding in noise; **Quiet**, items exploring speech understanding in quiet; **Detection**, items exploring auditory detection; **Total**, correlation coefficient across all items combined; **PTA** pure tone audiometry; **SIB** speech-in-babble; **Spectral** spectrally filtered speech; **T-C (mono)** time-compressed speech (monosyllable); **T-C (spondee)** time-compressed speech (spondee).

### 6.5.3 Carer burden in dementia

HII:SOP scores by group are shown in figure 6.4. Summary statistics indicated that all disease groups surpassed the threshold for at least mild carer burden (table 6.4). Visually inspecting the data, carer burden was higher in the FTD syndromes compared with the AD group, with the greatest burden in the nfvPPA group. Mean scores on the HII:SOP did not differ significantly between groups ( $F(5,48) = 1.836$ ,  $p = 0.145$ ) and variation within groups was wide (see table 6.5).



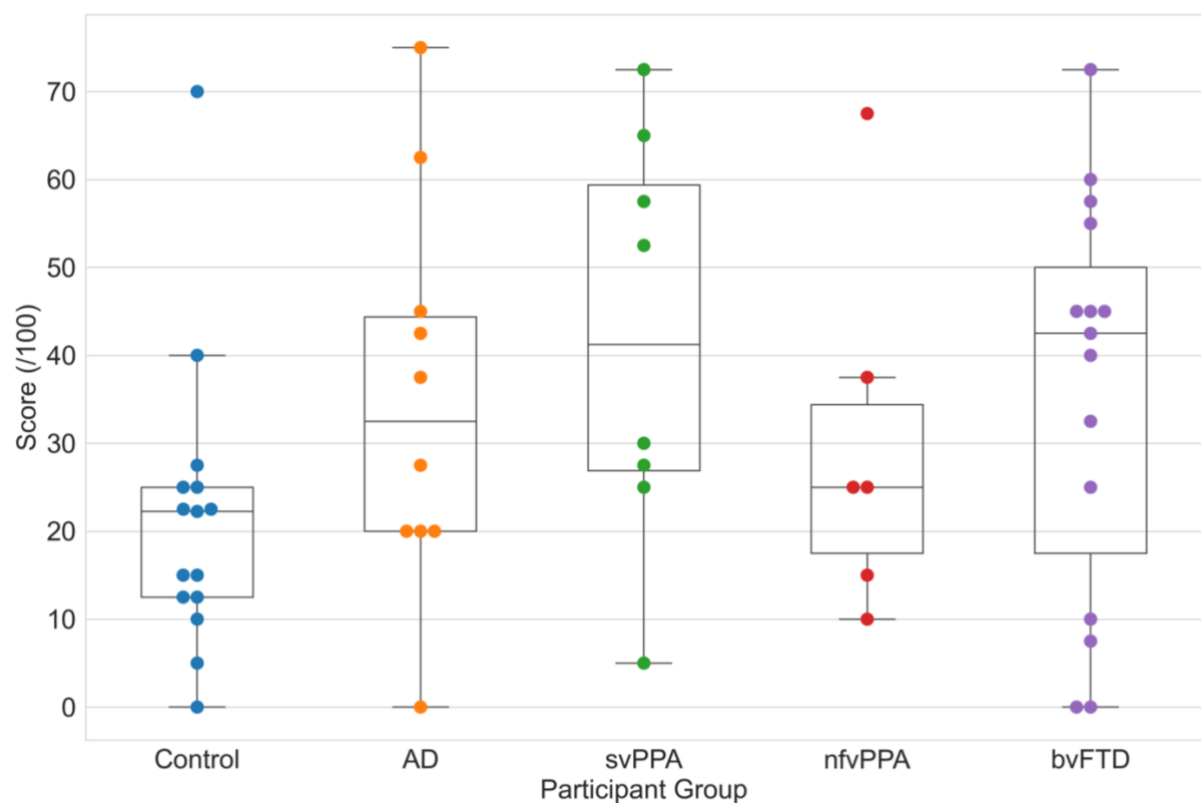
**Figure 6.3 Auditory handicap and carer burden**

HII:SOP scores by participant group. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. The cut-off score (20) for at least mild carer burden is indicated by the horizontal red line. **AD**, Alzheimer's disease; **svPPA**, semantic dementia; **nfvPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.



### 6.5.4 Hyperacusis in dementia

Hyperacusis scores by group are shown in figure 6.3. Summary statistics indicated that all disease group mean scores were higher than controls, with the svPPA showing the highest mean score (table 6.2). Visually inspecting the data, there was a trend toward higher scores in the disease groups, which appears most marked in the svPPA and bvFTD groups, however, mean scores on the hyperacusis questionnaire did not statistically differ significantly between groups ( $F(5,48) = 1.214$ ,  $p = 0.317$ ) and variation within groups was wide (table 6.3).



**Figure 6.4 Prevalence of hyperacusis in dementia**

Hyperacusis scores by participant group. Boxes code the interquartile range and whiskers the overall range of values in each group; the horizontal line in each box represents the median. **AD**, Alzheimer's disease; **svPPA**, semantic dementia; **nfvPPA**, progressive non-fluent aphasia; **bvFTD**, behavioural variant frontotemporal dementia.

## 6.6 Discussion

The findings presented in this chapter demonstrate that patients with canonical syndromes of FTD (svPPA, nvPPA and bvFTD) have significant auditory disability and handicap when assessed via questionnaire (mAID) compared to healthy control and AD patients. Within FTD, the nvPPA group was the most severely impaired, showing significantly greater disability and handicap compared to the bvFTD group, which was the least impaired. The svPPA group showed intermediate levels of hearing disability. There was significant carer burden across dementia syndromes, with all disease groups showing mean scores above the threshold for at least mild carer burden. The profile of carer burden paralleled the profile of auditory disability and handicap, with the AD group having the lowest mean score (least disability); the FTD syndromes also stratified similarly with highest carer burden score in the nvPPA group, lowest score in the bvFTD group and the svPPA group scoring in-between. No significant differences were demonstrated between healthy control participants and participants with dementia on a hyperacusis questionnaire.

### **Measuring hearing disability and handicap in dementia**

Capturing real-world auditory function presents multiple challenges, which are likely to be compounded by cognitive impairment (Panza *et al.*, 2015; Wayne and Johnsrude, 2015). First, real-world hearing encompasses a broad range of tasks that engage a variety of auditory cognitive processes, such as sound detection, speech processing or auditory localisation among others. These processes are subserved by both domain-general and domain-specific brain regions whose specificity and complexity mean there are a priori reasons to question the value of pure tone audiometry as a reliable and comprehensive proxy of real-world auditory ability. Indeed, there is ample evidence that pure tone audiometry alone is a poor predictor of real-world auditory function, which typically occurs in non-ideal (i.e., degraded) listening conditions (Akeroyd, 2008; Füllgrabe *et al.*, 2015; Musiek *et al.*, 2017; Billings and Madsen, 2018; Holmes and Griffiths, 2019; Yeend *et al.*, 2019; Lad *et al.*, 2020). Second, although the symptom focused approach of using auditory questionnaires broadens the scope of auditory functions that can be explored, certain functions may be more challenging to capture than others (e.g., auditory localisation), and/or the correlation between performance on certain functions and reported disability may be non-equivalent (for example, overestimating the disability caused by audibility issues, whilst diminishing the disability related to spatial hearing problems). Third, when dealing with people who have dementia, there is the added non-trivial issue of questionnaire reliability, particularly when questionnaire items are completed by proxy. Finally, the issues described above are somewhat circular in that questionnaires are used as proxies of central hearing and central hearing test performance is

used to establish the usefulness of questionnaires (Bamiou *et al.*, 2012). This issue can be cut through to some degree by demonstrating consistent correlation between central hearing tests and auditory symptom questionnaires as they are mutually endorsing.

The mAIAD captured significant auditory disability and handicap amongst FTD participants, with stratification of syndromes that mirrored the group performance profiles on the degraded speech tests described in chapter 4 (i.e., nvPPA group performing worst, bvFTD best and svPPA in-between). AD participants did not show significant disability and handicap compared with healthy control participants, which similarly mirrors the lack of significant difference between the AD group and healthy control group on the degraded speech tests presented in chapter 4. The poor predictive value of audiometric thresholds alone in the context of real-world auditory function was demonstrated by the almost universally weak correlation between audiometric thresholds and item responses on the mAIAD, which replicates previous findings (Meijer *et al.*, 2004). Similarly consistent was the finding that the various degraded speech tests (SiB, spectrally filtered speech, time-compressed speech (monosyllable) and time-compressed speech (spondee) tests) showed significantly stronger correlation with item responses on the mAIAD compared with audiometric thresholds. Of the degraded speech tests, SiB demonstrated the weakest correlation with item responses in general, while the strength of correlations was almost universally strongest for the time-compressed speech (spondee) test. Correlations with specific functional clusters showed that spectrally filtered speech was the most specific predictor of auditory disability, with weak correlations for auditory detection and auditory localisation questions, but moderate correlations with speech in quiet and speech in noise perception items. Correlations with the auditory localisation cluster were weakest across all tests, which one might expect, given that none of the degraded speech tests was designed to probe auditory localisation ability, which is likely to be supported by brain regions that are at least partly segregated from speech processing areas (Goll *et al.*, 2012a, Golden *et al.*, 2015a, 2016, Johnson *et al.*, 2021a).

The consistency of these findings provides supporting evidence for several key outcomes: first, degraded speech tests are better predictors of real-world auditory function than pure tone audiometry; second, there is moderate correlation between degraded speech tests and functional measures of auditory ability assessed by the mAIAD, with time-compressed speech (spondee) performing best and SiB performing worst; third, these findings are internally consistent as the profiles of degraded speech performance were reproduced by the mAIAD. Overall then, the mAIAD appears to be a good measure of auditory disability and handicap in dementia, which is moderately correlated with performance on various degraded speech tests.

## **Carer burden secondary to auditory impairment in dementia**

Predicting carer burden secondary to frequent communication with a hearing impaired partner is not straightforward and correlation between audiometric thresholds and quality of life is weak (Weinstein and Ventry, 1983; Preminger and Meeks, 2012). The HII:SOP identified a high prevalence of carer burden in participants with dementia, and although there was no statistical difference between participant groups (controls excluded), the profiles of carer burden paralleled those of auditory disability and handicap as measured by the mAIAD. This finding suggests that carer burden can be reliably predicted based on reported auditory disability and handicap using the mAIAD. Moreover, the coherence between the mAIAD and the HII:SOP lend further support for the superiority of degraded speech tests over audiometric thresholds when predicting carer burden.

## **Hyperacusis in dementia**

The hypothesised increased prevalence of hyperacusis amongst participants with dementia was not borne out statistically, although all groups demonstrated higher mean hyperacusis questionnaire scores than the healthy control group. Overall, the svPPA group exhibited the highest scores on the HQ, which would be in line with previous findings of increased prevalence of hyperacusis in svPPA (Mahoney *et al.*, 2011) and might be borne out with larger group sizes. Additionally, it may be that the ‘type’ of hyperacusis experienced by people with dementia is more specific, such as the previously described aversion to particular kinds of sounds or music across FTD syndromes and AD, as well as the aforementioned difficulty of capturing a subjective symptom by proxy (Fletcher *et al.*, 2015). Moreover, as described in the introduction to this chapter, the assessment of hyperacusis is problematic and the reliability and interpretability (hyperacusis is a subjective experience) of the widely used hyperacusis questionnaire employed in this study has been questioned (Fackrell *et al.*, 2015; Baguley and Hoare, 2018). Some of this uncertainty could be mitigated with sufficient data points, but these results suggest that aside from the svPPA group, the effect is likely to be small (if present) across dementia syndromes.

In summary, the mAIAD and the HII:SOP appear to be good measures of auditory disability and handicap in participants with dementia and their carers respectively. Compared with the weak correlation for audiometric thresholds, degraded speech tests show moderate correlations with mAIAD items. This represents a significant improvement and cautions against reliance on the pure tone audiogram when predicting auditory disability in dementia. Furthermore, it emphasises the importance of casting hearing as a multi-dimensional construct whose purpose is to support communication and interaction with our daily environment, rather than simply the ability to detect sound. This has important

implications for how to approach the assessment and treatment of 'hearing loss' in the context of dementia, which are explored in the next chapter.

## 7 General Discussion

### 7.1 Summary of experimental findings

This thesis set out to explore three core questions: the nature of the causal relationship between hearing loss and dementia, how canonical dementia syndromes drive specific auditory phenotypes through their individual effects on the auditory brain and how these functional changes translate into daily life auditory disability and handicap. A hierarchical approach was used, first assessing ‘low-level’ auditory processing abilities such as basic auditory sensitivity (pure tone audiometry) and temporal acuity (gap detection). ‘Higher-level’ aspects of auditory cognition were explored with pre-existing ‘central auditory tests’ such as dichotic listening and a speech-in-babble perception and extended to novel degraded speech tests manipulating the spectral and temporal features of speech. To explore the potential utility of auditory cognitive tests as syndrome specific markers of disease, performance on a phonemic discrimination task was explored, due to pre-existing evidence for a specific neuroanatomical basis for phonological processing in the IPL, a region which is an early and specific target in lvPPA. Finally, daily life auditory disability and handicap as well as carer burden associated with impaired communication in people living with dementia was assessed using auditory symptom questionnaires and correlated with auditory test performance. Key findings from each experimental chapter are summarised below.

#### 7.1.1 Chapter 3: Audiometry

- Age is the most significant predictor of baseline audiometric thresholds in patients with dementia
- Participants with AD, nvPPA and bvFTD had significantly elevated audiometric thresholds compared with healthy control subjects, with the most severe changes in the nvPPA group
- Dichotic listening has a significant effect on audiometric thresholds, suggesting that auditory specific cognitive factors significantly modulate audiometric performance, with the most marked effect in patients with nvPPA

#### 7.1.2 Chapter 4: Degraded Speech

- Patients with dementia have significant difficulties processing degraded speech compared to healthy control individuals and are therefore show promise as potential ‘stress tests’ of auditory cognitive function

- This effect is not generic, with variation in the sensitivity of individual tests to detect group differences in performance that are likely due to syndrome specific brain network involvement
- The spectrally filtered speech and time-compressed speech tests were able to stratify syndromic groups, suggesting a degree of specificity that may inform future work on the design of syndrome specific tests
- Overall, degraded speech tests may prove useful as physiological biomarkers of neurodegenerative disease

### 7.1.3 Chapter 5: Phonological processing

- Phonemic discrimination ability is correlated with grey matter volume in the left angular gyrus, a region that has been consistently reported in studies of phonological processing
- Phonemic discrimination indexes a core phenotypic feature of lvPPA

### 7.1.4 Chapter 6: Auditory Disability and Handicap

- Auditory symptom questionnaires are a useful measure of real-world auditory function and correlate moderately with degraded speech tests, but poorly with audiometric thresholds
- The time-compressed speech (spondee) test performed best overall, strongly correlated with daily life auditory symptoms and the spectrally filtered speech test was the most specific, with moderate to strong correlations with speech in quiet and noise symptoms, but weak correlations with detection, discrimination and localisation questions
- Carer burden is significantly increased in frequent communication partners of people with dementia and parallels auditory disability and handicap

## 7.2 Audiometry, cognition and dementia

Epidemiological evidence suggests that peripheral hearing loss is the most significant mid-life risk factor for developing dementia, estimated to account for 9% of incident cases. Importantly, these effects persisted after adjusting for factors that are associated with hearing loss (Lin *et al.*, 2011; Gallacher *et al.*, 2012; Deal *et al.*, 2016; Taljaard *et al.*, 2016; Livingston *et al.*, 2017; Loughrey *et al.*, 2018). The causal nature of this relationship is potentially of significant diagnostic and therapeutic importance but remains to be clarified. Prevailing theories of how hearing loss may be linked to dementia include a shared pathological substrate that affects both the cochlea and the brain, domain-general cognitive changes secondary to peripheral hearing loss that sensitise the brain to the effects of neurodegeneration (which do not invoke specific pathology) and cognitive impairment through monopolisation of domain-general cognitive resources (Wayne and Johnsrude, 2015; Griffiths *et al.*, 2020). A more recently proposed mechanism suggests a more specific interaction between changes in neural mechanisms important to auditory pattern analysis in the mesial temporal lobe (MTL) and AD pathology has been proposed. Three potential interactions are outlined in this model: first, neuronal overactivity could propitiate the accumulation and spread of AD pathology, second, synaptic changes secondary to AD pathology might be excitotoxic and third, hearing loss induces changes in gamma oscillatory activity in the MTL that exacerbates amyloid deposition in the hippocampus (Griffiths *et al.*, 2020). This final proposition has in my opinion the most merit, based on both theoretical grounds and biological findings in animal models. The concept was developed specifically in the context of AD and given that a proportion of incident cases will be non-AD pathology, a question remains as to whether this mechanism generalises to other dementia syndromes. Additionally, hearing loss has not been shown to be predictive of  $A\beta$  deposition in vivo, nor is it significantly correlated with imaging measures of brain age compared to individuals without hearing loss (Parker *et al.*, 2020; Rosemann and Thiel, 2021).

Important to all the models described above is the central role of the brain in auditory processing (auditory cognition). Due to the fundamental importance of pathological changes in the auditory brain outlined in the preferred model, a relevant question is how disease specific pathological changes, mediated by the functional reciprocity found throughout the auditory hierarchy, drive auditory cognitive phenotypes that may have differential sensitivity to the effects of peripheral hearing loss, due to their unique impacts on the auditory brain. The added potential benefit of this approach is an improved understanding of the impact of auditory cognitive processes on peripheral hearing function measured using pure tone audiometry, with evidence that cognitive change is a better predictor of



subsequent decline in peripheral hearing than traditional hearing-related risk factors (Kiely *et al.*, 2012). In other words, it may clarify the relative primacy of pathological changes occurring in the brain, versus loss of peripheral hearing sensitivity and may have significant impact on future therapeutic avenues, such as whether or not auditory amplification measures are likely to be beneficial and in which diseases.

To date, this latter approach has received little attention, with limited studies examining the impact of AD on peripheral hearing function and even fewer in FTD. In chapter 3 of this thesis, I showed that audiometric thresholds are variably affected in patients with AD and across canonical syndromes of FTD (bvFTD, svPPA and nvPPA), compared to healthy control participants. Patients with svPPA showed no significant difference in audiometric thresholds compared to controls, whilst nvPPA participants had the most severely elevated thresholds of any group. This result was rendered statistically insignificant when adjusting for performance on a specific measure of auditory cognitive function, the dichotic digits test, with a similar but less marked effect in AD. At the same time, a significant, but far less marked impact was found when adjusting for a less auditory specific test of cognition, namely MMSE score. Taken together these findings suggest that differential pathological involvement of auditory brain regions plays a key role in modulating performance on pure tone audiometry and lends support to the notion that pathological changes affecting the auditory brain are of primal importance in the story of peripheral hearing loss and dementia. The auditory brain and the auditory periphery form a dynamic functional hierarchy whereby deficiencies in either will have an impact on the other; I suggest that pathological changes in the auditory brain drive daily life hearing impairment in dementia both by causing central auditory dysfunction and by amplifying the effects of any peripheral hearing deficits. In this way, peripheral hearing deficits ‘stress’ the auditory brain, thereby acting as a proximity marker for incipient dementia. Whether this is through non-specific cognitive deficits, specific auditory cognitive deficits or by more direct neural effects that potentiate neurodegenerative pathology remains an interesting and open question that should be explored in future work.

### 7.3 Auditory phenotypes relevant to daily life listening

The work in chapter 3 established the central importance of auditory cognitive processes in even the most basic of listening tasks (i.e., sound detection), where it has hitherto largely been assumed to be of minimal importance. It also lends credence to the idea that degraded peripheral sensory encoding may act as ‘stress test’ of a failing auditory brain. A logical extension of this finding was to assess how canonical dementia syndromes affect the resolution of degraded speech signals, which more closely aligns with the challenges of daily listening and for which there is ample data stressing the importance of a large range of auditory cognitive processes (Füllgrabe *et al.*, 2015; Billings and Madsen, 2018;

Holmes and Griffiths, 2019; Yeend *et al.*, 2019; Lad *et al.*, 2020; Jiang *et al.*, 2021). Additionally, the extended engagement of distributed auditory cognitive brain regions during degraded speech processing is an opportunity to further characterise the ‘auditory phenotype’ of various dementias, as well as their possibly enhanced potential to act as dynamic ‘stress tests’ of the auditory brain (Price, 2012; Hardy *et al.*, 2016; Alain *et al.*, 2018; Jiang *et al.*, 2021, Johnson *et al.*, 2021a). Finally, due to the importance of rapid perceptual learning in degraded speech processing, degraded speech tests may act as a readout of synaptic function, which underwrites plasticity and adaptation (David *et al.*, 2009; Kuchibhotla *et al.*, 2017; Hardy *et al.*, 2018; Kuchibhotla and Bathellier, 2018). Together, these form an essential part of improving our understanding of the range of auditory deficits experienced by patients with dementia (and which may frequently go unnoticed), whilst simultaneously exploring the potential utility of degraded speech tests as diagnostic tools.

The findings in chapter 4 support the idea that degraded speech tests offer several advantages over pure tone audiometry as candidate diagnostic tools or biomarkers for dementia. First, the potential of degraded speech as a ‘stress test’ of auditory cognition was borne out by the fact that dementia patients had significant difficulty processing degraded speech compared with healthy control participants, even after adjusting for audiometric thresholds and in accord with previous data on the cognitive demands of successful processing of degraded speech. This appears to be especially true in patients with nvPPA, who demonstrated consistently severe deficits in degraded speech processing. Second, syndromic differences in performance on specific degraded speech tasks is consistent with the notion that degraded speech offers a useful way of elucidating the auditory phenotypes of various dementia pathologies. Third, the specific design of any degraded speech test is important in determining both the sensitivity of the test and its syndromic specificity. Due to the number of parameters that can be manipulated in creating degraded speech tests (e.g. spectral, temporal, syllable, single word, sentences etc.), there is significant scope to refine these tests in the future, as well as tailor them to their particular disease targets.

## 7.4 Auditory phenotypes and functional biomarkers

There is now substantial evidence for disease specific auditory phenotypes that are underwritten by unique syndromic patterns of auditory brain involvement, with the results described in chapter 4 reinforcing this perspective (Goll *et al.*, 2012a, b; Fletcher *et al.*, 2015, Golden *et al.*, 2015a; Hardy *et al.*, 2016, 2017b, 2020, Johnson *et al.*, 2021a). As alluded to in the previous section, there is good reason to believe that the syndromic specificity of auditory cognitive tests reflect the neuroanatomical and neuropathological characteristics of target diseases. An ideal group of diseases to explore this idea are

the primary progressive aphasia, are a rare group of language led dementias whose syndromic phenotypes are driven by their respective cognitive, neuroimaging and neuropathological profiles (Gorno-Tempini *et al.*, 2011; Spinelli *et al.*, 2017; Marshall *et al.*, 2018; Ruksenaite *et al.*, 2021). They are also frequently challenging to diagnose even amongst experienced clinicians and therefore would benefit from the support of specific diagnostic tools, including tools that move beyond the significant constraints of language.

In chapter 5, I demonstrated that phonological processing was specifically impaired in patients with lvPPA (and to a lesser degree AD), compared with patients with nvPPA and svPPA, the two other major primary progressive aphasia syndromes. Performance on the phonological task was correlated with grey-matter volume in the left AG, a subdivision of the IPL, a region which is known to play an important role in phonological processing and that is an early and specific target in lvPPA (Rauschecker and Scott, 2009, Rohrer *et al.*, 2010b; Turkeltaub and Branch Coslett, 2010; Price, 2012; Leyton *et al.*, 2014; Henry *et al.*, 2016; Giannini *et al.*, 2017, Hardy *et al.*, 2017b). A similar, but less marked profile was seen in patients with AD; this makes sense, as lvPPA is almost always underpinned by AD pathology and could be considered an extreme language phenotype of AD. One would therefore expect that patients with AD would have a degree of pathological involvement of structures around the temporo-parietal junction, including the IPL. Significantly, the nvPPA group, which share with the lvPPA group significant language impairment and poor phonological working memory was not significantly impaired on the PALPA-3 task compared with control participants. This underlines the specificity of the test, which was supported by the fact that even after adjusting for phonological working memory capacity, the results remained statistically significant. Overall then, the results of the experiment in chapter 5 lend further credence to the idea that auditory cognitive tests might be developed as disease specific diagnostic tools, with the added advantage that they also capture specific disease related auditory disability, an issue explored in more detail in chapter 6.

## 7.5 Measuring real-world auditory disability and handicap and its associated care burden

Results from chapters 3,4 and 5 demonstrate that patients with dementia have significant and wide-ranging deficits of auditory cognitive function, which are likely to generate significant auditory disability and handicap in daily life. Capturing real-world auditory disability and handicap is likely to be challenging because auditory cognitive symptoms can be difficult to recognise, particularly when framed purely as ‘hearing loss’ or ‘deafness’, which places central importance on the ability to detect sounds, rather than analyse them and use them to communicate effectively. This problem is compounded by the fact that

patients with dementia may have particular difficulty in recognising and/or reporting symptoms due to both auditory cognitive (e.g. speech) and general cognitive impairment, placing the burden of symptom recognition on their carer. It is also incumbent on physicians to determine how well deficits measured in experimental tests translate into real-world listening performance as this is of greatest functional importance to patients and carers alike.

Chapter 6 of this thesis examined how well the mAIAD was able to capture real-world auditory disability and handicap in patients with dementia, with their carers acting as proxy reporters. My results confirmed that patients with dementia demonstrated significantly poorer real-world hearing ability and significantly increased auditory disability and handicap compared with healthy older control participants, in line with expectations. Real-world auditory function was poorly correlated with audiometric thresholds but showed moderate or strong correlations with the various degraded speech tests described in chapter 5, with the novel, time-compressed (spondee) test showing the strongest correlations. These findings are important in that they are concordant with the evidence for superior characterisation of auditory function by degraded speech tests compared to pure tone audiometry laid out in chapters 3 and 4, and because they imply that more specific tests of auditory cognitive function are better able to represent real-world listening performance. Carer burden was captured using the HII:SOP, with results that paralleled the severity of auditory disability and handicap measured in patients with dementia. Improving the ability to capture auditory disability and handicap in patients with dementia is therefore likely to give important insights into carer experience, which can be used to improve counselling strategies for carers in a clinical setting.

Finally, a standard hyperacusis questionnaire was used to assess whether or not patients with dementia have increased sound sensitivity relative to control participants, following previous findings of hyperacusis in patients with svPPA and altered auditory hedonic phenotypes in AD and FTD (Mahoney *et al.*, 2011; Fletcher *et al.*, 2015). Results did not show a statistically significant difference between dementia patients and healthy control participants. This may be due to several reasons: first, there may be insufficient statistical power to reveal significant differences with the small group sizes, or relatedly, sub-syndromic variation may mean under sampling of relevant patients; second, it may be due to the difficulty of capturing a subjective symptom such as hyperacusis, or because the questionnaire itself is ill-equipped to do so; finally, existing questionnaires do not capture the relevant symptoms of altered experience/behavioural responses to sounds in diseases such as FTD (Baguley, 2003; Baguley and Hoare, 2018; Sedley, 2019).

## 7.6 Clinical translation

The findings reported in this thesis have potentially wide-ranging implications for clinical work. Pure tone audiometry has been a mainstay of audiological assessment for decades but has significant limitations that are especially prominent when considering the central importance of auditory cognitive performance in dementia. The identification of peripheral hearing loss as the major modifiable mid-life risk factor for dementia raises questions about whether hearing interventions such as hearing aids or cochlear implants are likely to be of benefit in either preventing or treating dementia (Griffiths *et al.*, 2020). The answer to these questions revolves in part around the ultimate underlying pathophysiological mechanism behind the association, but the findings reported herein imply that auditory cognitive mechanisms play a significant role in modulating performance on pure tone audiometry and any assessment of the benefits of hearing interventions should therefore assess changes in auditory cognition specifically. Amplification alone is unlikely to be of substantial benefit as it fails to address the broad range of hearing dysfunction that pathology produces in everyday listening through its effects on the auditory brain. Results from the small number of trials assessing hearing aid use and cognitive outcomes have been mixed (Griffiths *et al.*, 2020). Whilst addressing any peripheral hearing deficits should continue, these findings give impetus to the development of bespoke hearing aids that attempt to integrate the specific needs imposed by auditory cognitive change. What is also clear is that audiometric assessment is significantly less sensitive to auditory cognitive changes than tests that target the auditory brain, such as degraded speech tests or dichotic listening. These tests place significantly greater computational demand on auditory cognitive processes than audiometric assessment and are therefore more likely to index early cognitive changes (proverbial ‘canaries in the coalmine’) than audiometric measurement. Given the long lead time of pathological changes against functional decline, this makes them good candidates as early proximity markers of incipient dementia, as well as greater potential to be disease specific as they can be tailored to target specific auditory cognitive brain regions that are differentially affected by individual dementia syndromes.

Another important finding is that whilst degraded speech tests appear to be better suited to the assessment of auditory cognitive change than pure tone audiometry, it is also clear that the specific characteristics of any degraded speech test are likely to determine how sensitive and specific it is for detecting early cognitive impairment. This effect is not limited to degraded speech tests, but any test of auditory cognition, as demonstrated by the syndromic specificity of phonological processing deficits in lvPPA as compared to the other primary progressive aphasias. Rather than being a limitation of auditory cognitive tests, this raises the possibility that with thoughtful design and clinical refinement,

bespoke auditory tests may offer exciting future tools for the diagnosis and monitoring of dementia related changes in the auditory brain, as well as providing a more comprehensive understanding of the likely deficits experienced by patients during daily listening. This idea is reinforced by the stronger correlations between auditory symptom questionnaire items and degraded speech tests in comparison to audiometric thresholds.

## 7.7 Limitations

The experiments described in this thesis share several general limitations that could inform future work. Limitations specific to each chapter are presented separately in their respective discussions.

The syndromic group sample sizes here were small, which is likely to have inflated both the type I and type II error rates, meaning that findings should be interpreted with caution. This is an inherent problem when working with rare neurodegenerative syndromes, recruited via a single study centre. This could be overcome through multi-centre collaboration (for example, the GENFI initiative (Rohrer *et al.*, 2015)).

Syndromic groups were defined a priori following clinical criteria for canonical FTD syndromes, typical AD and lvPPA. Without either post-mortem pathological confirmation or comprehensive in vivo molecular biomarker support, the syndromic specificity of any auditory cognitive test remains partially speculative as clinico-pathological correlation varies depending on the clinical syndrome in question (Rohrer *et al.*, 2011; Spinelli *et al.*, 2017; Sivasathiseelan *et al.*, 2019). Future success will rest in part on follow-up with post-mortem findings as well as the development of in vivo biomarkers for syndromes other than AD. Furthermore, whilst the findings presented provide ‘proof of concept’ for the potential utility of auditory cognitive tests as functional biomarkers across dementia syndromes, they will have to be proven to be effective in the pre/early symptomatic stages of disease as they may simply be ‘replicating’ clinical findings. Pertinent to this is the fact that all the experiments conducted in this thesis were cross-sectional and therefore the results may only be relevant to this specific time-point, rather than being generalisable across the natural history of each disease. Whilst theoretical considerations suggest that this is unlikely to be entirely the case (for example, brain changes in early disease are more segregated than in late disease and therefore likely to have more specific profiles of auditory cognitive change), this may be addressed by a more prospective approach to the assessment of auditory cognitive changes through population-based screening longitudinally (and in particular, presymptomatic carriers).

Two further related limitations are the lack of more direct measures of neural function across the auditory hierarchy and a paucity of neuroanatomical data. Overcoming these would provide greater insights into neural correlates of variation in task performance and provide a more direct link between auditory cognitive measures and brain substrates of pathological change. The challenge of neuroanatomical correlation is likely to be related in large part to the small sample sizes, which vitiated efforts to elucidate VBM correlates of task performance here. Clearly, this issue could be addressed with larger sample sizes. The challenge of establishing pathophysiological mechanisms is related to experimental design and could be addressed with functional MRI, EEG and MEG paradigms.

## 7.8 Future directions

The three overarching themes of this thesis (the nature of the causal relationship between raised audiometric thresholds and dementia; how canonical dementia syndromes drive specific auditory phenotypes through their individual effects on the auditory brain; how these functional changes translate into daily life auditory disability and handicap) should inform future work. Direct, early pathological changes in auditory neural circuitry combined with the reciprocal functional interplay across all levels of the auditory hierarchy mean that auditory cognitive dysfunction is likely to be an early consequence of neurodegenerative dementias. This requires substantiation using physiologically grounded techniques such as OAE measurement, auditory brainstem responses, fMRI and electro/magnetoencephalography. These would allow the relative contributions of early auditory processing, top-down predictive and task modulatory effects to be dissected and may also help clarify the neural mechanisms of compensatory and therapeutic effects.

Several specific paradigms are suggested by my results: first, the functional interplay between auditory cognitive domains and changes in cochlear sensitivity could be clarified by the direct measure of cochlear function via OAEs. Previous work in nvPPA has provided evidence that the bulk of the auditory changes in this disease are likely to be top-down due to degeneration of frontal circuits central to predictive decoding of sensory inputs (Cope *et al.*, 2017). Results in chapter 3 suggest that audiometric sensitivity in this group in particular is also likely to be explained largely by these same top-down effects and OAE responses to contralateral suppression, combined with fMRI or EEG/MEG could be used to assess efferent effects on cochlear sensitivity. Additionally, significant auditory signal processing occurs in the auditory brainstem, with pathological changes in brainstem nuclei reported in AD (Parvizi *et al.*, 2001). Combining the techniques above with auditory brainstem responses may further disambiguate the functional relationships between the auditory brain and the auditory periphery in AD. Second, the phonological processing deficits demonstrated in lvPPA could be explored more eloquently as a model

of auditory object invariance by comparing neural dynamics in this syndrome compared with disease control groups. This could lend direct support to the more general hypothesis that the degenerative changes in higher-order multi-modal cortex that are the earliest target in dementia force greater dependence on lower-level acoustic sensory information, which is inherently noisy as a signal. Third, some of the difficulties illustrated in assessing more subjective phenomena such as hyperacusis or other auditory behavioural symptoms (e.g. misophonia) could be explored more directly by measurement of fronto-limbic connectivity changes using fMRI paradigms (Mahoney *et al.*, 2011; Fletcher *et al.*, 2015; Kumar *et al.*, 2017, 2021). Finally, the questions listed above could be complemented by parallel paradigms in animal models and through computational modelling techniques.

Detailed, longitudinal disease phenotyping with biomarker and ultimately histopathological support (accounting for healthy auditory ageing and comorbid disease) will be required to elucidate the auditory pathophysiological signatures of particular proteinopathies, to assess the relative importance of hearing impairment in different diseases and to clarify the role of peripheral hearing deficits in potentiating the neurodegenerative process (Griffiths *et al.*, 2020). If substantiated in longitudinal studies of at-risk populations, this would raise the exciting prospect of novel auditory ‘cognitive stress tests’ for detecting the early stages of neurodegeneration and identifying dynamic, physiological biomarkers of disease evolution, residual plasticity and therapeutic response (Hardy *et al.*, 2018). Such markers could represent red flags for targeting population-based screening and recruitment into dementia prevention trials from primary care settings and could be developed into ‘digital biomarkers’ that are highly scalable. For example, headphone-based tests of degraded speech perception or dichotic listening could be performed on-line (Gates *et al.*, 2011, Golden *et al.*, 2015c). Additionally, they may prove to be more effective at tracking functional changes related to disease modifying therapies that are on the horizon.

To date, a full assessment of the wide gamut of auditory cognitive symptoms experienced in daily life by patients with dementia has received little attention and is sorely needed; the work in this thesis is a potential starting point. Such an assessment would help to raise awareness among clinicians across disciplines as well as the wider public about the role of the brain in hearing, how dementia impacts this and the limitations of audiometric assessment, based on their poor correlation with daily life hearing. These will be key to earlier recognition and referral of patients with cognitive changes that will aid early diagnosis. The development and validation of questionnaires that are bespoke for dementia populations and designed to capture the range of auditory cognitive functions described throughout this thesis would offer deeper insights into real-world hearing disability and handicap across dementia



syndromes and may inform future interventions, such as the development of physiologically informed 'smart hearing aids'. These may offer improved real-world communication and interaction, but also provide a litmus test for some of the ideas regarding the importance of central hearing changes in dementia laid out above.

## 8 Appendix

### 8.1 Chapter 2: Methods

**Table 8.1** IWG-2 criteria for typical AD (Dubois *et al.*, 2007)

<b>Probable AD</b>	A plus one or more supportive features B, C, D, or E
<b>Core Diagnostic Criteria</b>	<p><b>A Presence of an early and significant episodic memory impairment that includes the following features:</b></p> <ol style="list-style-type: none"> <li>1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months</li> <li>2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled</li> <li>3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances</li> </ol>
<b>Supportive features</b>	<p><b>B Presence of medial temporal lobe atrophy:</b></p> <ul style="list-style-type: none"> <li>• Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)</li> </ul> <p><b>C Abnormal cerebrospinal fluid biomarker:</b></p> <ul style="list-style-type: none"> <li>• Low amyloid <math>\beta</math>1–42 concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three</li> <li>• Other well validated markers to be discovered in the future</li> </ul> <p><b>D Specific pattern on functional neuroimaging with PET:</b></p> <ul style="list-style-type: none"> <li>• Reduced glucose metabolism in bilateral temporal parietal regions</li> <li>• Other well validated ligands, including those that foreseeably will emerge such as Pittsburgh compound B or FDDNP</li> <li>• Proven AD autosomal dominant mutation within the immediate family</li> </ul>
<b>Exclusion Criteria for typical AD</b>	<p><b>History:</b></p> <ul style="list-style-type: none"> <li>• Sudden onset</li> <li>• Early occurrence of the following symptoms: gait disturbances, seizures, behavioural changes</li> </ul> <p><b>Clinical features:</b></p> <ul style="list-style-type: none"> <li>• Focal neurological features including hemiparesis, sensory loss, visual field deficits</li> </ul>

	<ul style="list-style-type: none"> <li>• Early extrapyramidal signs Other medical disorders severe enough to account for memory and related symptoms</li> <li>• Non-AD dementia</li> <li>• Major depression</li> <li>• Cerebrovascular disease</li> <li>• Toxic and metabolic abnormalities, all of which may require specific investigations</li> <li>• MRI FLAIR or T2 signal abnormalities in the medial temporal lobe that are consistent with infectious or vascular insults</li> </ul>
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**Table 8.2 Rascovsky diagnostic criteria for BvFTD** (Rascovsky *et al.*, 2011)

Level of diagnosis	Criteria
<b>I. Neurodegenerative disease</b>	Shows progressive deterioration of behaviour and /or cognition by observation or history (as provided by a knowledgeable informant)
<b>II. Possible bvFTD</b>	<p>Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria:</p> <ul style="list-style-type: none"> <li>A. Early behavioural disinhibition (one of the following must be present): <ul style="list-style-type: none"> <li>A.1 Socially inappropriate behaviour</li> <li>A.2 Loss of manners or decorum</li> <li>A.3 Impulsive, rash or careless actions</li> </ul> </li> <li>B. Early apathy or inertia (one of the following must be present): <ul style="list-style-type: none"> <li>B.1 Apathy</li> <li>B.2 Inertia</li> </ul> </li> <li>C. Early loss of sympathy or empathy (one of the following must be present): <ul style="list-style-type: none"> <li>C.1 Diminished response to other people’s needs and feelings</li> <li>C.2 Diminished social interest, interrelatedness or personal warmth</li> </ul> </li> <li>D. Early perseverative, stereotyped or compulsive/ritualistic behaviour (one of the following must be present): <ul style="list-style-type: none"> <li>D.1 Simple repetitive movements</li> <li>D.2 Complex, compulsive or ritualistic behaviours</li> <li>D.3 Stereotypy of speech</li> </ul> </li> <li>E. Hyperorality and dietary changes (one of the following must be present): <ul style="list-style-type: none"> <li>E.1 Altered food preferences</li> <li>E.2 Binge eating, increased consumption of alcohol or cigarettes</li> <li>E.3 Oral exploration or consumption of inedible objects</li> </ul> </li> <li>F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following must be present): <ul style="list-style-type: none"> <li>F1. Deficits in executive tasks</li> <li>F2. Relative sparing of episodic memory</li> <li>F3. Relative sparing of visuospatial skills</li> </ul> </li> </ul>
<b>III. Probable bvFTD</b>	<p>All of the following symptoms (A–C) must be present to meet criteria:</p> <ul style="list-style-type: none"> <li>A. Meets criteria for possible bvFTD</li> <li>B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)</li> <li>C. Imaging results consistent with bvFTD (one of the following must be present): <ul style="list-style-type: none"> <li>C.1 Frontal and/or anterior temporal atrophy on MRI or CT</li> <li>C.2 Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT</li> </ul> </li> </ul>

<b>IV. Behavioural variant FTD with definite FTLD pathology</b>	<p>Criterion A and either criterion B or C must be present to meet the criteria:</p> <ul style="list-style-type: none"> <li>A. Meets criteria for possible or probable bvFTD</li> <li>B. Histopathological evidence of FTLD on biopsy or at post-mortem</li> <li>C. Presence of a known pathogenic mutation</li> </ul>
<b>V. Exclusionary Criteria for bvFTD</b>	<p>Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD:</p> <ul style="list-style-type: none"> <li>A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders</li> <li>B. Behavioural disturbance is better accounted for by a psychiatric diagnosis</li> <li>C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process</li> </ul>

**Table 8.3 Gorno-Tempini diagnostic criteria for PPA** (Gorno-Tempini *et al.*, 2011)

Level Diagnosis	nfvPPA	svPPA	lvPPA
<b>I. Clinical</b>	At least one of:	Both of:	Both of:
Core Features	<ol style="list-style-type: none"> <li>1. Agrammatism in language production</li> <li>2. Effortful, halting speech with inconsistent speech sound error and distortions (apraxia of speech)</li> </ol>	<ol style="list-style-type: none"> <li>1. Impaired confrontation naming</li> <li>2. Impaired single-word comprehension</li> </ol>	<ol style="list-style-type: none"> <li>1. Impaired single-word retrieval in spontaneous speech and naming</li> <li>2. Impaired repetition of sentences and phrases</li> </ol>
Other Features	At least two of:	At least three of:	At least three of:
	<ol style="list-style-type: none"> <li>1. Impaired comprehension of syntactically complex sentences</li> <li>2. Spared single-word comprehension</li> <li>3. Spared object knowledge</li> </ol>	<ol style="list-style-type: none"> <li>1. Impaired object knowledge, particularly for low-frequency or low-familiarity items</li> <li>2. Surface dyslexia or dysgraphia</li> <li>3. Spared repetition</li> <li>4. Spared speech production (grammar and motor speech)</li> </ol>	<ol style="list-style-type: none"> <li>1. Speech (phonological) errors in spontaneous speech and naming</li> <li>2. Spared single-word comprehension</li> <li>3. Spared motor speech</li> <li>4. Absence of frank agrammatism</li> </ol>
<b>II. Imaging Supported</b>	One or more of:	One or more of:	One or more of:
	<ol style="list-style-type: none"> <li>1. Predominant left posterior fronto-insular atrophy on MRI or</li> <li>2. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET</li> </ol>	<ol style="list-style-type: none"> <li>1. Predominant anterior temporal lobe atrophy</li> <li>2. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET</li> </ol>	<ol style="list-style-type: none"> <li>1. Predominant left posterior peri-Sylvian or parietal atrophy on MRI</li> <li>2. Predominant left posterior peri-Sylvian or parietal hypoperfusion or hypometabolism on SPECT or PET</li> </ol>
<b>III. Pathologically Definite</b>	Criterion I and II (above) or III (below) <ol style="list-style-type: none"> <li>1. Histopathological evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other)</li> <li>2. Presence of a known pathogenic mutation</li> </ol>		

## 8.2 Chapter 4: Speech perception tests in dementia

**Table 8.4 Bark Scale**

Number	Center-frequency (Hz)	Cut-off frequency (Hz)	Bandwidth (Hz)
		20	
1	50	100	80
2	150	200	100
3	250	300	100
4	350	400	100
5	450	510	110
6	570	630	120
7	700	770	140
8	840	920	150
9	1,000	1,080	160
10	1,170	1,270	190
11	1,370	1,480	210
12	1,600	1,720	240
13	1,850	2,000	280
14	2,150	2,320	320
15	2,500	2,700	380
16	2,900	3,150	450
17	3,400	3,700	550
18	4,000	4,400	700
19	4,800	5,300	900
20	5,800	6,400	1,100
21	7,000	7,700	1,300

22	8,500	9,500	1,800
23	10,500	12,000	2,500
24	13,500	15,500	3,500

The table shows the Bark Scale of auditory filters, derived from experimental work by Bark and colleagues. Each filter number, its corresponding centre frequency (Hz), upper cut-off frequency (Hz) and the corresponding bandwidth of each auditory filter (Hz).



### 8.3 Chapter 5: Phonological processing in dementia

**Table 8.5 Details of excluded cases by participant group**

	Control	AD	svPPA	nfvPPA	lvPPA
Hearing aid users	1	0	1	1	0
Non-native English speakers	1	0	3	1	0
Didn't meet reading criterion	0	1	4	3	1
Unable to speak (so no reading score)	0	0	0	7	0
Didn't understand PALPA-3 instructions	0	0	0	5	3
Presence of pathogenic mutation	0	0	1	2	1
Missing reading data	0	0	3	5	2
Missing data on age of onset or gender	7	0	0	0	1
Total	9	1	12	24	8

The table shows details of potential participants excluded for not meeting inclusion criteria for this study. lvPPA, patient group with logopenic variant primary progressive aphasia; nfvPPA, patient group with nonfluent/agrammatic variant primary progressive aphasia; svPPA, patient group with semantic variant primary progressive aphasia; tAD, patient group with typical Alzheimer's disease.

## 8.4 Chapter 6: Auditory symptoms disability and handicap in dementia

### Modified Amsterdam Inventory for disability and handicap

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- |               |  |              |              |  |
|---------------|--|--------------|--------------|--|
| 1.            | Can you understand a shop assistant in a crowded shop?   |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 2.            | Can you carry on a conversation with someone in a quiet room?                                  |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 3.            | Do you immediately hear from what direction a car is approaching when you are outside?         |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 4.            | Can you hear cars passing by?  |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 5.            | Do you recognize members of your family by their voices?                                       |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 6.            | Can you recognize melodies in music or songs?  |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 7.            | Can you carry on a conversation with someone during a crowded meeting?                         |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 8.            | Can you carry on a telephone conversation in a quiet room?                                     |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 9.            | Can you hear from what corner of a lecture room someone is asking a question during a meeting? |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 10.           | Can you hear somebody approaching from behind?   |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 11.           | Do you recognize a presenter on TV by his/her voice?   |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |
|               |  |              |              |  |
| 12.           | Can you understand text that's being sung?   |              |              |  |
| Almost always | Frequently   | Occasionally | Almost never |  |

13. Can you easily carry on a conversation with somebody in a bus or car?  
 Almost always              Frequently              Occasionally              Almost never
14. Can you understand the presenter of the news on TV?  
 Almost always              Frequently              Occasionally              Almost never
15. Do you immediately look in the right direction when somebody calls you in the street?  
 Almost always              Frequently              Occasionally              Almost never
16. Can you hear noises in the household, like running water, vacuuming, a washing machine?  
 Almost always              Frequently              Occasionally              Almost never
17. Can you discriminate the sound of a car and a bus?  
 Almost always              Frequently              Occasionally              Almost never
18. Can you follow a conversation between a few people during dinner?  
 Almost always              Frequently              Occasionally              Almost never
19. Can you understand the presenter of the news on the radio?  
 Almost always              Frequently              Occasionally              Almost never
20. Can you hear from what corner of a room someone is talking to you in a quiet house?  
 Almost always              Frequently              Occasionally              Almost never
21. Can you hear the door-bell at home?  
 Almost always              Frequently              Occasionally              Almost never
22. Can you distinguish between male and female voices?  
 Almost always              Frequently              Occasionally              Almost never
23. Can you hear rhythm in music or songs?  
 Almost always              Frequently              Occasionally              Almost never

24. Can you carry on a conversation with someone in a busy street?  
Almost always      Frequently      Occasionally      Almost never

25. Can you distinguish intonations and voice inflection in people's voices?  
Almost always      Frequently      Occasionally      Almost never

26. Do you hear from what direction a car horn is coming?  
Almost always      Frequently      Occasionally      Almost never

27. Do you hear birds singing outside?  
Almost always      Frequently      Occasionally      Almost never

28. Can you recognize and distinguish different musical instruments?  
Almost always      Frequently      Occasionally      Almost never

## The Hearing Impairment Impact-Significant Other Profile

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1. Do you feel like you are shouting all the time because of your SO's hearing loss?  
Yes                      Sometimes                      No
2. Do you have to make sure your SO is looking at you when you speak to him/her?  
Yes                      Sometimes                      No
3. Do you get irritated when you try to talk with your SO but she/he cannot understand you?  
Yes                      Sometimes                      No
4. Do you feel that your SO's hearing loss hampers your social life?  
Yes                      Sometimes                      No
5. Does having to repeat what you say to your SO all the time make you feel tired?  
Yes                      Sometimes                      No
6. Do you have to make sure your SO can see your face when you talk with him or her?  
Yes                      Sometimes                      No
7. Does your SO's hearing loss make you feel frustrated?  
Yes                      Sometimes                      No
8. Do you and your SO avoid social gatherings because of his/her hearing loss?  
Yes                      Sometimes                      No
9. Do you think your SO's hearing loss has made your relationship less satisfying?  
Yes                      Sometimes                      No
10. Do you think that communicating with your SO requires a lot of effort because of his/her hearing loss?  
Yes                      Sometimes                      No
11. Do you find yourself annoyed because your SO turns the TV up too loud?  
Yes                      Sometimes                      No
12. Do you and your SO avoid going to restaurants because of your SO's hearing loss?  
Yes                      Sometimes                      No
13. Do you feel that your SO's hearing loss has a negative effect on the intimate communication between the two of you?

Yes                      Sometimes                      No

14. Does your SO's hearing problem make you feel angry?

Yes                      Sometimes                      No

15. Do you have to repeat what you say to your SO because of his/her hearing loss?

Yes                      Sometimes                      No

16. Does your SO's hearing loss cause the two of you to argue?

Yes                      Sometimes                      No

17. Because of your SO's hearing loss, do you talk less often than you used to?

Yes                      Sometimes                      No

18. Do you find that it is difficult to enjoy social gatherings because of your SO's hearing loss?

Yes                      Sometimes                      No

19. Do you have to get up and go over to your SO when you need to talk with him/her?

Yes                      Sometimes                      No

20. Do you think your SO's hearing loss has created tension in your relationship?

Yes                      Sometimes                      No

### The Modified Khalfa Hyperacusis Questionnaire

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1. Do you have trouble concentrating in a noisy or loud environment?  
Yes                      Sometimes                      No
  
2. Do you have trouble reading in a noisy or loud environment?  
Yes                      Sometimes                      No
  
3. Do you ever use earplugs or earmuffs to reduce your noise perception? (Do not consider the use of hearing protection during abnormally high exposure situations)  
Yes                      Sometimes                      No
  
4. Do you find it harder to ignore sounds around you in everyday situations?  
Yes                      Sometimes                      No
  
5. Do you find it difficult to listen to speaker announcements (such as airport, airplanes, trains, etc.)?  
Yes                      Sometimes                      No
  
6. Are you particularly sensitive to or bothered by street noise?  
Yes                      Sometimes                      No
  
7. Do you “automatically” cover your ears in the presence of somewhat louder sounds?  
Yes                      Sometimes                      No
  
8. When someone suggests doing something (going out, to the cinema, to a concert, etc.), do you immediately think about the noise you are going to have to put up with?  
Yes                      Sometimes                      No
  
9. Do you ever turn down an invitation or not go out because of the noise you would have to face?  
Yes                      Sometimes                      No
  
10. Do you find the noise unpleasant in certain social situations (e.g. Nightclubs, pubs or bars, concerts, firework displays, cocktail receptions)?  
Yes                      Sometimes                      No
  
11. Has anyone you know ever told you that you tolerate noise or certain kinds of sound badly?

Yes                      Sometimes                      No

12. Are you particularly bothered by sounds others are not?

Yes                      Sometimes                      No

13. Are you afraid of sounds others are not?

Yes                      Sometimes                      No

14. Do noise and certain sounds cause you stress and irritation?

Yes                      Sometimes                      No

15. Are you less able to concentrate in noise toward the end of the day?

Yes                      Sometimes                      No

16. Do stress and tiredness reduce your ability to concentrate in noise?

Yes                      Sometimes                      No

17. Do you find sound annoy you and not others?

Yes                      Sometimes                      No

18. Are you emotionally drained by having to put up with all daily sounds?

Yes                      Sometimes                      No

19. Do you find daily sounds have an emotional impact on you?

Yes                      Sometimes                      No

20. Are you irritated by sounds others are not?

Yes                      Sometimes                      No



## 8.5 Division of labour

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

### 8.5.1 Chapter 3: Pure tone audiometry and dementia

Experimental design: JCSJ, CJDH, DEB, NU, JDW

Construction of tests: JCSJ

Data collection: JCSJ, EB, MRK, HS, JJ

Data analysis: JCSJ

### 8.5.2 Chapter 4: Speech perception tests in dementia

Experimental design: JCSJ, CJDH, DEB, NU, JDW

Construction of tests: JCSJ

Data collection: JCSJ, EB, MRK, HS, JJ

Data analysis: JCSJ

### 8.5.3 Chapter 5: Phonological processing in dementia

Experimental design: JCSJ, CJDH, JDW

Construction of tests: N/A

Data collection: CJDH, CRM, HS, EB, HG, JG, PF, RB, LR

Data analysis: JCSJ, CJDH

### 8.5.4 Chapter 6: Auditory symptoms disability and handicap in dementia

Experimental design: JCSJ, CJDH, DEB, NU, JDW

Construction of tests: N/A

Data collection: JCSJ, EB, MRK, HS, JJ

Data analysis: JCSJ

## 8.6 Publications

### 8.6.1 Publications arising as a direct result of the work conducted in this thesis

**Johnson JCS**, Jiang J, Bond RL, Benhamou E, Requena-Komuro M, Russell LL, et al. Impaired phonemic discrimination in logopenic variant primary progressive aphasia. *Ann Clin Transl Neurol* 2020; 7: 1252–7.

**Johnson JCS**, Marshall CR, Weil RS, Bamiou D-E, Hardy CJD, Warren JD. Hearing and dementia: from ears to brain. *Brain* 2021; 144: 391–401.

**Johnson JCS**, McWhirter L, Hardy CJD, Crutch SJ, Marshall CR, Mummery CJ, Rohrer JD, Rossor MN, Schott JM, Weil RS, Fox NC, Warren JD. Suspecting Dementia. *Practical Neurology*. Jul 2021; Volume 21, Issue 4. Doi: 10.1136/practneurol-2021-003019.

### 8.6.2 Other substantial contributions

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