AUDITORY SCENE ANALYSIS IN ALZHEIMER'S DISEASE

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DECLARATION

I, Hannah Louise Golden, 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 (Appendix 4).

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ABSTRACT

This thesis explores the behavioural and neuroanatomical picture of Auditory Scene Analysis (ASA) in Alzheimer's disease (AD). Central auditory dysfunction is an understudied symptom of AD and there has been little connection between the neuropathological profile of the disease, its relationship to generic ASA functions, and real-world listening situations. Utilising novel neuropsychological batteries alongside structural and functional imaging techniques, this thesis aims to bridge this gap through investigations of auditory spatial, speech in noise, and (as a specialised auditory scene) music processing.

Spatial location discrimination and motion detection of sounds was impaired in both typical AD and posterior cortical atrophy; this was associated with atrophy in right inferior parietal and posterior medial regions. A functional imaging investigation of auditory spatial processing in typical AD revealed abnormalities in posterior medial cortical areas when sounds were changing in location. Functional imaging of an everyday auditory scenario (hearing one's own name over background babble) highlighted alteration in a right inferior parietal region. Novel neuropsychological tasks assessing components of musical 'scenes' found that global aspects of pitch pattern processing were impaired in both the typical and language variant of AD while local aspects were preserved; both global and local forms of temporal processing were also intact. These patients also exhibited diminished tonality perception and musical stream segregation based on familiar templates.

These investigations delineate reduced ASA capacity in a number of components that make up everyday auditory scenes. This has real world implications for both typical AD and its rarer phenotypes. Furthermore, ASA dysfunction may inform us about network breakdown, network function, and sources of phenotypic similarity in AD.

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TABLE OF CONTENTS

DECLARATION **2**
ABSTRACT **3**
ACKNOWLEDGEMENTS **4**
TABLE OF CONTENTS **5**
TABLE OF FIGURES **9**
TABLE OF TABLES **10**
ABBREVIATIONS **11**
1 GENERAL INTRODUCTION **12**
1.1 Diagnosis of typical AD 13
1.2 Phenotypic variability in AD 14
1.3 Neuroanatomical characteristics of AD 15
1.4 DMN function 18
1.5 DMN and the neuropsychological profile of AD 20
1.5.1 PMC: memory and visuospatial impairment in AD 20
1.5.2 Temporoparietal cortex: executive, attentional, working memory, lexical access and visuospatial deficits in AD 22
1.5.3 AD neuropsychological deficits and ASA 23
1.6 Central auditory processing: mechanisms and anatomy 23
1.6.1 Cortical auditory processing pathways 24
1.6.2 Conceptualisations of ASA 26
1.6.3 The role of attention 27
1.6.4 Schema based processing 28
1.6.5 Auditory spatial processing 29
1.6.6 Specialized applications of auditory scene analysis 30
1.6.6.1 Speech 30
1.6.6.2 Music 31
1.6.7 DMN regions involved in ASA processing 32
1.7 A review of auditory processing in AD 35
1.7.1 Peripheral hearing in AD 35
1.7.2 Neuropsychological aspects of central auditory function in AD 36
1.7.3 Music processing in AD 41
1.7.4 Neuroanatomical aspects of central auditory function in AD 42
1.7.5 Electrophysiological studies of central auditory function in AD 43
1.8 DMN and ASA in AD 45
1.9 Thesis aims and outline 48
2 METHODS OVERVIEW **50**
2.1 Participants 50
2.1.1 Typical AD patients 51
2.1.2 PCA patients 51
2.1.3 lvPPA patients 52
2.1.4 naPPA patients 52
2.1.5 Healthy control participants 52
2.2 Peripheral audiometry assessment 52
2.3 Pitch discrimination musical screening task 53
2.4 Musical background questionnaire 53
2.5 Neuropsychological assessment 54
2.6 Generation and presentation of auditory stimuli 55

2.6.1 Spatial sound generation 55
2.7 Image acquisition 57
2.7.1 Structural MRI 57
2.7.2 Functional MRI 57
2.8 Image preprocessing 58
2.8.1 Structural MRI 59
2.8.2 Functional MRI 59
2.8.3 Study specific mean image 59
2.8.4 Small volume generation 60
2.9 Statistical analysis 60
2.9.1 Demographic, neuropsychological and peripheral audiometry analysis 60
2.9.2 Behavioural analysis 61
2.9.3 Brain imaging analysis 61
2.9.3.1 VBM 62
2.9.3.2 Functional imaging 62
2.9.3.3 Correction for multiple comparisons 63
3 AUDITORY SPATIAL PROCESSING IN AD: A NEUROPSYCHOLOGICAL AND STRUCTURAL NEUROANATOMICAL INVESTIGATION 64
3.1 Introduction 64
3.2 Hypotheses 65
3.3 Methods 66
3.3.1 Participants 66
3.3.2 Background neuropsychometry 68
3.3.3 General structure of experimental battery 68
3.3.4 Externalised versus non-externalised sound discrimination 70
3.3.5 Moving versus stationary sound discrimination 71
3.3.6 Stationary sound position discrimination 71
3.3.7 Auditory control tasks 72
3.3.8 Visual spatial control tasks 72
3.3.9 Procedure 73
3.3.10 Behavioural analysis 74
3.3.11 VBM analysis 75
3.4 Results 76
3.4.1 Demographics, neuropsychology and peripheral audiometry 76
3.4.2 Auditory spatial tasks 77
3.4.3 Auditory control tasks 81
3.4.4 Visual spatial control tasks 81
3.4.5 Correlations between parameters 81
3.4.6 Effect of perceptual parameter 84
3.4.7 Neuroanatomical associations 86
3.5 Discussion 90
4 AUDITORY SPATIAL PROCESSING IN AD: AN FMRI INVESTIGATION 95
4.1 Introduction 95
4.2 Hypotheses 96
4.3 Methods 97
4.3.1 Participants 97
4.3.2 Experimental design and stimuli 98
4.3.3 Procedure 100
4.3.3.1 Stimulus presentation and brain image acquisition 100
4.3.3.2 Post-scan behavioural task 100

4.3.4 fMRI analysis 101
4.3.5 VBM analysis 103
4.3.6 Analysis of behavioural data 103
4.4 Results 104
4.4.1 Demographic, neuropsychological and peripheral audiometry characteristics 104
4.4.2 Post-scan behavioural task 106
4.4.3 Structural neuroanatomy 106
4.4.4 Functional neuroanatomy 107
4.5 Discussion 115
5 AUDITORY MASKING IN AD: AN FMRI INVESTIGATION 121
5.1 Introduction 121
5.2 Hypotheses 122
5.3 Methods 123
5.3.1 Participants 123
5.3.2 Experimental design and stimuli 125
5.3.3 Procedure 127
5.3.3.1 Stimulus presentation 127
5.3.3.2 Post-scan behavioural task 127
5.3.4 fMRI analysis 129
5.3.5 Voxel-based morphometry analysis 131
5.3.6 Behavioural analysis 131
5.4 Results 131
5.4.1 Demographic, neuropsychological and peripheral audiometry characteristics 131
5.4.2 Post-scan behavioural task 132
5.4.3 Structural neuroanatomy 132
5.4.4 Functional neuroanatomy 133
5.5 Discussion 141
6 ASSESSING PITCH, TEMPORAL, STREAMING AND KEY FUNCTIONS AS 'MUSICAL SCENE' ELEMENTS IN AD: A NEUROPSYCHOLOGICAL INVESTIGATION 148
6.1 Introduction 148
6.1.1 Pitch and melody perception 148
6.1.2 Key perception 150
6.1.3 Rhythm and metre perception 151
6.1.4 Musical streaming 152
6.1.5 Designing a dementia-specific musical scene battery 153
6.2 Hypotheses 155
6.3 Methods 155
6.3.1 Participants 155
6.3.2 General structure of experimental battery 160
6.3.3 Local-global pitch deviance detection 160
6.3.3.1 Main task 160
6.3.3.2 Easy version 161
6.3.4 Key deviance detection 162
6.3.5 Local-global temporal deviance detection 162
6.3.6 Timbre deviance detection control 163
6.3.7 Embedded tune detection 163
6.3.7.1 Tune recognition control 164
6.3.8 Behavioural analysis 165

6.3.8.1 Deviance detection tasks 165
6.3.8.1.1 Pitch deviance detection 166
6.3.8.1.2 Key deviance detection 166
6.3.8.1.3 Temporal deviance detection 166
6.3.8.1.4 Timbre control task 166
6.3.8.1.5 Embedded tunes 166
6.4 Results 167
6.4.1 Demographic, neuropsychological and peripheral audiometry characteristics 167
6.4.2 Local-global pitch deviance detection 168
6.4.2.1 Easy version 169
6.4.3 Key deviance detection 170
6.4.4 Local-global temporal deviance detection 171
6.4.5 Timbre deviance detection control 172
6.4.6 Embedded tune detection 173
6.4.6.1 Recognition task 173
6.4.6.2 Main task 174
6.5 Discussion 176
7 GENERAL DISCUSSION 184
7.1 Summary of findings 184
7.2 ASA and neural networks in AD 185
7.3 ASA processing in AD phenotypic variants 188
7.4 Top down and executive factors 190
7.5 Can ASA aid diagnosis of AD? 190
7.6 ASA and naturalistic listening situations in AD 191
7.7 Limitations 192
7.8 Future directions 193
REFERENCES 194
APPENDICES 229
Appendix 1: Participation of individual typical AD patients by study 229
Appendix 2: Items used in the musical experience questionnaire 230
Appendix 3: Items used in the embedded tunes task 231
Appendix 4: Division of Labour 232
Appendix 5: Publications 233

TABLE OF FIGURES

Figure 1.1 – Schematic representation of the DMN, AD pathology and atrophy progression. 17
Figure 1.2 – Schematic representation of auditory processing streams 25
Figure 1.3 – Schematic representation of neuroanatomical regions involved in both ASA and DMN 47
Figure 3.1 – Schematic representation of experimental battery 70
Figure 3.2 – Verbal instructions and visual aids used in experimental auditory tests 74
Figure 3.3 – Individual raw scores for each experimental task 80
Figure 3.4 – Group mean d prime scores 85
Figure 3.5 – Grey matter associations with auditory spatial task performance 88
Figure 4.1 – Schematic representation of all conditions 99
Figure 4.2 – Post-scan behavioural task visual guide 101
Figure 4.3 – Small volumes used for analysis of functional data 103
Figure 4.4 – Atrophy map of the AD group compared to healthy controls 106
Figure 4.5 – Functional neuroanatomy of auditory stimulation 108
Figure 4.6 – Functional neuroanatomical data: within-group contrasts 111
Figure 4.7 – Functional neuroanatomical data: between-group contrasts 112
Figure 5.1 – Schematic representation of fMRI stimulus conditions 127
Figure 5.2 – Visual guide shown to participants in post-scan behavioural testing 129
Figure 5.3 – Small volumes used for analysis of functional data 130
Figure 5.4 – Atrophy map of the AD group compared to healthy controls 133
Figure 5.5 – Functional neuroanatomy of auditory stimulation 134
Figure 5.6 – Functional neuroanatomical data – within group contrasts 136
Figure 5.7 – Functional neuroanatomical data – between group contrasts 138
Figure 6.1 – Schematic representation of musical task stimuli 164
Figure 6.2 – Individual corrected-detection-scores for local-global pitch deviance detection 170
Figure 6.3 – Individual corrected-detection-scores for key deviance detection 171
Figure 6.4 – Individual corrected-detection-scores for local-global temporal deviance detection 172
Figure 6.5 – Individual corrected-detection-scores for timbre deviance detection control 173
Figure 6.6 – Individual proportion correct scores for embedded tune detection 174
Figure 7.1 - Schematic representation of proposed associations between DMN and ASA in AD: integration with findings of current investigations 188

TABLE OF TABLES

Table 1.1 – Summary of behavioural studies investigating aspects of ASA in AD 39
Table 2.1 – Participant assignment to each generic HRTF.....57
Table 3.1 – General demographic, clinical and neuropsychological data for participant groups.....67
Table 3.2 – Summary of group performance on experimental tasks 78
Table 3.3 – Summary of performance correlations (Spearman's rho) between experimental tasks and relevant general neuropsychological functions 83
Table 3.4 – Summary of neuroanatomical associations for experimental auditory spatial tasks in the patient groups.....89
Table 4.1 – Demographic and post-scan behavioural task data.....97
Table 4.2 – Neuropsychological profile of experimental groups.....105
Table 4.3 – Summary of AD group regional grey matter atrophy 107
Table 4.4 – Summary of fMRI data for experimental contrasts of interest in participant groups.....113
Table 5.1 – General demographic, clinical, neuropsychological and behavioural data for participant groups.....124
Table 5.2 – Summary of AD group regional grey matter atrophy 133
Table 5.3 – Summary of fMRI data for experimental contrasts of interest in participant groups.....139
Table 6.1 – General demographic, clinical and neuropsychological profiles.....157
Table 6.2 – Summary of group level performance for each experimental task .175

ABBREVIATIONS

(t)AD	(typical) Alzheimer's disease
ADRDA	Alzheimer's Disease and Related Disorders Association
ASA	Auditory scene analysis
BOLD	Blood oxygen level dependent
CI	Confidence interval
CSF	Cerebro-spinal fluid
dB	Decibel
DMN	Default mode network
EEG	Electroencephalography
EPI	Echo planar image
ERP	Event related potential
(f)MRI	(Functional) magnetic resonance imaging
FWE	Family-wise error
HRTF	Head-related transfer function
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobe
IRN	Iterated ripple noise
IRR	Incidence risk ratio
lvPPA	logopenic variant primary progressive aphasia
MBEA	Montreal battery for the evaluation of amusia
MEG	Magnetoencephalography
MMSE	Mini-mental state examination
MMN	Mismatch negativity
MNI	Montreal neurological institute
mPFC	Medial prefrontal cortex
MTL	Medial temporal lobe
naPPA	nonfluent/agrammatic primary progressive aphasia
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
OR	Odds ratio
PCA	Posterior cortical atrophy
PCC	Posterior cingulate cortex
PET	Positron Emission Topography
PMC	Posterior medial cortex
PPA	Primary progressive aphasia
PT	Planum temporale
SD	Semantic dementia
SMG	Supramarginal gyrus
SPM	Statistical parametric mapping
STS/G	Superior temporal sulcus/gyrus
TIV	Total intracranial volume
VBM	Voxel-based morphometry

1 GENERAL INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting approximately 30 million people worldwide (Barnes & Yaffe, 2011; Brookmeyer et al., 2007) and accompanied by huge social, economic and personal burden. In the field of Alzheimer's research, information that aids early and accurate diagnosis is essential, especially when disease modifying drugs become available. However, phenotypic heterogeneity and variable evolution of cognitive function pose a significant barrier to such an understanding. There is still a lack of information about exactly how pathophysiology relates to the symptoms presented: AD arises from aggregations of intracellular amyloid and extracellular tau in the brain, but this can lead to variable neuroanatomical and clinical presentations. Whilst these are categorized by phenotypic boundaries (for example 'typical' memory-led AD versus posterior cortical atrophy: PCA), AD neurocognitive patterns may be better conceptualised as a spectrum, whereby particular neuroanatomical regions that are centred on particular functional networks, or connected to specific 'hub' regions, are vulnerable to different degrees (Migliaccio et al., 2009; Warren et al., 2012). Current research reveals that aspects of AD neuropathology, atrophy and functional abnormalities target a network of brain regions pertinent to healthy brain functioning, known as the Default Mode Network (DMN: e.g. Buckner et al., 2008; Greicius et al., 2009; Seeley et al., 2009). Thus focusing solely on memory symptoms and medial temporal lobe regions may restrict the wider picture of everyday functioning in AD, how different non-amnestic symptoms can contribute to our understanding of AD as a network disease, and what particularly disease-vulnerable brain areas may tell us about commonalities between AD variants.

This thesis aims to address some of these problems by investigating how the auditory world is processed in AD. It will present a number of studies that examine 'Auditory Scene Analysis' (ASA: Bregman, 1990) in action, with the intention of highlighting the problems patients experience with real-world auditory challenges. This involves neuropsychological and neuroanatomical study of spatial, speech-in-noise and musical auditory processing. In basic terms, ASA describes the processing of numerous sounds occurring simultaneously in our environment, and how our brains come to interpret this mixture as a collection of individual entities arising from separable, identifiable sound sources. ASA is relevant to AD on a number of grounds. Symptomatically, patients frequently report difficulties in busy auditory situations. Anatomically, regions governing both core DMN and ASA processing in the healthy brain are implicated in AD. Functionally, the computational demands of ASA may overlap with certain processing roles of DMN regions. Furthermore, assessing a function that transcends traditional phenotypic boundaries may reveal both cognitive and neuroanatomical areas of common involvement across diagnostic variants. I will review the evidence to support these statements by examining the literature on ASA in the healthy brain, as well as neuropsychological and neuroanatomical aspects of AD that could affect ASA. I will first give a brief overview of the neuroanatomical and neuropsychological profile of AD.

1.1 Diagnosis of typical AD

Whilst older NINCDS−ADRDA clinical criteria for AD (McKhann et al., 1984) focus on performance on neuropsychological tests of cognition and general function such as the Mini-Mental State Exam (MMSE: Folstein et al., 1975), these criteria have been revised for both clinical and research purposes (Dubois et al., 2007, 2014; McKhann et al., 2011), utilising advancements in biomarker technologies and defining typical and atypical variants. The core clinical symptoms of typical AD are still characterized as an insidious progressive disorder of primarily memory followed by other

cognitive functions, where memory deficits are best detected using delayed recall without benefit from cueing. Advancement of classification stems from the addition of supporting biomarkers such as medial temporal lobe (MTL) atrophy on structural imaging, an increased ratio of total tau to beta-amyloid$_{1-42}$ in CSF and temporoparietal hypometabolism indexed by PET imaging. Currently a definite diagnosis of AD in an individual presenting with an AD phenotype can only be obtained by genetic confirmation of a known autosomal dominant mutation or histopathological evidence of characteristic protein aggregates in the brain after death.

1.2 Phenotypic variability in AD

Typical AD provides a clinical picture of primary memory impairment. However, phenotypic variation is common. PCA provides one example, as a predominantly visuoperceptual or visuospatial syndrome with relatively preserved memory, disproportionately affecting parietal and occipital brain regions (Crutch et al., 2012; Galton et al., 2000; McMonagle et al., 2006; Renner et al., 2004). Neuropathological studies have found that the majority of cases presenting with this phenotype have Alzheimer's pathology (Renner et al., 2004), however no consensus criteria for diagnosis have yet been developed (Crutch et al., 2012, 2013a). Another more recently defined variant of AD attacks language function, known as logopenic variant primary progressive aphasia (lvPPA). Presenting symptoms here are most often word finding difficulty with long word finding pauses, but preserved grammatical expression and language comprehension. Consensus criteria focus on the difficult differentiation of presenting cognitive phenotypes of this syndrome from non-fluent and semantic variant PPA (Gorno-Tempini et al., 2011). Neuroanatomical investigations show more extensive atrophy in dominant temporoparietal regions (Rohrer et al., 2010); pathological findings link this phenotype predominantly to AD (Mesulam et al., 2008; Rohrer et al., 2012a). The posterior temporal and parietal atrophy exhibited in these less common

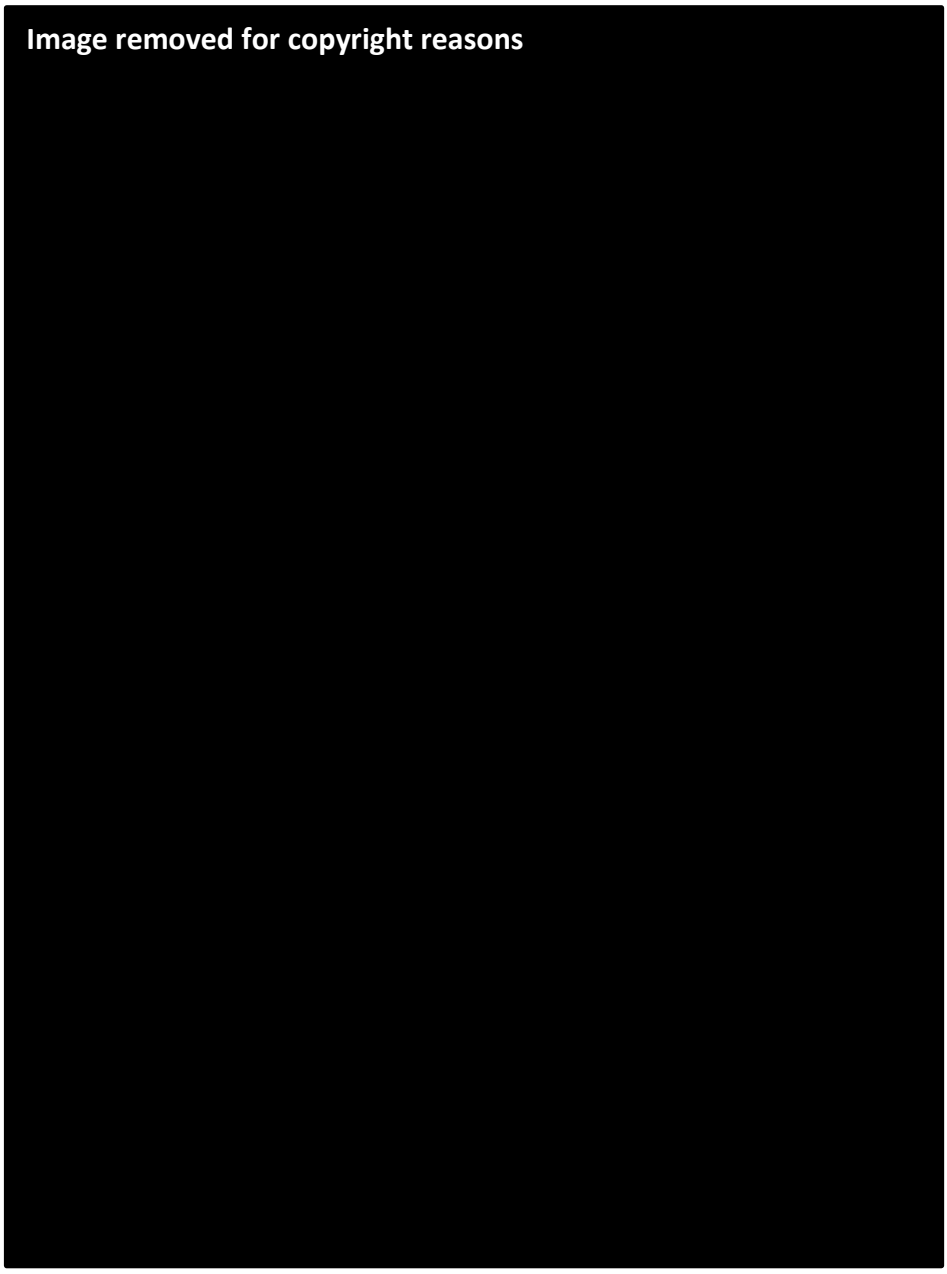
variants do show some neuroanatomical overlap with typical AD, with some authors suggesting the rare variants of PCA and lvPPA are at opposite ends of an AD spectrum (Migliaccio et al., 2009). Additionally, cases of frontal variant AD have been documented (Johnson et al., 1999; Snowden et al., 2007). Even within the 'typical AD' category, variation in neuropsychological profile is evident (Snowden et al., 2007; Stopford et al., 2007, 2008). Stopford et al. (2008) proposed that AD phenotypes may exist on a continuum, with the further suggestion that this may result from differential involvement of core DMN regions (Warren et al., 2012). What initiates these different patterns is unknown, but they do highlight the need for further investigation into unifying tasks that access core 'hub' functions that may share involvement across phenotypes. Whilst phenotypic variability clearly has an important role to play in deciphering the link between neuropathology and clinical profile, the following two sections mainly focus on the neuroanatomical and neuropsychological findings of patients who have been classified with a typical, amnestic syndrome and how they link to DMN anatomy and ASA.

1.3 Neuroanatomical characteristics of AD

The picture of neuroanatomical decline in AD is emerging as a systematic breakdown of areas comprising a functionally coherent network in the healthy brain: the DMN. This involves core regions such as posterior medial cortex (PMC, encompassing precuneus, posterior cingulate and retrosplenial cortex: Leech & Sharp, 2014; Vogt & Laureys, 2005), medial prefrontal cortex (mPFC), inferior parietal lobe (IPL: supramarginal and angular gyri), lateral temporal cortex and hippocampal formation, illustrated in Figure 1.1 (Buckner et al., 2008). The DMN's implication in AD has been demonstrated through various methods. Analysis of structural MRI reveals atrophy in grey matter regions involved in the DMN (Buckner et al., 2005; Scahill et al., 2002; Seeley et al., 2009; Thompson et al., 2003). PET imaging indicates hypometabolism in DMN regions (Chételat et al., 2008; Herholz, 1995; Minoshima et al., 1997) and AD

patients exhibit weakened correlation in spontaneous activity fluctuation between DMN nodes (Greicius et al., 2004; Lustig et al., 2003). Damoiseaux et al., (2012) showed that connectivity decreases over the disease span using longitudinal measures, indicating that the altered activity of the DMN is related to disease status. Whilst resting state fMRI studies implicate compromised DMN connectivity, task-based fMRI studies have also shown reduced DMN deactivation when participants are engaged in a memory task (Celone et al., 2006; Dickerson & Sperling, 2008; Pihlajamäki & DePeau, 2008).

Figure 1.1 – Schematic representation of the DMN, AD pathology and atrophy progression.



Adapted from Buckner et al. (2008). The medial (right) and lateral (left) surfaces of the left hemisphere are represented. Top left: areas in blue indicate where the brain is most active in the absence of external stimulation (DMN regions); top right: areas in red indicate distribution of amyloid pathology in the AD brain; bottom: areas in blue indicate progression of structural atrophy in AD as measured by longitudinal MRI

The cortical 'hub' of the DMN is in PMC, with a high resting metabolic rate and highly connected to other regions in the healthy brain (Fransson & Marrelec, 2008; Raichle et al., 2001). In particular, this region also shows low metabolism in AD (Matsuda, 2001; Minoshima et al., 1997) as well as convergence of involvement across multiple imaging modalities (Buckner et al., 2005) and very early involvement in the disease using structural imaging methods (Scahill et al., 2002). Buckner et al. (2005, 2009) suggest that its role as a highly connected processing hub is what makes this region so vulnerable to dysfunction in AD, and may direct how pathology spreads along the DMN. Work investigating common regions between early-onset AD variants of amnestic, visual and language presentations has revealed that PMC is affected across all three phenotypes in terms of cortical thickness (Lehmann et al., 2010) and functional connectivity (Lehmann et al., 2013). Further study of this along with other core DMN regions to assess their function in both the healthy brain and AD may therefore resolve some of the issues surrounding phenotypic heterogeneity and modelling of disease progression.

1.4 DMN function

Delineating the primary function of the DMN has been problematic due to the conditions that elicit its activity. Using functional imaging in the healthy brain, DMN regions show higher activity in baseline 'rest' conditions compared to conditions requiring engagement in an active task (Raichle et al., 2001; Shulman et al., 1997). DMN nodes also show correlation of spontaneous fluctuation in activity measured by resting state fMRI, indicating functional coherence in these regions (Damoiseaux et al., 2006; Fox et al., 2005; Fransson, 2005; Greicius et al., 2003; Greicius & Menon, 2004). This has also been supported by structural relationships between DMN network areas (Greicius et al., 2009; He et al., 2007). Another interesting finding is that of Anticevic et al. (2010), who observed that greater DMN deactivation during a working memory task elicits

better performance, indicating that both the activation and the deactivation of DMN regions serve a functional purpose.

However, the question arises: if the DMN is most active in the absence of any task, what is its significance in AD, a memory-led disorder? Its main function has often been linked to 'stimulus independent thought' as the putative "default mode" of brain function (Buckner et al 2008); however there are some functions that elicit greater activity in a number of core DMN regions. In the healthy brain, some or all of the DMN regions have been found to be more active in tasks such as episodic memory (Spreng & Grady, 2010; Svoboda et al., 2006), prospective memory (Schacter & Addis, 2007; Schacter et al., 2008; Spreng & Grady, 2010), theory of mind (Spreng & Grady, 2010), general introspection (Mason et al., 2007), moral dilemmas (Harrison et al., 2008) and imagery (Agnati et al., 2013; Zvyagintsev et al., 2013). In their review of DMN function, Buckner & Carroll (2007) tie these functions together to propose a common process of 'self projection': placing oneself mentally in a situation other than the present. Most of these functions listed require the individual to focus attention internally, which may not be limited to memory. This has been shown in studies detailing Theory of Mind deficits in AD patients (Moreau et al., 2013; Zaitchik et al., 2004, 2006). An additional piece of the DMN puzzle may be that it does not subserve one single process (Laird et al., 2009; Leech & Sharp, 2014; Leech et al., 2011). One alternative theory has given the DMN the role of external monitor (Gilbert et al., 2006, 2007; Gusnard & Raichle, 2001; Hahn et al., 2009; Raichle et al., 2001; Shulman et al., 1997), whereby it acts as a wide-spotlight attentional 'sentinel' (Buckner et al., 2008). These authors draw on Balint's syndrome, which, can occur as a result of damage to the medial parietal cortex (a key DMN region), inducing a 'spotlight' type of attention, rendering the patient unable to attend to the visual scene as a whole (Mesulam, 2000). A wide spotlight of attention may be particularly applicable to ASA, as this is a

function performed almost continually (however see section 1.6.3 for a further discussion on the interaction of attention and ASA).

Activity in the DMN has been found to be anti-correlated with a different functionally coherent network related to externally directed attention (Fox et al., 2005; Fransson, 2005), with PMC hub regions often linked to attention tracking and controlling the breadth of attentional focus (Cavanna & Trimble, 2006; Leech & Sharp, 2014). Leech and Sharp (2014) argue that the PMC is functionally heterogeneous, but may control the orienting of attention, which could go some way to reconciling the contrasting views of DMN as either governing internally directed or a wide spotlight of attention. Furthermore, the DMN exists as a structurally as well as functionally coherent network (e.g. Greicius et al., 2009), therefore its degeneration may give rise to impairments in processes that involve one or some of its parts. The next section will explore this in more detail.

1.5 DMN and the neuropsychological profile of AD

The implication of the hippocampal formation and MTL regions in episodic memory impairment in AD is well documented (Deweer et al., 1995; Dubois et al., 2007; Fox et al., 1996; Hyman et al., 1984; Di Paola et al., 2007). However, there is also evidence to suggest that other DMN regions contribute to this core function, as well as many of the additional deficits seen later on in the disease course, such as semantic difficulties, visuospatial processing, attention and executive function (Bäckman et al., 2005; Baddeley et al., 1991; Johnson et al., 2009; Lambon Ralph et al., 2003; Stopford et al., 2012). The next two sections will focus on posterior DMN regions, in particular PMC and temporoparietal cortex (including IPL) and their involvement in neuropsychological characteristics of AD.

1.5.1 PMC: memory and visuospatial impairment in AD

Tulving (2002, p.5) states that episodic memory 'makes possible mental time travel through subjective time, from the present to the past, thus

allowing one to re-experience, through autonoetic awareness, one's own previous experiences'. This description shows parallels with some of the proposed functions of the DMN (Buckner & Carroll, 2007; Buckner et al., 2008), therefore it may be predicted that the hub region in this network is implicated in the memory deficit in AD. In a PET study, Nestor et al. (2006) showed that a semantic variant PPA (svPPA) group had a similar level of MTL hypometabolism to an AD group despite a double dissociation in terms of episodic and semantic memory function. These authors suggested that connections to MTL efferent areas, such as posterior cingulate cortex (PCC), could be responsible for the greater episodic memory impairment in AD, indicating that these deficits may arise from a distributed network breakdown. An association between PMC hypometabolism and performance on a memory test was also found by Desgranges et al. (2002).

Although PMC shows reduced volume and metabolism in AD (Buckner et al., 2005; Chételat et al., 2008; Herholz, 1995; Minoshima et al., 1997; Scahill et al., 2002; Seeley et al., 2009; Thompson et al., 2003), task-related fMRI studies have shown that a failure to *deactivate* these regions relates to the memory impairments seen in this cohort. Using memory tasks, a series of studies has shown aberrant increase of activation in DMN regions during information encoding in AD patients compared to healthy controls (Celone et al., 2006; Pihlajamäki & DePeau, 2008; Pihlajamäki & Sperling, 2009; Sperling et al., 2003, 2010). PMC has also been implicated in visuospatial processing in AD using fMRI methods. One study showed higher activation in an AD group compared to healthy controls in these and other dorsal visual areas when successfully completing a location matching task (Bokde et al., 2010); other studies have shown varying levels of over- or under-active PMC areas during visuospatial tasks (Jacobs et al., 2012; Thiyagesh et al., 2009; Vannini et al., 2008)

1.5.2 Temporoparietal cortex: executive, attentional, working memory, lexical access and visuospatial deficits in AD

Temporoparietal cortex comprises multimodal association areas; inferior parietal regions are also involved in higher-order processes such as attention (Downar et al., 2000; Singh-Curry & Husain, 2009). When assessing anatomical correlations for working memory impairment in AD, Amici et al. (2007) found that one measure of working memory, backward digit span, was most associated with atrophy in dorsolateral frontal cortex and IPL. PET hypometabolism in left temporoparietal junction was associated with phonological working memory (digit span) whereas bilateral temporoparietal junction and left middle frontal gyrus was linked to performance on a visuospatial working memory task in AD patients (Desgranges et al., 1998). This suggests that temporoparietal regions may contribute to the disintegration of the 'central executive' in working memory; a proposal similar to that of Huntley & Howard's (2010) review. In one PET study, hypometabolism of temporoparietal cortex was related to performance in four out of five executive functioning tasks (Woo et al., 2010); however performance on these tasks was also correlated with mid-dorsolateral frontal cortex activity. One other structural study found correlations between bilateral temporoparietal and frontal atrophy and executive function when adjusting for memory performance (Nho et al., 2012).

PET and fMRI studies have also revealed a role of temporoparietal cortices in the breakdown of semantic processing in AD (Desgranges et al., 1998; Grossman et al., 2003). This may reflect greater involvement in lexical access (Gesierich et al., 2012), which is particularly pertinent to the clinicopathological syndrome of lvPPA, where greater involvement of temporoparietal lobes is paired with prominent word-finding difficulties. However, structural correlates have linked the more classically 'semantic' region of left anterior temporal lobe with picture naming performance in AD (Domoto-Reilly et al., 2012). IPL is also involved in aspects of

visuospatial processing in AD. DeIpolyi et al. (2007) found that atrophy in right hippocampal and inferior parietal cortex was correlated with performance in a spatial navigation task. Another fMRI study found that AD patients showed less activation than healthy controls in precuneus, IPL and middle occipital gyrus in response to increasing difficulty of an angle discrimination task (Vannini et al., 2008).

1.5.3 AD neuropsychological deficits and ASA

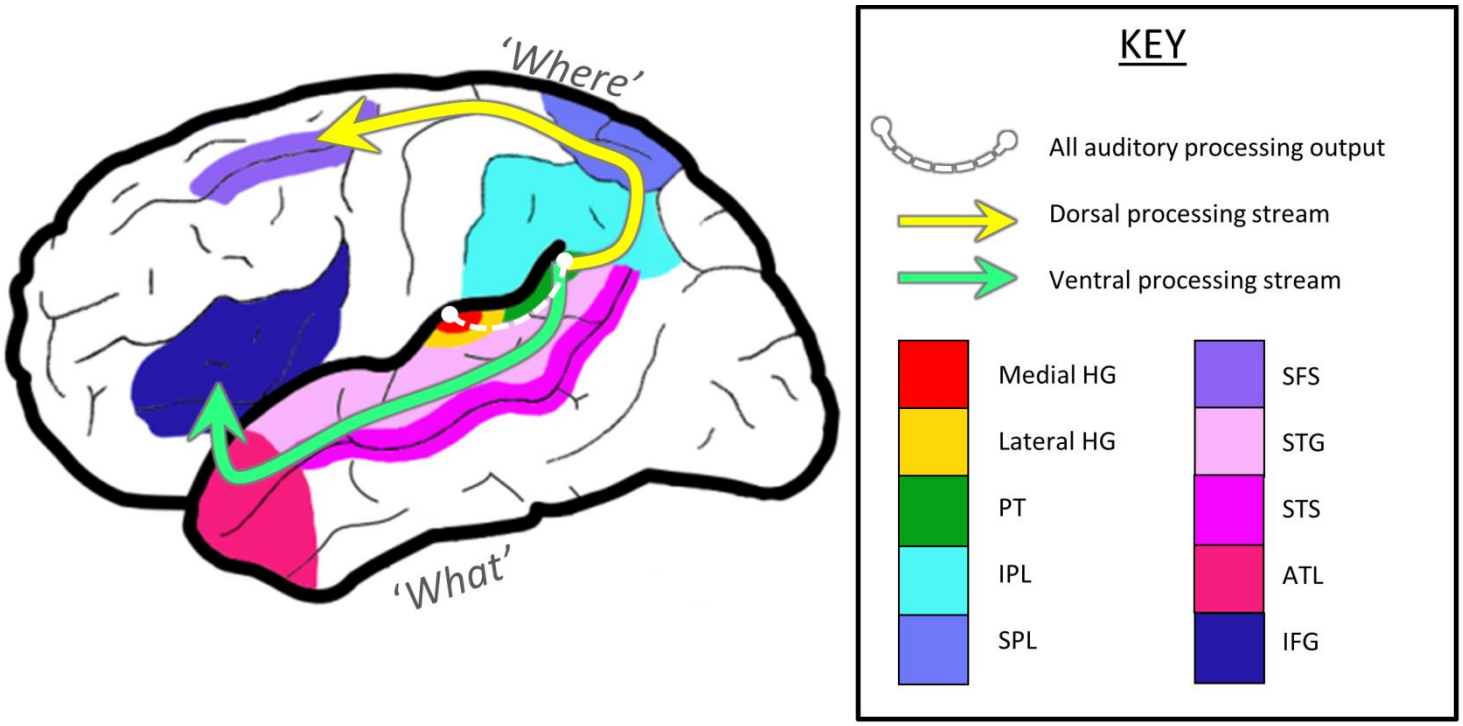
Reviewing the evidence surrounding posterior DMN regions and neuropsychological deficits in AD raises a number of issues related to ASA in AD. Firstly, when considering the design of tasks to assess ASA in AD, patients' memory deficits should be taken into account; performance may be confounded by working or episodic memory function. Phonological loop function is impaired in AD, which may also apply to the integration of any auditory components held online. Furthermore, cognition involving spatial elements may be particularly at risk in AD populations due to the atrophy in both temporoparietal and PMC regions; this may extend to auditory spatial processing. The studies reviewed in the previous two sections highlight the interesting relationship between brain function/metabolism and cognition in AD; this may have been overlooked in preference of structural associations with neuropsychological dysfunction. Additionally, compensatory activation may constitute a valid neurocognitive signature of disease and may generalise to a number of cognitive tasks, including those assessing ASA. Lastly, brain areas involved in the DMN share anatomy with a number of functions, reflected by the multi-domain cognitive decline in AD. Therefore functions that share anatomy with DMN regions are particularly vulnerable in AD. The following sections will first review the psychological mechanisms involved in ASA before examining evidence that brain areas implicated in DMN are crucial to ASA processing.

1.6 Central auditory processing: mechanisms and anatomy

1.6.1 Cortical auditory processing pathways

Neural coding of sound stimuli begins in the inner ear where the basilar membrane of the cochlea responds variably along its length according to frequency. Here the fundamental principle of auditory processing is apparent: tonotopic (a spatial map where location codes for frequency) organization of sound arises very early, a principle that is preserved through to the cortex (Kaas & Hackett, 2000). A medial area on the superior temporal plane comprises primary auditory cortex in humans, which forms part of Heschl's gyrus (HG). The auditory processing pathway then extends laterally on HG and into planum temporale (PT), an area posterior to HG on the superior temporal plane. As processing becomes more complex, the higher order processing of auditory signals is thought to obey the parallel processing concepts that have been well documented in the visual system (Milner & Goodale, 2008; Ungerleider & Mishkin, 1982). Dorsal and ventral auditory processing streams have been proposed to focus on 'what' and 'where' (Rauschecker & Tian, 2000), which has been validated to some extent in human studies (Adriani et al., 2003; Alain et al., 2001; Clarke et al., 2000, 2002; Hart et al., 2004). The dorsal stream extends from PT to inferior and superior parietal regions, then on to dorsal frontal areas. The ventral stream projects more anteriorly along the superior temporal gyrus (STG) and superior temporal sulcus (STS) to the inferior frontal gyrus (IFG). Whilst the 'what/where' dichotomy has been challenged by those proposing that the dorsal stream facilitates preparation for action in terms of speech processing (Hickok & Poeppel, 2007; Warren et al., 2005), the idea of parallel streams processing separable aspects of the auditory signal (for example binaural information signifying the location of a sound compared to the spectrotemporal modulation of speech) is widely accepted. A schematic representation of the auditory processing streams is shown in Figure 1.2.

Figure 1.2 – Schematic representation of auditory processing streams



Ventral (green arrow) and dorsal (yellow arrow) auditory streams are represented in this figure. Medial regions such as HG and PT are represented laterally for display purposes. ATL, anterior temporal lobe; HG, Heschl's gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobe; PT, planum temporale; SFS, superior frontal sulcus; SPL, superior parietal lobe; STG, superior temporal gyrus; STS, superior temporal sulcus.

1.6.2 Conceptualisations of ASA

In our everyday lives we are constantly performing highly complex neural computations. One auditory illustration of this was first described as ASA by Bregman (1990). This refers to our ability to segment and group the auditory scene into a coherent collection of 'auditory objects' (the binding of particular acoustic features that are grouped and differentiated from background – for further discussion see section 1.6.4) – one commonly cited example of this is the 'cocktail party effect' (Cherry, 1953). Whilst most often used to delineate the phenomenon of processing one conversation over a noisy background (as at a cocktail party), this ability applies to the both the segregation of any sound source from a competing source or sources, and the grouping of sound elements to the correct unifying sound source. A typical cocktail party commonly involves music playing, environmental sounds such as glasses clinking, and many different voices from different speakers emitting a variety of words. A number of frequencies will belong to the same source whilst frequencies from different sources will often overlap, yet we can ascribe the correct sound sources to this mixture relatively easily. Considering the frequency encoding properties of the auditory system, this is a remarkable achievement. As auditory signals are intrinsically events that unfold over time, we can also make use of temporal signals such as temporal coherence of frequencies from the same sound source, and the coordination of signals between the two ears. Bregman suggests that successful ASA results from a combination of processes: bottom up segregation/grouping of incoming sound signals, top down processing to match these incoming signals to previously learned information, or 'schemata' (also termed 'templates': Griffiths & Warren, 2002) and attention to determine salience of particular information.

A wide body of research has revealed various different ways we segregate or indeed group together different elements in the auditory scene. Whilst

grouping is an essential component of ASA (Darwin, 1997), here I will focus on the mechanisms underpinning auditory stream segregation. One commonly used method involves the manipulation of two repeated tones (Miller & Heise, 1950; Van Noorden, 1975) whereby a percept of one or two streams is elicited, depending on the rate of presentation, or the separation in frequency (Bregman, 1990; Carlyon, 2004). Two main theories surround the mechanisms behind streaming. The forward suppression theory suggests that neural response to one tone suppresses the response to the next tone, therefore the two tones are only perceived as separate streams when their responses no longer overlap (separated by either frequency or time interval: Fishman et al., 2001; Gutschalk et al., 2007; Micheyl et al., 2007). However this approach has tended to focus on streaming based on frequency separation. Another theory emphasises the importance of temporal coherence to bind together signals likely to arise from the same sound source (Elhilali et al., 2009a; Shamma et al., 2013; Teki et al., 2013). The temporal aspect of sound processing is highlighted in Micheyl et al.'s (2007) review, highlighting how streaming often relies on build-up over time.

1.6.3 The role of attention

Looking beyond low-level streaming mechanisms, some evidence suggests that wider brain regions are involved in ASA, and that top down influences such as attention and previous knowledge can modulate these bottom-up processes. Returning to the cocktail party analogy, a particular sound source (for example our own name) can capture our attention to enable its tracking against the acoustic background. In the streaming literature, stimuli presented at certain rates can elicit a bistable percept, whereby the perception of one or two streams can switch spontaneously or voluntarily. This suggests that higher order processes can influence simple streaming mechanisms. Shamma et al. (2013) point out that attention may be needed to bind together all the features that make up an auditory object. A number of studies support this notion. Some find

that build-up of streaming only occurs when attention is focused on the stimuli comprising the streaming percept (Carlyon et al., 2001a; Cusack et al., 2004), with similar results when sounds are presented to the contralesional ear in unilateral neglect patients (Carlyon et al., 2001). Directing attention to certain aspects of the auditory stream may also have downstream effects on bottom-up processing mechanisms, shown by altered magnetoencephalography (MEG) responses to a target even when attention was directed to the distractor 'background' (Elhilali et al., 2009b). When considering these processes in AD, patients' attentional deficits may affect their ability to bind elements, or attribute salience in auditory scenes. To counter the view that full attention is required for all streaming, some auditory objects do 'pop-out' without focused attention, for example the sound of our own name in the cocktail party effect (Moray, 1959). Other research has also shown that streaming is processed at a high enough level to interfere with performance on other attention-directed tasks (Jones et al., 1999; Macken et al., 2003) or to elicit an electrophysiological response associated with oddball detection (Sussman et al., 1999).

1.6.4 Schema based processing

Bridging the gap between higher order attentional processes and automatic stimulus-driven bottom-up processes is the use of prior knowledge. Bregman (1990) discusses this in terms of 'schema-based' processing, whilst Griffiths and Warren (2002) use 'template' processing. Both refer to the use of learned information about the properties of previously heard auditory objects to aid in the segregation of busy acoustic environments. The ability to recognise particular auditory signals converges with the issue of auditory object definition (Griffiths & Warren, 2004) – for example a familiar person's voice will activate many potential 'templates' (identification of voice sound, speaker and word) however an unfamiliar voice will still activate voice and word templates, demonstrating how the 'source' of the sound can be identified at

different levels. Furthermore, particular words can be identified regardless of delivery (shouting, speaking or whispering). As the authors discuss, identification of an auditory object is likely to be defined by perceptual grouping and categorisation as well as attention. Shamma (2001) suggests that our auditory system categorizes object 'boundaries' along the dimensions of frequency and time, which mirror the processing properties of auditory anatomy as early as the cochlear. The integration of signals along both of these dimensions is likely to bind features together to constitute an 'object'.

Griffiths and Warren (2002) cite the PT as a possible region for completing this template processing. One useful method to examine this is the use of overly learned templates, such as speech sounds or music, which commonly comprise the sound mixtures we encounter in everyday life. Billig et al. (2013) showed that lexical information of speech sounds can alter the streaming percept by using stimuli that would either form words or nonwords when streamed. Streaming occurred for items that produced words rather than nonwords. Turning to music, Bey & McAdams (2002) found that exposure to a short tone sequence aided subsequent discrimination judgements of the sequence presented with distractor tones. Dowling (1973) also showed that familiarity can aid melody detection, but only when the target, not the background, is familiar. Temporoparietal damage that subsumes PT may impair the ability to perform these functions in AD; ASA schema processing in particular applies to most functional daily activities and may contribute to the symptoms described in clinic.

1.6.5 Auditory spatial processing

One other cue we can use to segregate objects in the auditory scene is their location. Localisation of objects outside the field of vision also widens the area in which we can gain information about the world. We make use of binaural cues such as interaural time and intensity difference,

as well as monaural filtering from the pinna (Blauert, 1997; Butler, 1975; Gardner & Gardner, 1973; Heller & Richards, 2010). Griffiths and Warren (2002) argue that learned templates representing this information provide us with the neural tools we need to localise sounds. Whilst a potentially useful cue, a number of studies have shown that location has a minimal effect in streaming (Boehnke & Phillips, 2005; Stainsby et al., 2011). However, one study revealed that the effect of head movement acted to reset the streaming perception, and that it may be particularly useful for disambiguating sounds in front of or behind the head (Kondo et al., 2012). Bremen & Middlebrooks (2013) also showed that spatial cues may have more influence when frequency is low and the auditory system makes use of interaural time difference cues.

1.6.6 Specialized applications of auditory scene analysis

1.6.6.1 Speech

One of the most specialized functions of the auditory system is processing speech. While the vast literature on speech processing is beyond the scope of this thesis, certain aspects are pertinent to the general theme of ASA. Speech is rarely processed in quiet, and many central auditory function tasks focus on processing speech in competition with noise or additional speech (Cherry, 1953; Strouse et al., 1995). Adequate processing of speech in noisy situations is essential to human functional daily living, and is often cited as one of the most frustrating aspects of hearing loss (Shinn-Cunningham, 2009). In their review, Scott & McGettigan (2013) outline two ways noise can interfere with speech signals. Energetic masking refers to competition in the peripheral auditory pathway, where frequencies from different sound sources may overlap in the basilar membrane (broadband noise for example). Informational masking signifies interference resulting from competition in higher order processing areas, such as speech masked with speech. Processing speech in the presence of other speakers may stress the auditory, attentional and semantic systems (Nakai et al., 2005). Many of the general principles

behind ASA apply to hearing speech in noise: it forms one of its most relatable examples (cocktail party effect) and taps into the idea of overlapping frequencies as a computational problem. Temporal aspects of ASA have also been applied in 'glimpsing' – the theory that the amplitude modulations in speech allow us small 'glimpses' where the attended speech stream may be least affected by background noise (Cooke, 2006; Festen & Plomp, 1990; Vestergaard et al., 2011). It is also one of the most debilitating effects of central auditory dysfunction, which warrants further study on its influence on daily living function in AD.

1.6.6.2 Music

Another modality where ASA principles may be applied is music (Bregman, 1990). Just as vocal and environmental sounds in other situations, music constitutes an auditory scene in its own right. It is a highly complex auditory stimulus and often requires the coding of a number of separable components such as timbral, pitch and temporal (rhythm, metre) information. These combine over various time periods to form auditory 'objects' that may be classified according to any or all of these dimensions. Furthermore, most music hinges on 'key' or 'tonality' (the relationship between pitches Krumhansl, 2000; McDermott & Oxenham, 2008), adding further structure to these events that unfold over time; parallels with this and syntax in language are drawn by some researchers (Koelsch & Siebel, 2005; Koelsch et al., 2002). Music commonly makes use of presenting multiple musical objects concurrently and whether consciously or not, composers often take advantage of the human auditory system to produce their desired percept (Huron, 2001; Pressnitzer et al., 2011). We are directed to separate out musical 'streams' in polyphonic compositions – or indeed to combine them in homophonic music. Considering applications of general theories of ASA, the principle of frequency separation to cue the percept of one or more streams shares parallels with fundamental streaming experiments (Bregman & Campbell, 1971; Carlyon, 2004; Miller & Heise, 1950), whilst

temporal coherence theories (Elhilali et al., 2009a; Shamma et al., 2013; Teki et al., 2013) apply to auditory fusion (or lack thereof) in homophonic versus polyphonic textures. Whilst polyphonic music traditionally assigns a 'voice' to a single part, timbre has also been used to shape musical streams by switching instruments within a stream, also known as 'Klangfarbenmelodie', the closest translation being 'tone colour melodies' (e.g. Schoenberg, *Five pieces for orchestra,* Op. 16).

Musical listening often requires tracking of auditory information over long time periods, therefore placing high demands on ASA processes. Like any auditory scene, elements of the acoustic input are often separated into musical foreground and background. This can be influenced by attention and previous knowledge (for example familiar melodies: Bey & McAdams, 2002; Dowling, 1973; Dowling et al., 1987; Szalárdy et al., 2014). Auditory spatial processing has been utilised by composers (e.g. Stockhausen, *Kontakte,* 1958-60) and in modern popular music techniques such as panning (e.g. The Beatles, *Strawberry Fields Forever,* 1967). Thus, learned acoustic cues regarding spatial location, timbre, tonal structure and pitch/rhythmic pattern (melodies) can all be conceived as musical 'templates' or 'schema' to aid us in our navigation of the musical landscape. As a complex, rule-governed nonverbal stimulus, music provides a rich context in which to assess higher-order auditory processing, and represents a real-world application for assessing ASA processing in AD.

1.6.7 DMN regions involved in ASA processing

Whilst ASA is not likely to represent the primary function of the DMN (see section 1.4), there is a considerable overlap between some of its nodes and regions identified as crucial to human ASA processing. Streaming using cues such as pure tones is likely computed in primary auditory areas (Hill et al., 2011; Wilson et al., 2007). However, PT has been implicated in streaming based on interaural time differences (Schadwinkel & Gutschalk,

2010), spectrotemporal structure (timbre: Deike et al., 2004; 2010) and complex tones (Gutschalk et al., 2007). IPL regions have shown activation when segregation of acoustic cues relied on temporal coherence (Overath & Kumar, 2010; Teki et al., 2011); subjective perception of bistable streaming stimuli has also been shown to correlate with IPS or IPL activity (Cusack, 2005; Kondo & Kashino, 2009). Neuropsychological evidence has also implicated temporoparietal cortex in streaming (Carlyon et al., 2001b; Cusack et al., 2000). Thus, regions close to and including IPL exhibit functions that may represent the integration of bottom-up and top-down ASA elements. Additional support for this proposal arises from an fMRI study that utilised catch trials to assess neural preparation for attention to particular aspects of a complex auditory environment (Hill & Miller, 2010). Various parietal and superior temporal areas responded depending on whether subjects needed to attend to speaker location or frequency, indicating that attention may prepare certain higher-order auditory areas for more specialized processing of the auditory scene. A further study highlights the widespread neural populations involved in streaming perception: Dykstra et al. (2011) used electrophysiological measurements in pre-surgery epilepsy patients to reveal that STG, MTG, inferior and superior parietal cortex, and inferior and middle frontal gyrus all responded to changes in frequency separation in a streaming stimulus.

Turning to more specific applications of ASA, auditory spatial processing has been shown to elicit activity in PT (Alain et al., 2001; Altmann et al., 2007, 2008; Krumbholz et al., 2005; Warren & Griffiths, 2003), IPL (Alain et al., 2001; Brunetti et al., 2005, 2008; Bushara et al., 1999; James et al., 2008; Krumbholz et al., 2005; Maeder et al., 2001; Weeks et al., 1999; Zimmer et al., 2006; Zündorf et al., 2013), PMC (Alain et al., 2001; Bushara et al., 1999; Mayer et al., 2006, 2007; Shomstein & Yantis, 2006; Zündorf et al., 2013) and prefrontal cortex (Bushara et al., 1999; Maeder et al., 2001), in accordance with the dorsal auditory processing stream. In neuropsychological cohorts, Clarke's studies (2002, 2000) seem to support

this notion, and signify a clear anterior-what posterior-where dichotomy, however alternate findings suggest this distinction may not be so clear cut (Adriani et al., 2003; Zatorre et al., 2002a).

Speech processing may engage both auditory processing streams: identity of speech sounds pass through the ventral stream to access conceptual knowledge in more anterior temporal areas (Evans et al., 2013; Obleser et al., 2007; Scott & McGettigan, 2013a; Scott et al., 2000, 2004). However the assessment of energetic masking via speech in noise processing has elicited dorsal auditory regions such as IPL (Scott et al., 2004; Wong et al., 2008); PT (Nakai et al., 2005) and PMC (Wong et al., 2008) have also been implicated. This pathway has been suggested to govern the preparation for action when perceiving speech (Hickok & Poeppel, 2007; Warren et al., 2005). Focusing on music processing, posterior STS and PT have shown activation when processing the contour and interval of pitch patterns (melodies). Using a machine learning fMRI technique, Lee et al. (2011) found a network of regions including left STS, right IPL and anterior cingulate cortex involved in processing melodic contour. Processing of tonal relations has been linked to mPFC (Janata et al., 2002), however IFG has also been implicated in violating tonal context, albeit in stimuli involving harmonies (Brown & Martinez, 2007; Koelsch, 2006; Koelsch et al., 2003, 2005, 2006; Tillmann et al., 2003). Temporoparietal regions such as PT and IPL have been elicited in both active and passive paradigms of rhythmic processing (Chen et al., 2008; Konoike et al., 2012). Whilst motoric regions are implicated in fMRI studies of beat processing (Grahn & Rowe, 2009; 2013), neuropsychological impairments of beat processing have arisen as a result of temporoparietal lesions (Di Pietro et al., 2004; Robin et al., 1990; Wilson et al., 2002). The literature surrounding acquired amusia commonly implicates temporoparietal regions in many dimensions, including pitch patterns, rhythm, metre, timbre and tonality (Stewart et al., 2006), however their specific contributions to each modular aspect of music cognition is often difficult to ascertain.

The largest areas of anatomical overlap between functions involved in both ASA and DMN anatomy are in IPL and PMC; these likely serve to integrate a number of different sensory inputs. IPL has been implicated in the attribution and detection of salient events in the environment more generally (Cohen, 2009; Downar et al., 2000; Lee et al., 2014a). PMC is proposed to govern attentional monitoring and internally-directed functions (Leech & Sharp, 2014; Vogt & Laureys, 2005). These functions may be particularly suited to auditory inputs. Salience must be attributed to events that occur in the entire 360^{o} of space; possible only via the auditory system. Furthermore, sounds are commonly transitory and may require internal representations and internally directed assessment of sensory imagery. In order to test such ideas in their application to AD, links between any central auditory deficit and brain abnormalities should be sought. Before detailing the studies in this thesis that sought to fulfil some of these requirements, I will review the existing evidence surrounding central auditory processing in AD.

1.7 A review of auditory processing in AD

1.7.1 Peripheral hearing in AD

Before any claim can be made about central auditory deficits in AD, peripheral hearing ability must be taken into account. Uhlmann et al. (1989) found that peripheral hearing was significantly worse in AD compared to healthy controls (with a difference of 3dB). Gates et al. (2010) also found that peripheral hearing thresholds correlated with executive function in control and AD groups. A prospective cohort study found that incidence of AD (and all dementia) was higher among those who showed peripheral hearing impairment at baseline (Lin et al., 2011), which a further study indicated was related to atrophy in the right temporal lobe (Lin et al., 2014). However, other studies testing peripheral hearing alongside central auditory function have not found any differences between patients and controls (Gates et al., 2002; Goll et al.,

2012; Idrizbegovic et al., 2011; Rahman et al., 2011; Strouse et al., 1995). Gates et al. (2008) did find higher pure tone detection thresholds in patients compared to controls, but even when controlling for this, central auditory deficits remained.

1.7.2 Neuropsychological aspects of central auditory function in AD

Various tests of central auditory processing have revealed a deficit in AD. A summary of the behavioural findings from these studies can be found in Table 1.1. Impairments have been found in synthetic sentences with ipsilateral competing message identification (Gates et al., 1995; 2008; Strouse et al., 1995), duration pattern identification (Hellström & Almkvist, 1997; Strouse et al., 1995) and dichotic listening, involving either sentences or digits (Claus & Mohr, 1996; Duchek & Balota, 2005; Gates et al., 1995; 2008; Grady et al., 1989; Grimes et al., 1985; Idrizbegovic et al., 2011; Mohr et al., 1990; Strouse et al., 1995). Impairments in some of these domains have also been found pre-clinically (Gates et al., 1996, 2002, 2011; Idrizbegovic et al., 2013; Rahman et al., 2011). Some studies used large population cohorts to assess central auditory function in healthy participants and found that those who scored in the abnormal range were more likely to go on to develop AD, suggesting that central auditory dysfunction may be a 'harbinger' of AD (Gates et al., 2002; 2011). Pitch perception is often reported as preserved (Goll et al., 2012; Kurylo et al., 1993; Strouse et al., 1995) but other studies have documented impairment (Gates et al., 2011; Goll et al., 2011; Rahman et al., 2011). An inability to identify words at an acoustic level despite intact peripheral hearing has been shown (Caza & Belleville, 2008; Eustache et al., 1995; Rapcsak et al., 1989); however other studies have indicated preserved speech processing (Kurylo et al 1993; Idrizbegovic et al 2011). This difference in speech processing between such investigations may be due to a predominant acoustic deficit that can benefit from semantic processing in the latter two studies, whereas speech sounds devoid of semantic information such as nonwords and

phonemes, used in the former studies, cannot. A similar 'acoustic' deficit has been demonstrated using nonverbal sounds (Eustache et al., 1995; Jeon & Lee, 2009); one further study also suggests an auditory apperceptive deficit in AD, evidenced by an inability to identify degraded nonverbal sounds (Goll et al., 2011). Combined, these studies do illustrate a central rather than peripheral or entirely semantic basis for impairment. Only one study has investigated auditory spatial processing in AD, demonstrating impairment in localization of sound (Kurylo et al 1993). Other processing that may be linked to central auditory function is prosody perception, which Testa et al. (2001) showed was impaired for affective information in speech.

One of the most consistent deficits reported has been performance in dichotic listening. Previous studies have found this the central auditory task that most closely predicts onset of AD (Gates et al., 2008, 2010, 2011; Idrizbegovic et al., 2011). However, one issue with dichotic listening is the difficulty in unpicking the various bottom-up and top-down processes involved in successful performance. One interesting finding has been that of the right ear advantage (preferential processing of items presented to the right ear): often found in healthy participants but exaggerated in AD (Bouma & Gootjes, 2011; Duchek & Balota, 2005). These authors attributed the deficit to an inability to inhibit a prepotent response (i.e. words presented to the right ear are mostly subserved by the left hemisphere, which is language dominant). Considering the visuospatial and auditory spatial processing impairment in AD, this deficit may also be related to the allocation of spatial attention to a specific ear. Grady et al (1989), in their paper using dichotic listening in AD patients, concluded that divided attention was the primary function behind dichotic listening impairment, as other monaurally presented tasks were not as impaired in their study cohort. However, their monaural tasks involved degrading speech via presentation rate or low-pass filtering, rather than competing messages presented to the same ear such as used by later studies (Gates

et al., 1995, 2008; Strouse et al., 1995). The finding that competing information presented to the same ear is also impaired in AD suggests that a bottom-up parsing of auditory information may still be one culprit of failure in these tasks. Whilst many dichotic listening studies may be influenced by the linguistic properties of the stimuli, generic ASA processing is also deficient in AD. Goll et al. (2012) showed that AD patients were impaired on tasks assessing grouping and segregation based on pitch or timbre. In this study and in that of Gates et al. (2010), working memory and executive function were shown to play a part in performance on these tests, however central auditory processing did contribute to disease status over and above these functions.

Table 1.1 – Summary of behavioural studies investigating aspects of ASA in AD

Study	Relevant Participants	Central auditory component						Other impairments	Anatomical associations
		Pitch	Timbre	Pitch pattern	SSI-ICM	Dichotic tasks	Nonverbal sound ID		
Bouma & Gootjes 2011	AD; control	n/t	n/t	n/t		+	n/t	n/t	n/t
Caza & Belleville 2008	AD; control	n/t	n/t	n/t	n/t	n/t	n/t	Nonverbal STM	n/t
Claus & Mohr, 1996	AD; control	n/t	n/t	n/t	n/t	+	n/t	n/t	n/t
Duchek & Balota 2005	AD; control	n/t	n/t	n/t	n/t	+	n/t	n/t	n/t
Eustache et al. 1995	AD; control	n/t	n/t	n/t	n/t	n/t	+	n/t	n/t
Gates et al. 1995	AD; control	n/t	n/t	n/t	+	+	n/t	n/t	n/t
Gates et al. 1996	Prospective population*	n/t	n/t	n/t	+	n/t	n/t	n/t	n/t
Gates et al. 2002	Prospective population*	n/t	n/t	n/t	+	n/t	n/t	n/t	n/t
Gates et al. 2008	AD; MCI; control**	n/t	n/t	+	+	+	n/t	n/t	n/t
Gates et al. 2010	AD; MCI; control	n/t	n/t	n/t	+	+	n/t	Correlation with executive function	n/t
Gates et al. 2011	Prospective population*	n/t	n/t	n/t	+	+	n/t	n/t	n/t
Goll et al. 2011	AD; control	+	-	n/t	n/t	n/t	+	Apperceptive processing of degraded environmental sounds	n/t
Goll et al. 2012	AD; control	-	-	n/t	n/t	n/t	n/t	Generic ASA processes of grouping and segregation	left posterior STG, PCC
Grady et al. 1989	AD; control	n/t	n/t	n/t	n/t	+	n/t	Degraded speech	atrophy in bilateral ATL; metabolism in left STG
Grimes et al. 1985	AD; control	n/t	n/t	n/t	n/t	+	n/t	n/t	Temporal lobe

Hellstrom & Almkvist, 1997	AD; MCI; control**	n/t	n/t	n/t	n/t	n/t	n/t	Duration pattern	n/t
Hsieh et al. 2011	AD; control	n/t	n/t	n/t	n/t	n/t	+	n/t	Anterior PHG†
Hsieh et al. 2012	AD; control	n/t	n/t	n/t	n/t	n/t	n/t	Recognition of musical emotion	Posterior IFG; temporal pole†
Idrizbegovic et al. 2011	AD; MCI; control**	n/t	n/t	n/t	n/t	+	n/t	n/t	n/t
Idrizbegovic et al. 2013	AD; MCI; SMC	n/t	n/t	n/t	n/t	+	n/t	only AD showed impairment	n/t
Jeon & Lee 2009	AD; MCI; control**	n/t	n/t	n/t	n/t	n/t	+	n/t	n/t
Kurylo et al. 1993	AD; control	-	+	n/t	n/t	n/t	n/t	Sound localization	n/t
Mohr et al. 1990	AD; control	n/t	n/t	n/t	n/t	+	n/t	n/t	n/t
Rahman et al. 2011	MCI; control	n/t	n/t	+	n/t	+	+	n/t	n/t
Rapcsak et al. 1989	AD; control	n/t	n/t	n/t	n/t	n/t	+	n/t	n/t
Strouse et al. 1995	AD; control	-	n/t	n/t	+	+	n/t	Duration pattern	n/t
Testa et al. 2001	AD; control	n/t	n/t	n/t	n/t	n/t	n/t	Affective information from prosody	n/t
White & Murphy, 1998	AD; control	-	n/t	n/t	n/t	n/t	n/t	Nonverbal STM	n/t

+ (red boxes), significant impairment in group of interest (AD/MCI); - (green boxes), no significant impairment found; *significance for these studies indicates where poor performance on this task was predictive for dementia/AD incidence at follow-up; ** main impairments found could distinguish between AD, MCI and control; † conducted by combining AD with non-AD disease groups; AD, Alzheimer's disease; ASA, auditory scene analysis; ATL, anterior temporal lobe; ID, identification; IFG, inferior frontal gyrus; MCI, mild cognitive impairment; PCC, posterior cingulate cortex; PHG, parahippocampal gyrus; SMC, subjective memory complaints; n/t, not tested; SSI-ICM, synthetic sentence identification with ipsilateral competing message; STG, superior temporal gyrus; STM, short-term memory.

1.7.3 Music processing in AD

Music processing in AD has focused on either memory for melodies, or the advantageous effect of music on cognition or mood. Recognition of familiar tunes in AD has produced varying results (Baird & Samson, 2009; Bartlett et al., 1995; Cuddy & Duffin, 2005; Cuddy et al., 2012; Hsieh et al., 2011; Johnson et al., 2011; Vanstone & Cuddy, 2010; Vanstone et al., 2012), perhaps reflecting a partial loss of musical semantic information – for example AD patients score higher than semantic dementia patients yet lower than healthy controls in such tasks (Hsieh et al., 2011). An impairment in memory for novel tunes has also been shown (Bartlett et al., 1995; Halpern & O'Connor, 2000; Vanstone et al., 2012). As with verbal information, working memory for tunes is impaired compared to controls (Ménard & Belleville, 2009; White & Murphy, 1998). Despite this musical cognitive profile, music has been shown to aid functions such as verbal fluency, lyric retrieval, mood and involuntary autobiographical memories in AD (El Haj et al., 2012; Irish et al., 2006; Moussard et al., 2014; Simmons-Stern et al., 2010; Thompson et al., 2006), suggesting that patients can still access some of music's beneficial aspects. This has been found even when listening to unfamiliar music. A small number of case studies have reported preserved musical skills in the context of severe cognitive decline (Beatty et al., 1999; Cuddy & Duffin, 2005; Omar et al., 2010), however these are often conducted with highly skilled or professional musicians, therefore difficult to generalize to the wider population, especially in the context of potential musical training-induced neural plasticity (Baird & Samson, 2009).

Different musical components can be applied to aspects of auditory objects more generally; therefore assessing these components may go some way to revealing how AD patients process their auditory scene. For example, pitch discrimination may be preserved (Johnson et al., 2011; White & Murphy, 1998) (however see discussion in section 1.7.2) as well

as melody discrimination (Johnson et al., 2011). Intact emotional processing of music has been shown (Drapeau et al., 2009; Gagnon et al., 2009), however (Hsieh et al., 2012) demonstrated a deficit in matching emotional valence to musical excerpts. Timbre perception has again produced variable results. Kurylo et al. (1993) found impaired timbre discrimination, however Goll et al. (2011; 2012) found that patients performed similarly to controls on tasks requiring differentiation of timbre. This may in part stem from the multidimensional nature of timbre; variation along the axes of both spectral and temporal structure of sound elicits various timbral percepts. These different aspects of musical processing all combine to create auditory objects, such as instruments, or a particular melody, however it seems that these basic components may be preserved until relatively late in the disease process.

1.7.4 Neuroanatomical aspects of central auditory function in AD

Neuropathologically, HG shows neuronal alteration in AD patients (Baloyannis et al., 2011), which would suggest that there is a loss of the computational tools available to successfully process auditory inputs. However, few studies linking central auditory dysfunction to neuroanatomical abnormality in AD have been conducted. Hypometabolism in anterior and posterior temporal lobe has been linked to dichotic listening performance in AD patients (Grady et al., 1989; Grimes et al., 1985). With the enhanced spatial accuracy of more recent neuroimaging techniques, Goll et al. (2012) found that atrophy in posterior STG and PCC was correlated with performance in generic ASA functions of grouping and segregation. Auditory association areas and in particular temporoparietal regions along the dorsal auditory stream, along with PMC related to auditory spatial attention, are vulnerable to AD related dysfunction; further investigation into exactly which central auditory processes relate to the AD brain is warranted. Despite a lack of functional neuroimaging studies directly examining central auditory processing in AD, one study related to sentence encoding demonstrates

how the behaviour of early auditory areas influences performance in a higher-level task. Whilst in no way an ASA paradigm, Dhanjal et al. (2013) showed using fMRI that auditory cortex suppression at encoding was related to more successful retrieval of sentences, and that AD patients were less able to suppress auditory cortex activity. The authors suggested this could be due to a lack of memory or semantic systems exerting a sufficient influence over low-level auditory processing. Here, top down suppression was integral to performance, and may offer clues as to why AD patients find it difficult to process the auditory scene coherently: inability to suppress particular auditory stimulus-related activity may render patients less able to successfully segregate the scene into coherent auditory objects. This may also apply to the findings in dichotic listening studies. Two other studies assessing activation during phonological processing indicate that AD patients may recruit different areas of the brain for simple decision or repetition tasks in areas such as superior and inferior temporal gyrus (Peters et al., 2009) or IPL (Saykin et al., 1999). However, no fMRI/PET studies investigating neural activation in non-verbal aspects of central auditory processing have been conducted.

1.7.5 Electrophysiological studies of central auditory function in AD

Despite the lack of high spatial resolution functional imaging studies, methods with high temporal resolution have been used to reveal a number of auditory functional alterations in AD. EEG or MEG has been used to record auditory evoked potentials or auditory evoked fields, often in response to deviant tones in a single-tone stream. Some studies have shown that automatic stimulus change detection, as measured by the mismatch negativity (MMN/MMNm) is preserved in AD (Hsiao et al., 2014; Pekkonen & Jousmäki, 1994; Pekkonen et al., 2001). This occurs in both passive and active oddball paradigms, indicating that bottom-up processing of simple auditory stimuli is preserved. However, when the inter-stimulus interval is lengthened, patients show a delay in MMN compared to controls, indicating that auditory sensory memory may

decline with AD (Pekkonen & Jousmäki, 1994). One recent MEG study (Cheng et al., 2012) found higher MMNm amplitudes that may be linked to an earlier response (P50) and an inability to inhibit redundant auditory inputs.

Further work revealing a dysfunctional habituation of the P50 component in response to double click stimuli in AD (suppression of the P50 in response to the second click is seen in healthy controls) supports this idea (Cancelli et al., 2006; Jessen et al., 2001), and has also been found for oddball paradigms (Pekkonen et al., 1996). Thomas et al. (2010) found that reduced P50 suppression in ADs correlated with frontal neuropsychological functions, despite this component's purported involvement in primary auditory cortex and its adjacent association areas (Godey et al., 2001). Golob et al. (2007) suggest that the P50 also could be modulated by areas in frontal cortex or nucleus basalis of Meynert. This dysfunctional neural habituation to auditory stimuli may relate to a more general deficit of prepotent response inhibition and top-down influences on low-level processes, discussed in sections 1.6.3 and 1.7.2. One study implicates temporal and frontal regions later in the time course of auditory processing. Bender et al. (2014) found that a late frontal positivity paired with a temporal negativity 500ms after stimulus onset was reduced in AD compared to controls. These components did not correlate with sensory gating, but were associated with auditory working memory as measured by verbal digit span. Therefore responses for even very simple auditory tasks may be affected by widely distributed functions independently of sensory gating.

Some work has shown that auditory oddball paradigms elicit abnormal auditory evoked potentials in preclinical populations. These studies have shown various neural response component differences, including P50 (Golob et al., 2002, 2007; Irimajiri et al., 2005) and P300 (Golob et al., 2002; 2007) in MCI and N100, P200 and P300 in autosomal dominant

familial AD mutation (both PSEN1 and APP) carriers (Golob et al., 2009). Confirmation of altered auditory processing in subjects who are presymptomatic yet neuropathologically guaranteed to develop AD provides strong evidence that the pathophysiology of AD affects auditory-related cognition early in disease evolution. The P300 component is thought to reflect activity in association areas in temporal, parietal and frontal regions (Golob et al., 2007; Marsh et al., 1990). These studies exemplify potentially generic information processing deficits very early in the disease process in response to auditory stimuli.

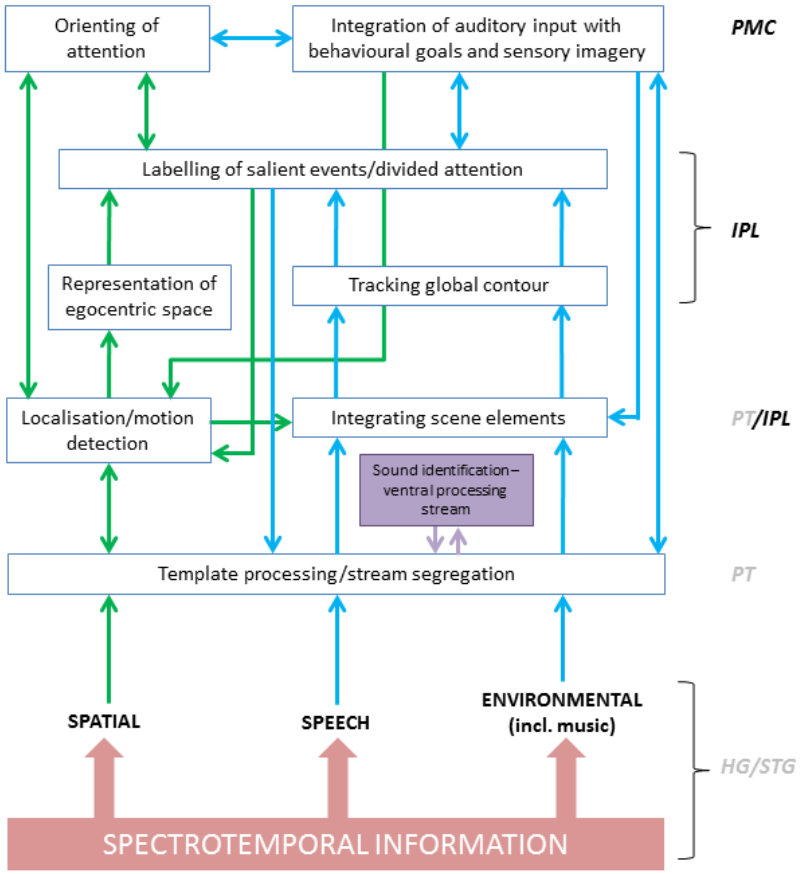
One further idea of interest is the finding that neural oscillations at certain rates may be dysfunctional in AD. An enhanced steady-state response (where oscillations around the 40Hz rate match the rate of a periodic stimulus) has been found in response to auditory stimuli in AD (van Deursen et al., 2011; Osipova et al., 2006), indicating reduced neural habituation. This warrants interest as 40Hz oscillations could relate to the temporal binding required for successful auditory processing (Joliot et al., 1994; however see Engel & Singer, 2001). Temporal structure may be particularly pertinent to auditory processing as the nature of auditory stimuli requires their evolution over time: its importance has been highlighted in ASA (for a review see Rimmele et al., 2014). The preceding statements must be qualified: patients are still able to form many cohesive sensory representations and indeed in many of the oddball paradigms their behavioural performance is at control levels. However, a reduction in oscillation suppression may hinder fully coherent perception, germane to an inability to suppress redundant information and therefore perform successful ASA.

1.8 DMN and ASA in AD

To summarise the previous sections, three main assertions are pertinent to hypotheses surrounding ASA processing in AD: 1) The neuroanatomical and neuropsychological picture of AD can in many cases result from DMN

abnormalities, with posterior hub regions serving numerous functions and linking heterogeneous AD phenotypes; 2) ASA processing involves regions such as lateral temporoparietal cortex and PMC in the healthy brain, which overlap with DMN hub regions; 3) central auditory processing is impaired in AD, in some cases preclinically. However, there is a disconnect between evidence surrounding central auditory deficits examined in the AD population and ASA processes that occur in everyday listening situations. Investigation of how DMN dysfunction may lead to impaired ASA processes in AD is also lacking. A schematic depiction of how this may occur is shown in Figure 1.3. This thesis will focus on three main aspects of ASA that relate to functionally relevant processes in everyday life: auditory spatial processing, speech in noise processing, and aspects of music processing.

Figure 1.3 – Schematic representation of neuroanatomical regions involved in both ASA and DMN



This figure represents the proposed ASA functions that may be impaired due to regional atrophy in AD. Three classes of auditory information are represented, in correspondence with the specific investigations of ASA conducted in this thesis. Green arrows signify spatial components; blue arrows are non-spatial. The purple box indicates ventral auditory processes; these are most likely subserved by anterior regions in the temporal lobe and consequently are not the focus of this model. The right hand column represents anatomical regions thought to subserve each process; regions in grey are hypothesised as less vulnerable to the pathological processes of AD compared to the regions labelled in black.

1.9 Thesis aims and outline

This thesis aims to provide a link between the symptoms that patients with AD report in clinic and the generic central auditory processing deficits described in previous studies. It also seeks to explore the relationship between the pattern of neural abnormalities (DMN) in AD and any behavioural deficits found. Therefore, 4 experimental studies were designed to assess neuropsychological and neuroanatomical dysfunction in applied areas of ASA in the AD spectrum. Three specific areas were focused on: auditory spatial processing, one conceptualisation of the cocktail party effect, and musical processing.

Chapter 3 utilises a novel neuropsychological battery via virtual space techniques to assess auditory spatial processing in typical AD and PCA. It also investigates any links between behavioural deficits and regional reduction in grey matter volume. This chapter aims to characterise any specific difficulties or differences both across and between the two phenotypes, and to examine how the DMN may link to any auditory spatial processing impairments.

Chapter 4 aims to extend the work in Chapter 3 by assessing the functional neuroanatomical profile of typical AD when processing spatial (compared to nonspatial) sounds and whether over- or under-activation of particular brain regions (with particular focus on DMN) contributes to any generalised auditory spatial processing deficit.

Chapter 5 also makes use of functional imaging to investigate any neural dissociations between typical AD and healthy control participants during the process of hearing one's own name over background noise – one of the most commonly applied ASA functions. Differences in activation of DMN regions in response to speech-in-noise stimuli will also be targeted here.

Chapter 6 applies ASA to music processing, utilising famous tunes as a tool to assess highly familiar nonverbal auditory template processing amongst distractor tunes. It also examines global and local processing of pitch and temporal components of music alongside tonal hierarchy processing, utilising a novel deviance detection paradigm. These assessments form a novel neuropsychological battery to investigate a number of dimensions that combine to form a musical 'scene', administered to typical AD and lvPPA patients as the primary groups of interest. The aims of this study are to better characterise music processing in the wider AD population, in order to reconcile contradictory accounts of generic ASA dysfunction yet preservation of musical aptitude in single cases.

2 METHODS OVERVIEW

This chapter will outline the general experimental methods used in this thesis. Where individual experiments deviate from the procedures and materials delineated here, a description will be provided in the specific chapter.

2.1 Participants

As all the studies in this thesis assessed different aspects of central auditory (ASA) function, participants were excluded from recruitment if they had a history of clinical hearing loss (defined as requiring a hearing aid, regardless of whether it was used). This was in order to reduce the effects of peripheral hearing ability. Potential participants with confounding longstanding neurological or psychiatric illness were also not recruited. Mini-mental state examination (MMSE: Folstein et al., 1975) scores were collected for all participants, and symptomatic treatment and disease duration information in all patient groups was noted either via information provided in clinic or at the time of testing via carer reports. Where possible, patients underwent a volumetric MRI brain scan and/or a lumbar puncture. Patients were not recruited If significant cerebrovascular disease was apparent from their MR image; however patients with vascular risk factors were included. A small subset of patients also participated in an 18F-amyloid (Florbetapir) PET imaging study which was used to support the diagnosis of AD in experimental participants, relevant to chapters 3 and 6. Patients were identified through a tertiary referral cognitive disorders clinic at the National Hospital for Neurology and Neurosurgery, with a small number of additional patients referred from a tertiary service in Barking and Havering, and a memory clinic in Camden and Islington. All participants gave informed consent in accordance with the Declaration of Helsinki.

Recruiting from tertiary specialist cognitive disorders clinics was accompanied by benefits and disadvantages: referrals of typical, late-onset, amnestic AD patients were relatively low; however the much higher proportion of younger onset and rare variants of dementia cases reduced the likelihood of comorbidities such as vascular disease or peripheral heating loss, and allowed inclusion of individuals representing a wider section of the AD spectrum. Where possible and depending on each individual's research burden at the time of testing, I was able to draw upon patients with diagnoses of typical AD, PCA, lvPPA as well as one cohort falling under the classification of frontotemporal dementia: nonfluent/agrammatic primary progressive aphasia (naPPA), which was used as a disease control group. Criteria for diagnosis are outlined briefly below.

2.1.1 Typical AD patients

Patients who fulfilled revised NINCDS-ADRDA criteria for typical AD (Dubois et al., 2014) were recruited into all experimental studies. Criteria consisted of predominant episodic memory loss and additional cognitive dysfunction, with imaging or cerebral fluid biomarkers suggestive and supportive of an AD syndrome. In chapters 4 and 5, these patients are abbreviated to 'AD'; however in chapters 3 and 6 they are denoted as 'tAD' (typical AD) to differentiate this group from any atypical phenotypic cohorts. An overview of overlap of individual participation for each study is documented in Appendix 1.

2.1.2 PCA patients

Patients fulfilling criteria for PCA with predominant visual perceptual deficits and relatively preserved episodic memory (Crutch et al., 2012, 2013a; Tang-Wai et al., 2004) were also recruited into the study described in chapter 3; none of this group experienced prominent hallucinations or signs of corticobasal syndrome. Further characterisation of

pathophysiological biomarkers indicative of AD in this patient group can be found in section 3.3.1.

2.1.3 lvPPA patients

Patients fulfilling consensus diagnostic criteria for lvPPA (Gorno-Tempini et al., 2011), exhibiting marked word-finding pauses and impaired sentence repetition with preserved single word repetition were recruited into the study described in chapter 6; further characterisation of this patient group can be found in section 6.3.1.

2.1.4 naPPA patients

This diagnosis is classified through agrammatism (both receptive and expressive), apraxia of speech alongside preservation of conceptual knowledge and single word comprehension (Gorno-Tempini et al., 2011). I included patients fulfilling these criteria in chapter 6 to compare with the profiles of typical and language variants of AD.

2.1.5 Healthy control participants

Healthy older control participants were recruited from a previously established participant database to match patient groups as far as possible in terms of age and gender in all studies.

2.2 Peripheral audiometry assessment

Peripheral hearing ability was assessed in each participant at the time of testing using pure tone audiometry, administered via headphones from a notebook computer in a quiet room. The procedure was adapted from a commercial screening audiometry software package (AUDIO CDTM®, http://www.digital-recordings.com/audiocd/audio.html). Five frequency levels (500, 1000, 2000, 3000, 4000 Hz) were assessed. At each frequency, participants were presented with a continuous tone that slowly and linearly increased in intensity. Participants were instructed to indicate as soon as they were sure they could detect the tone. This response time was measured and stored for offline analysis. Hearing was assessed in

either the right ear alone or both ears; specific details are documented in each experimental chapter.

2.3 Pitch discrimination musical screening task

All participants entered into the studies detailed in chapter 6 completed an elementary pitch discrimination task to assess their suitability for undertaking certain subsections of the musical tasks, as a number of these demanded a reasonably high level of pitch discrimination for successful completion the task. Low scores on this task would indicate a potential confounding factor in assessing task performance and was used as a rudimentary screen for amusia (e.g. Stewart, 2011). The screening task consisted of 20 note pairs, 10 same and 10 different. Notes were derived from a synthetic piano sound (Musescore®) and corresponded to pitch values in traditional Western music, with a duration of 1s and an inter-note gap of 1s. Different pairs were separated by a range of one to six semitones (mean = 2.7 semitones). Participants were instructed to indicate whether note pairs were 'same' or 'different' after each pair was played. Examples and practices were used to familiarise participants with the task requirements. Patients who scored under 80% correct in a screening task did not subsequently undertake the local-global pitch pattern task or the key deviant detection task (this affected 1 naPPA and 3 tAD participants). A score of 80% or greater was an entry criterion for the control group, therefore this experimental group completed all parts of the experimental battery (5 healthy control participants were screened and did not enter due to this criterion).

2.4 Musical background questionnaire

For the study in chapter 6, a musical background questionnaire was administered to all healthy control and patient participants; carers assisted where necessary. This was in order to ascertain an individual's level of formal musical training and current exposure to music, used in a previous study (Hailstone et al., 2009) and detailed in Appendix 2.

2.5 Neuropsychological assessment

All participants underwent a comprehensive neuropsychological battery to obtain a picture of general cognitive functioning whilst also highlighting particular areas of weakness. The battery incorporated tasks assessing general intellect using the Wechsler Abbreviated Scale of Intelligence (WASI: Wechsler, 1999), which incorporates both 'verbal' and 'performance' domains. Episodic memory was tested using long or short versions of the Recognition Memory Test (RMT: Warrington, 1984, 1996). Specific details of which participants completed a particular version of the RMT are documented in individual chapters. Verbal working memory capacity was assessed via forward digit span from the Wechsler Memory Scale-Revised (WMS-R: Wechsler, 1987); executive skills were captured using reverse digit span (also WMS-R) and a Stroop task from the Delis-Kaplan Executive System (D-KEFS: Delis et al., 2001). Verbal skills were specifically investigated using the Graded Naming Test (GNT: McKenna & Warrington, 1983), British Picture Vocabulary Scale (BPVS: Dunn et al., 1982) and the National Adult Reading Test (NART: Nelson, 1982). Posterior cortical skills were assessed using the Graded Difficulty Arithmetic Test (GDA: Jackson & Warrington, 1986) and the object decision subtest of the Visual Object and Spatial Perception battery (VOSP: Warrington & James, 1991).

For chapters 3 and 4, additional visuospatial processing tasks were administered: the dot counting subtest of the VOSP and a spatial span task from the Wechsler Memory Scale-III (WMS-III: Wechsler, 1997). For chapters 4 and 6, additional items were added to the general neuropsychological battery, providing extra information on episodic memory from the Camden Paired Associates Learning (PAL: Warrington, 1996), and more extensive tests of executive function: letter fluency, category fluency, trail-making A and B (Reitan, 1992) and the Wechsler Adult Intelligence Scale-Revised digit symbol task (WAIS-R: Wechsler,

1981). Chapter 6 also included in-house measures of graded difficulty word and sentence repetition to further characterise the language profile of lvPPA and naPPA patients. In chapter 3, the PCA group in particular struggled with some of the task materials due to their severe visual deficits, therefore did not complete all of the tasks; this is documented in more detail in the specific chapter.

2.6 Generation and presentation of auditory stimuli

Sounds were created in MATLAB v 7.0/2012a (The Mathworks, Inc.) for chapters 3, 4 and 5; Musescore© (www.musescore.org) was additionally utilised in the synthesis of stimuli for chapter 6. All experimental sound stimuli were stored as wavefiles at a 44100Hz sampling rate. Within any test, sounds were matched for mean intensity (root-mean-square) over trials and all sounds created in MATLAB were windowed with 20ms onset-offset temporal ramps to prevent click artefacts. All sound stimuli were presented binaurally via headphones through a notebook computer running the Cogent extension (http://www.vislab.ucl.ac.uk/cogent_2000.php) for MATLAB at a comfortable listening level (at least 70dB). Where sounds required presentation in an MRI scanner, they were delivered via electrodynamic headphones (http://www.mr-confon.de/) at a level fixed for all participants.

2.6.1 Spatial sound generation

To create a percept of sounds in space for use in chapters 3 and 4, head-related transfer functions (HRTFs: Wightman & Kistler, 1989a, 1989b) were convolved with iterated ripple noise (IRN). This was chosen as a broadband sound carrier able to maintain as uniform a sound across the various subtests and conditions as possible – for example using pitch judgements as control conditions is enabled through the use of this sound carrier (e.g. Warren & Griffiths, 2003). A percept of pitch is created by applying delay-and-add functions to Gaussian noise (Yost, 1996). All

sounds were synthesised with fixed passband 500-5000Hz, convolved with HRTFs and post-filtered (5000Hz low-pass) to remove high frequency artefacts created after convolution. Convolution with HRTFs simulates the pinna filter functions and in normal listeners generates a percept of a sound source associated with a particular position in external space; sequential dynamic updating of HRTFs across different spatial positions simulates the perceptual effect of a moving sound source (Warren et al., 2002). Five HRTF-specific versions of the externalised spatial stimulus set were created, allowing the corresponding generic HRTF to be matched with an individual participant's gender and height, which satisfied the requirements of the studies used in this thesis as sound position was only varied along the azimuth. Individual study information about numbers assigned to each HRTF are shown in Table 2.1.

Table 2.1 – Participant assignment to each generic HRTF

HRTF I.D.	Gender	Height	Total participants (chapter 3)	Total participants (chapter 4)
SJX	F	68.0"	9	3
SOU	F	65.0"	18	11
SOS	M	74.0"	29	15
SOW	M	75.0"	2	1

Height and gender data (Wightman and Kistler, 1989b) on individuals sampled to generate generic head-related transfer functions (HRTFs) used in the experiments addressed in this thesis; the number of participants for whom each HRTF was used is indicated.

2.7 Image acquisition

2.7.1 Structural MRI

If no contra-indications for MRI scanning were present, participants underwent volumetric brain MRI on a Siemens 3Tesla Trio scanner using a 32 channel phased array head coil (Siemens, Erlangen, Germany), applicable to chapters 3, 4 and 5. T1-weighted volumetric brain images were obtained using a sagittal 3-D magnetization prepared rapid gradient echo sequence (echo time/repetition time/inversion time = 2.9/2200/900ms, dimensions of 256 × 256 × 208, voxel size of 1.1 × 1.1 × 1.1 mm). These scans were undertaken for the purpose of either voxel-based morphometry (VBM) to assess the relationship between regional grey matter atrophy and specific task performance in the experimental patient groups, or to allow coregistration of structural and functional data.

2.7.2 Functional MRI

Brain images for functional data (chapters 4 and 5) were also acquired on a 3Tesla TIM Trio MRI scanner (Siemens Healthcare, Erlangen, Germany) using a 12-channel RF receive head coil. Two functional runs were presented in each experiment; single-shot gradient-echo planar image (EPI) volumes were acquired each with 48 oblique transverse slices

covering the whole brain (slice thickness 2mm, inter-slice gap 1mm and 3mm in-plane resolution, TR/TE 70/30ms, echo spacing 0.5ms, matrix size 64 x 64 pixels, FoV 192 x 192mm, phase encoding (PE) direction anterior-posterior). A slice tilt of -30^{o} (T>C), z-shim gradient moment of +0.6 mT/m*ms and positive PE gradient polarity were used to minimise susceptibility-related loss of signal and blood-oxygen-level-dependent (BOLD) functional sensitivity in the temporal lobes, following optimisation procedures described previously (Weiskopf et al., 2006). Sparse-sampling EPI acquisition (Hall et al., 1999) with repetition time 11.36s (corresponding to an inter-scan gap of 8s) was used to reduce any interaction between scanner acoustic noise and auditory stimulus presentations. The initial two brain volumes in each run were performed to allow equilibrium of longitudinal T1 magnetisation but discarded from further analysis.

The acquisition methods for a B0 field-map varied slightly between chapters 4 and 5, due the use of different scanners (the scanners were however the same model and scanner did not vary within a study). For chapter 4, a gradient echo field-map (TR = 688ms; TE1 = 4.92ms, TE2 = 7.38ms, 3x3x3mm resolution, no interslice gap; matrix size = 80 x 80 pixels; FoV = 192 x 192mm; phase encoding direction = A-P) was utilised. For chapter 5, the field-map was acquired using a gradient double-echo FLASH sequence (TE1 = 10ms, TE2 = 12.46ms, 3x3x2mm resolution, 1mm gap; matrix size = 64 x 64 pixels; FoV = 192 x 192mm, phase encoding direction = A-P). These field-maps were obtained to allow post-processing geometric distortion corrections of EPI data due to B0 field inhomogeneities.

2.8 Image preprocessing

All brain imaging data were preprocessed using statistical parametric mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm) running under MATLAB 2012a (The Mathworks, Inc.).

2.8.1 Structural MRI

Pre-processing of patient brain MRIs for VBM analysis utilised the New Segment and the DARTEL toolboxes (Ashburner, 2007; Ridgway et al., 2008). Normalisation, segmentation and modulation of grey and white matter images were performed using default parameter settings, with a smoothing Gaussian full-width-half-maximum of 6mm. In order to adjust for individual differences in head size during subsequent analysis, total intracranial volume (TIV) was calculated for each participant by summing grey matter, white matter and CSF volumes following segmentation of all three tissue classes.

2.8.2 Functional MRI

In initial image pre-processing, the EPI functional series for each participant was realigned using the first image as a reference, and images were unwarped incorporating field-map distortion information (Hutton et al., 2002). The DARTEL toolbox (Ashburner, 2007) was used to spatially normalise all individual functional images to a group mean template image in Montreal Neurological Institute (MNI) standard stereotactic space; to construct this group brain template, each individual's T1 weighted MR image was first coregistered to their EPI series and segmented using DARTEL tools (New Segment); this segment was then used to estimate a group template that was aligned to MNI space. Each participant's functional images were normalised to MNI space using the DARTEL group template and smoothed using a 6mm full-width-at-half-maximum Gaussian smoothing kernel.

2.8.3 Study specific mean image

For the purpose of rendering statistical parametric functional maps, study-specific mean structural brain image templates were created by warping all bias-corrected native space whole-brain images to the final DARTEL template and calculating the average of the warped brain images.

2.8.4 Small volume generation

This thesis centres on hypotheses about the convergence of DMN and ASA brain regions in AD, therefore each neuroimaging study made use of small volume correction in testing of study-specific hypotheses relating to both functional and structural imaging. These volumes were derived from Oxford-Harvard cortical (Desikan et al., 2006) and Jülich histological (Eickhoff et al., 2005) maps via FSLview (Jenkinson et al., 2012). Some of these regions encompassed areas much larger than the specified region (for example posterior STG extended anteriorly to and past HG); therefore were edited in MRICron® (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Some regions, such as PMC, were not delineated in either of the prespecified maps, therefore were created first-hand in MRICron® (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Further details of small volumes are described in the corresponding chapters.

2.9 Statistical analysis

Statistical analyses were performed via STATA v12 (Stata Corporation, College Station, TX, USA), whilst brain imaging analysis was conducted using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) in MATLAB v2012a (The Mathworks, Inc.).

2.9.1 Demographic, neuropsychological and peripheral audiometry analysis

Demographic data such as age and years of education were compared using non-parametric Wilcoxon rank sum tests, or Kruskal-Wallis analysis of variance if more than two experimental groups; gender distribution between groups was compared a using χ^2 or Fisher's exact test. Group scores on individual subtests of the general neuropsychological battery were compared using non-parametric methods (Kruskal-Wallis/Wilcoxon rank-sum test) due to skewed data arising from ceiling (in the control group) or floor (in a patient group) effects. Tone detection thresholds on audiometry screening and performance on post-scan behavioural tasks on

experimental stimuli were analysed using linear regression models with clustered, robust standard error due to unequal variance. In the audiometry analysis, the main effect of patient group was assessed whilst controlling for age and frequency type, as well as assessing for any interaction between group and frequency. Specific interactions and between group differences were tested via the Wald post-estimation test of coefficients if necessary (e.g. if more than one condition or more than two experimental groups).

2.9.2 Behavioural analysis

Various regression methods were used for behavioural analysis and varied with the nature of the data for specific experimental tasks. Regression models allow correction for unequal variance by using a robust standard error and adjusting for clusters; bootstrapping ameliorates some of the effects of skewness. Importantly, these models also allow controlling for potential confounding factors. To use an example, working memory is often poorer in patient groups compared to healthy age matched controls. It is possible to control for this by adding a working memory task score as a covariate into the regression model. This can apply to any variable, such as specific test performance, peripheral hearing ability or demographic data. Wald tests were also used here to investigate specific hypotheses, or to deconstruct post-hoc any interactions of interest. All statistical tests for behavioural tasks conducted in this thesis were thresholded at $p < 0.05$ significance level.

2.9.3 Brain imaging analysis

Both structural and functional imaging analysis in SPM is based on a General Linear model, where either voxel intensity or activity can potentially be explained by a certain variable, or variables and a certain amount of error, or noise. This is expressed in the following equation: $Y = \beta * x + \varepsilon$, where Y represents a matrix of observed data (voxel intensity/BOLD signal), β the parameters to be estimated at the least

amount of error, x a design matrix and Ɛ the error signifying the difference between the observed data and that predicted by the model.

2.9.3.1 VBM

In this thesis, VBM analysis was used for two purposes: 1) to examine associations between specific experimental task performance and regional grey matter atrophy in patient groups; 2) to provide a map signifying areas of highest atrophy in patient groups compared to healthy age-matched controls. For task-atrophy association analysis, individual voxel intensity (grey matter volume) was modelled as a function of experimental test score in a linear regression model. For patient-control comparisons of grey matter, groups were compared using voxel-wise two-sample one-tailed t-tests. For all VBM models, nuisance covariates of age, gender and TIV were included – specific chapters detail any additional covariates used for a particular study. To help protect against voxel drop-out due to marked local regional atrophy, I applied a customised explicit brain mask based on a specified 'consensus' voxel threshold intensity criterion (Ridgway et al., 2009) whereby a voxel was included in the analysis if grey matter intensity at that voxel was > 0.1 in > 70% of participants (rather than in all participants, as with the default SPM8 mask).

2.9.3.2 Functional imaging

Pre-processed functional images were entered into a first-level design matrix incorporating the experimental conditions modelled as separate regressors convolved with the standard haemodynamic response function, and also including 6 head movement regressors generated from the realignment process, for each of the two functional runs. For each participant, first-level t-test contrast images were generated for the main effects and interactions of interest (study specific contrasts are documented in the corresponding chapters). Contrast images for each participant were entered into a second-level random-effects analysis in

which effects within each experimental group and between the healthy control and AD groups were assessed using voxel-wise t-test contrasts. Both 'forward' and 'reverse' contrasts were assessed in each case.

2.9.3.3 Correction for multiple comparisons

Conducting a large number of voxel-wise t-tests in SPM creates a risk of Type I error. Therefore family-wise error (FWE) correction was utilised to account for these multiple comparisons, either across the whole brain or within study-specific predefined small volumes.

3 AUDITORY SPATIAL PROCESSING IN AD: A NEUROPSYCHOLOGICAL AND STRUCTURAL NEUROANATOMICAL INVESTIGATION

3.1 Introduction

The ability to localize sounds in space enables detection of events outside the range of the current visual field, or in situations where vision is reduced such as in dark conditions. From an evolutionary perspective, knowing where a sound is coming from allows us to then direct greater attention to a potential threat. As discussed in section 1.6.5, successful auditory spatial processing involves integration of sound signals between the two ears and computation of filters from the outer ears (pinna), which are likely to be fed into the dorsal auditory stream for higher-order processing of auditory spatial information (see section 1.6.7). Given the temporoparietal abnormality and central auditory dysfunction in AD (see sections 1.3 and 1.7), auditory spatial processing may be particularly vulnerable in this disease population. Kurylo et al (1993) found an auditory spatial localization deficit in AD patients, yet further investigations into this impairment are sparse. Furthermore, certain aspects of auditory spatial processing may dissociate (Blauert, 1997; Middlebrooks & Green, 1991), which may also be the case for AD. For example, Ducommun et al. (2004) documented a right temporal lobe resection case with a selective deficit for auditory motion. This has been corroborated in studies using healthy individuals (Ducommun et al., 2002; Getzmann & Lewald, 2012; Krumbholz et al., 2005; Richter et al., 2013); preference for sound motion in the IPL was demonstrated in an fMRI study (Krumbholz et al., 2005).

Some authors have suggested that spatial processing is a multimodal function, and that certain regions in the parietal lobe subserve multimodal spatial representations (Bremmer et al., 2001; Cohen, 2009;

Lewald et al., 2002; Salo et al., 2013). This is of interest for two reasons. Firstly, typical AD (tAD) is associated with visuospatial impairment (see section 1.5) therefore neuroanatomical associations between both visual and auditory spatial performance may be able to enhance our understanding of multimodal spatial processing. Secondly, the posterior variant of AD (PCA), which affects visuospatial processing to a higher degree, may show a greater level of impairment compared to tAD if the two modalities are governed by the same region (however it may also be the case that atrophy spreads to auditory regions). Assessing auditory spatial processing may further clarify the commonalities or divergence between these two phenotypic variants. One further region of interest is the PMC; a region implicated in both the orienting of auditory spatial attention and as the cortical 'hub' of the DMN (see sections 1.3 and 1.6.7). This region has been implicated in generic ASA processing in tAD (Goll et al., 2012).

This study sought to assess a number of different auditory spatial components in both tAD and PCA. Utilising virtual space techniques, sounds with the percept of fixed or moving locations around the head were created to comprise an auditory spatial battery, along with non-spatial auditory control and visual spatial tasks. Performance on these tasks in both patient groups were compared to that of a healthy older control group and neuroanatomical associations of auditory spatial deficits were performed using VBM of patients' brain MRIs.

3.2 Hypotheses

Three main hypotheses arise in relation to this investigation. 1) tAD patients will be impaired at auditory spatial tasks compared to controls. 2) PCA patients will show greater impairment in auditory spatial tasks compared to tAD patients, due to a greater degree of parietal atrophy. 3) Auditory spatial impairment in these disease groups will associate with

regional grey matter atrophy in lateral temporoparietal cortex or PMC; regions that have been previously implicated in auditory spatial analysis.

3.3 Methods

3.3.1 Participants

Twenty consecutive patients (7 female) formed a tAD group and 12 patients (7 female) a PCA group, alongside 26 healthy age matched individuals (13 female). . Brain MRI scans acquired (using the method described in section 2.7.1) for 17 patients in the tAD group and all patients in the PCA group were reviewed by an experienced neurologist. In the tAD group, 12 patients showed a profile of disproportionate hippocampal volume loss with additional more widespread cortical atrophy and 5 patients showed diffuse cerebral atrophy; while in the PCA group, 7 patients showed atrophy focussed in posterior cortical areas with symmetrical involvement of the cerebral hemispheres and relative sparing of the hippocampi, 4 patients showed both posterior cortical and hippocampal atrophy and 1 patient showed mild generalised atrophy. No brain MR images showed a significant cerebrovascular burden. These images were also utilised in VBM analysis. Where available, lumbar punctures and 18F-amyloid (Florbetapir) PET imaging in 11 patients with tAD and 6 patients with PCA showed a total CSF tau: beta-amyloid$_{1-42}$ ratio >1 or positive amyloid on visual rating of brain scans, compatible with underlying AD pathology in all cases. At the time of testing, in the tAD group 17 patients were receiving symptomatic treatment with donepezil and 1 memantine; in the PCA group, 10 patients were receiving donepezil and 2 memantine. All participants were administered a peripheral audiometry assessment in both ears. Demographic and clinical details of the experimental groups are summarised in Table 3.1.

Table 3.1 – General demographic, clinical and neuropsychological data for participant groups

Characteristic	Healthy controls[a]	tAD	PCA
General			
No. (m:f)	26 (13:13)	20 (13:7)	12 (5:7)
Age (yrs)	66.7(7.2)	66.0(6.0)	60.5(5.4)**
Education (yrs)	16.6(1.9)	14.3(2.8)*	14.5(1.7)*
MMSE (/30)	29.5(1.0)	20.8(4.5)*	20.2(5.0)*
Symptom duration (yrs)	n/a	6.0(2.7)	6.1(3.2)
Symptomatic treatment (no.)	n/a	18	12
Neuropsychological assessment			
Episodic memory			
RMT Faces[†] (Z-score)	0.24(1.47)	**-2.05(1.72)***	-1.75(2.4)*
RMT Words[†] (Z-score)	0.89(0.52)	**-2.43(1.07)***	-1.78(2.19)*
Executive skills			
WASI Matrices (/32)[b]	24.4(3.7)	12.1(8.1)*	**4.6(5.0)****
WASI Block design (/71)	45.6(18.0)	13.5(12.4)*	**-**
WMS-R digit span forward (/12)[c]	9.2(1.6)	6.8(2.0)*	6.3(2.1)*
WMS-R digit span reverse (/12)[c]	6.9(2.0)	5.3(2.6)*	3.3(2.4)**
WMS-III spatial span forward (/16)[c]	7.3(2.1)	5.4(2.2)*	-
WMS-III spatial span reverse (/16)[c]	7.0(1.7)	4.0(2.2)*	-
Verbal skills			
WASI Vocabulary (/80)	70.0(5.6)	51.3(14.7)*	57.0(9.0)*
WASI similarities (/48)	43.0(8.0)	28.2(8.8)*	-
GNT[††] (/30)	26.5(2.9)	15.4(8.4)*	14.9(6.5)*
BPVS (/150)	152.5(22.6)	132.9(22.9)*	-
NART (/50)[d]	44.0(3.8)	32.6(11.4)*	-
Schonell (/100)[e]	-	-	90.9(5.8)*
Posterior cortical skills			
GDA (/24)[f]	14.4(5.1)	6.3(5.1)*	**2.0(3.0)****
VOSP Object Decision (/20)[g]	18.0(2.2)	14.7(2.4)*	**9.5(4.8)****
VOSP Dot Counting (/10)[c]	9.9(0.3)	8.6(2.6)*	**3.6(4.3)****

Mean (standard deviation in parentheses) performance scores are shown unless otherwise indicated. Maximum scores on neuropsychological tests are shown in parentheses. Results in bold indicate mean score < 5th percentile; *significantly different from control group; **significantly different from control and other patient group ($p < 0.05$). †PCA patients completed short RMT (25 items), tAD patients completed long RMT (50 items), groups therefore not compared on this test; ††PCA patients completed GNT to verbal definition; - not administered. Due to time constraints, subsets of participants completed particular tasks as follows: **a** data for 20 healthy controls unless otherwise stated; **b** 10 PCA patients; **c** 26 healthy controls; **d** 19 tAD patients; **e** 9 PCA patients; **f** 18 tAD disease patients, 11 PCA patients; **g** 11 PCA patients.

3.3.2 Background neuropsychometry

A general neuropsychological assessment was performed for all patients and a subset of controls (see Table 3.1). Due to the PCA group's visual impairment, not all tasks were appropriate to administer and were therefore not undertaken. All controls were assessed on a subset of these tasks where performance on each test may relate to performance on the experimental tasks: forward and backward digit span as an index of nonspatial auditory working memory; forward and backward spatial span to examine visual spatial working memory; dot counting as a test of visuospatial function.

3.3.3 General structure of experimental battery

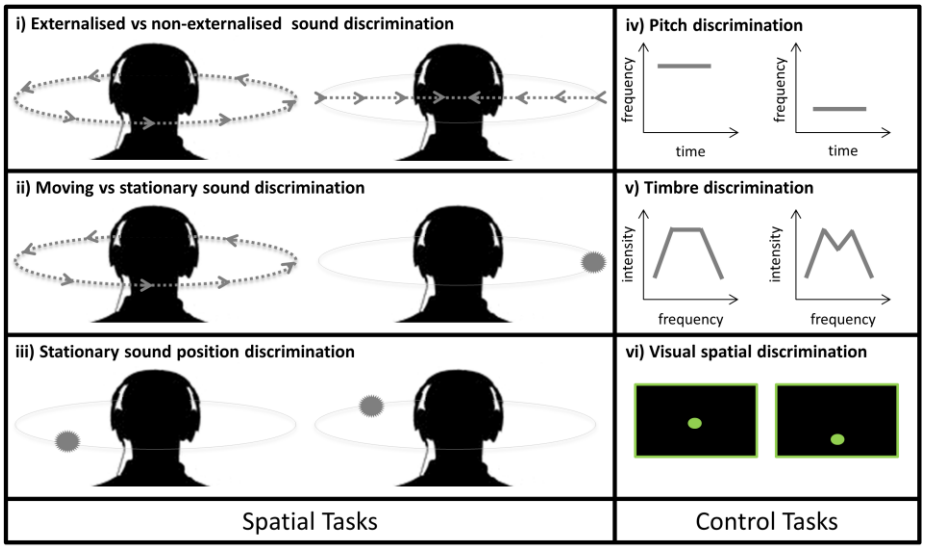
A schematic diagram of all experimental tasks can be found in Figure 3.1. Spatial sounds were synthesised using the methods described in section 2.6.1. Three tests were devised to access different dimensions of auditory spatial analysis:

1) Externalised versus non-externalised sounds – the discrimination of sounds with a percept of rotating around the head in external space as opposed to sounds with a percept of swaying between the ears. The key factor assessed was perception of cues relevant to any external location of sound.
2) Moving versus stationary sounds – the discrimination between sounds located in a fixed position outside the head and externalised, rotating sounds. This assessed perception of sound motion cues.
3) Stationary sound position – the discrimination of sounds located in different stationary positions outside the head.

In order to minimise extraneous cognitive demands from cross-modal labelling and executive processes that are potentially vulnerable in AD (Stopford et al., 2012) all experimental tests were based on a two-alternative-forced-choice response procedure requiring the participant to

make ‘same/different?’ judgements on pairs of serially presented sounds. Within each test, half the pairs were identical, and half different. Sound durations were fixed within an experimental test and the sounds in each pair were separated by a 1s silent gap. Two sound levels were used over trials but were matched within pairs. Where feasible, the key experimental perceptual parameter in a test was manipulated to create different parameter ‘difficulty’ levels, to allow assessment of a wider range of auditory spatial competence in patients and healthy individuals. Auditory control tasks based on timbre and pitch discrimination with other parameters matched to the spatial tests were designed to index spectrotemporal processing and nonverbal auditory working memory, respectively. Finally, in order to compare auditory and visual spatial processing in the tAD group, participants were assessed on tests of visual spatial processing and visual motion perception. Due to the severity of the PCA patients’ visuospatial abilities, only the visual motion task was administered to this group.

Figure 3.1 – Schematic representation of experimental battery



In auditory spatial tests, perceived stimulus locations externalised in the azimuthal plane are shown; arrowed lines represent perceived trajectories of sound motion and filled circles represent perceived locations of stationary sounds. Each sound pair here represents a 'different' trial.

3.3.4 Externalised versus non-externalised sound discrimination

Here we presented sound pairs that were matched for dynamic properties; the only parameter that was manipulated was the externalizing effect of the HRTFs, giving rise to sounds perceived as externalised or non-externalised by simulating the filter effects of the pinna. Externalised sounds normally perceived as rotating smoothly around the head were generated by updating and interpolating HRTFs over discrete positions around the azimuth (adapted from a previously described method: Warren et al., 2002). These stimuli were arranged to begin at either 90 or -90 degrees positions around the head (to match the percept of non-externalised stimuli beginning at either the right or left ear), with equal number of trials for each start position, presented in a pseudorandomised order (all participants were presented with the same pre-randomised order). Externalised sounds were presented with angular velocity 3.93 rad/sec, corresponding to 3 complete 'revolutions' per stimulus. Non-externalised sounds were created using a composite HRTF (an average of the HRTFs of each ear) to retain the same spectrotemporal

complexity of the externalised sounds, without the spatial cues. These sounds were instead subjected to amplitude modulation, giving rise to an amplitude, rather than frequency based binaural beat and the perception of sounds 'swaying' between each ear (Joris et al., 2006), with speed equivalent to the angular velocity of the externalised sounds. All sounds were 3.2s in duration and matched for start and finish position, both within and between each sound pair. 20 pairs were presented for this task.

3.3.5 Moving versus stationary sound discrimination

Both sound conditions in this task were convolved with HRTFs: either to create a percept of sounds rotating externally (using the same method as described for the externalised sounds in section 3.3.4) or in a fixed location around the head. Moving sounds were presented at 3 angular velocities (fixed within a trial): 3.93, 1.97 or 0.33 rad/s. Sounds started and finished at the same location, except when presented at 0.33 rad/s, when velocity was too slow to complete a revolution within the stimulus presentation time. Start positions were varied between 45 degree intervals around the azimuthal plane (i.e. 0, 45, 90 degrees etc.; 0 degrees elevation). Stationary sounds were amplitude modulated synchronously in both ears to match overall spectrotemporal variation to the moving sounds, therefore presented at three modulation rates. This form of modulation creates a percept of a vibrato source located in a fixed position in a particular azimuthal location. All sounds were 3.2s in duration and matched within pairs for start position and modulation rate. Each modulation rate contained 20 items.

3.3.6 Stationary sound position discrimination

Pairs of sounds normally perceived as stationary in external space were created by convolving with HRTFs corresponding to pairs of positions covering the azimuth (0 degrees elevation). To create 'different' trials, sounds in a given pair were separated by 30, 45 or 60 degrees, to allow

any perceptual step effects to be assessed; the spatial step from the first to the second sound in each pair was randomised as directionally clockwise or anticlockwise, but never crossed the hemispheric midline (i.e., spatial lateralisation alone could not be used as a discrimination cue). All sounds were 1s in duration, with each perceptual step consisting of 20 items.

3.3.7 Auditory control tasks

The IRN carrier was manipulated in two ways to create nonspatial sounds contributing to two separate auditory control tasks. Spectrotemporal structure was manipulated to create a percept of different timbres. Certain frequencies along the sound bandwidth were attenuated to varying degrees in order to produce four separate spectral envelopes, or timbres (see Goll et al., 2010). Two levels of frequency attenuation were applied, corresponding to two levels of task difficulty (20 items for each level with a total of 40 items). A second control task, primarily devised in order to test nonverbal auditory working memory, varied the pitch of the IRN carrier. Pitch values were based on a 12-step division of frequencies between 100 and 200Hz. Frequency differences were intended to correspond to intervals not normally heard in Western music; frequency values were separated by an equal number of Hz, therefore sound pairs higher in frequency were more difficult to discriminate. This pitch task consisted of 20 items. All auditory control stimuli were 1s in duration.

3.3.8 Visual spatial control tasks

A visual spatial position discrimination task was devised to match the auditory spatial position discrimination parameters as closely as possible. This required participants to discriminate the spatial position of pairs of green circles (20mm diameter) presented sequentially on a black background within a 240x120mm green outlined rectangle. The circles were presented at 1s duration each, with positions either 0, 90 180 or 270 degrees radially from the centre. Circle pairs were presented randomly at

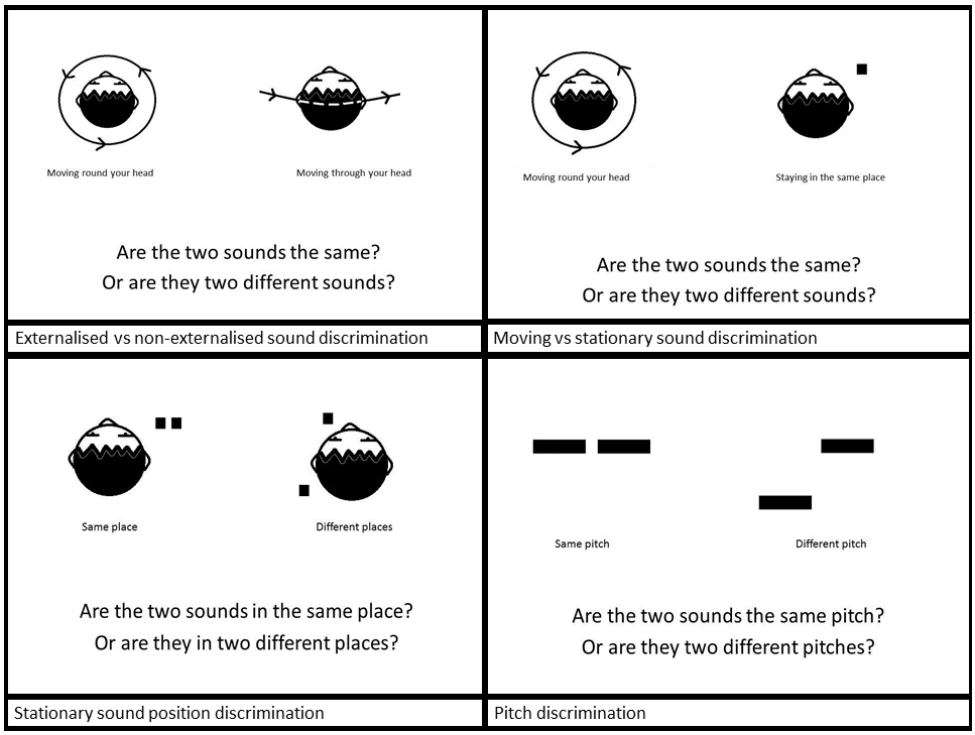
any of these positions either twice ('same' trials), or a combination of central plus one other position for 'different' trials; on 'different' trials, circles were separated by 5, 10 or 30mm; 20 pairs of each of these perceptual steps were included in this task.

A test of visual motion coherence (aiming to index visual rather than auditory motion detection) was adapted from Braddick et al. (2000). Participants were presented with an array of randomly moving white dots on a black computer monitor screen; a total of 80 trials were presented and on half the trials, the motion of dots was random while on the remaining trials the proportion of dots moving coherently was varied as 90, 70, 50 or 30%. Trials were presented in 20-item blocks according to perceptual step (% coherent). The task on each trial was to decide whether coherent motion was present ('yes' or 'no').

3.3.9 Procedure

For all tasks, each block had an equal number of same and different pairs; presented in a pseudorandomised order (each participant received the same pre-randomised order. Only a subset of 14 healthy controls, 13 tAD and 11 PCA patients completed the visual motion coherence task. Using blocked presentation allowed for discontinuation of the test if a participant's performance fell to chance; in this event a chance score was given for all subsequent blocks. The task on each trial was to decide if the two sounds were the same or different (except motion coherence, where a yes/no response was required). No feedback about performance was given and no time limits were imposed. Prior to testing, participants were familiarised with the experimental procedures, including practice trials; visual aids were used where possible, to ensure the participant understood the task (see Figure 3.2).

Figure 3.2 – Verbal instructions and visual aids used in experimental auditory tests



3.3.10 Behavioural analysis

Demographic, neuropsychological and peripheral audiometry data were analysed using the methods described in section 2.9.1. As experimental data did not conform to normality assumptions, we implemented a cluster-adjusted logistic regression model with robust standard error to assess odds of correct response (OR). This meant the dependent variable was dichotomous (either correct or incorrect response), rather than continuous (i.e. total score). Auditory spatial task types (discrimination of externalized vs non-externalized sounds, moving vs stationary sounds, stationary sound position), auditory control and visual task types (timbre, pitch, visual spatial and motion coherence) and group (healthy control, tAD, PCA) were entered concurrently as predictors of interest. Interactions between group and test type were fitted to assess group-associated effects on particular tasks whilst controlling for performance on other tasks. Age, peripheral hearing performance, years in education and reverse digit span (as an index of both auditory working memory

capacity and disease severity: Baddeley et al., 1991; Perry & Hodges, 1999) were included as additional covariates of no interest. Correlations between experimental task scores and neuropsychological variables were assessed using Spearman's rank tests. We also examined further those tests that included blocks of varying perceptual parameter level, using d-prime as an index of discriminability. We used linear regression models with robust clustered standard error to assess the effect of perceptual parameter level on discriminability for each task type and experimental group separately, controlling for age and peripheral hearing performance.

3.3.11 VBM analysis

At the time of behavioural assessment, 17 patients in the tAD group and all patients in the PCA group underwent volumetric brain MRI. Regional grey matter volume correlations with performance on auditory experimental tasks were examined only for tasks in which the combined patient cohort exhibited behavioural deficits compared to the healthy control group. For each task, voxel intensity (grey matter volume) was modelled as a function of experimental test score across the combined patient cohort, within and between syndromic groups. In addition to the covariates of no interest detailed in section 2.9.3.1, syndromic group and reverse digit span were included in the statistical model. In addition, grey matter correlates of performance on the visual spatial discrimination tasks within the tAD group was assessed in a separate model. A subset of 11 tAD and 10 PCA patients had completed the visual motion coherence task and had brain scans available; these scan were therefore also subjected to VBM analysis with the same covariates as used for the auditory spatial tasks.

Statistical parametric maps of regional grey matter volume correlating with score on each auditory experimental test were examined at threshold $p < 0.05$ after FWE correction for multiple comparisons over the whole brain and after small volume correction using anatomical regions

based on our prior anatomical hypotheses. These small volumes included key areas previously implicated in ASA and spatial processing (Arnott et al., 2004; Goll et al., 2012; Mayer et al., 2006; Spierer et al., 2008; Warren & Griffiths, 2003; Warren et al., 2002; Zatorre et al., 2002a) posterior superior temporal lobe and IPL (supramarginal and angular gyri) and PMC in each cerebral hemisphere.

3.4 Results

3.4.1 Demographics, neuropsychology and peripheral audiometry

Participant groups did not differ significantly in gender distribution and patient groups did not differ on global measures of disease stage and severity (MMSE score, symptom duration; Table 3.1). Whereas the tAD and healthy control groups were well matched for age, the PCA group was on average significantly younger than both the control group ($W = 1006.23$, $z = 2.24$, $p = 0.03$) and the tAD group ($W = 655.16$, $z = 2.27$, $p = 0.03$). Both the tAD group ($W = 1834.70$, $z = 2.93$, $p = 0.003$) and PCA group ($W = 907.82$, $z = 2.95$, $p = 0.003$) had significantly fewer years of education than the healthy control group. Mean scores for each experimental group can be found in Table 3.1. Syndromic diagnoses in the tAD and PCA groups were corroborated by these data, with global decline relative to controls in the tAD group, but predominant impairment in memory, whereas PCA patients were disproportionately impaired for visual tasks. When assessing peripheral audiometry, data for the left ear were not available for two tAD patients due to a computer error. The regression analysis found no main effect of group [$F_{(2,57)} = 2.74$, $p = 0.07$] with no interaction [$F_{(8,57)} = 0.84$, $p = 0.57$] and no main effect of ear [$F_{(1,57)} = 0.04$, $p = 0.84$]. Due to the missing data and lack of ear effect, a composite peripheral audiometry score summing the thresholds for all frequencies in the right ear only was used as a nuisance covariate in the main experimental analysis.

3.4.2 Auditory spatial tasks

A summary of experimental test performance for each group is presented in Table 3.2; individual data are in Figure 3.3. Qualitatively, healthy control participants and patients all perceived the effect of HRTF convolution as a sound source in virtual acoustic space. Due to time constraints, 1 tAD and 1 PCA patient did not complete the externalised vs non-externalised sound discrimination test. ORs indexing effect of patient group on correct response derived from logistic regression models when run in parallel to include or to exclude these two cases were very similar (0.55 vs 0.58 respectively); these cases were therefore included in analyses and coded as missing values on the relevant tests. The healthy control group performed at sub-ceiling level on experimental tests apart from externalized vs. non-externalized sound discrimination, for which control performance was more variable.

There was a significant interaction between patient group and test type [χ^2 (11) = 28.6, p = 0.003]. Both the tAD group and the PCA group performed comparably to healthy controls on externalized vs non-externalized sound discrimination [tAD: OR = 0.87, CI 0.5 to 1.6, p = 0.64; PCA: OR = 0.74, 95% CI 0.4 to 1.5, p = 0.40]. However, both patient groups performed significantly worse than controls on both moving vs stationary sound discrimination [tAD: OR = 0.36, CI 0.2 to 0.7, p = 0.001; PCA: OR = 0.20, CI 0.1 to 0.4, p < 0.001] and stationary sound position discrimination [tAD: OR = 0.46, CI 0.3 to 0.7, p = 0.001; PCA: OR = 0.31, CI 0.2 to 0.6, p < 0.001]. The PCA group performed significantly worse than the tAD group on moving vs stationary sound discrimination [OR = 0.55, CI 0.3 to 0.9, p = 0.03] but there were no significant performance differences between the patient groups on stationary sound position discrimination [OR = 0.67, CI 0.4 to 1.2, p = 0.18].

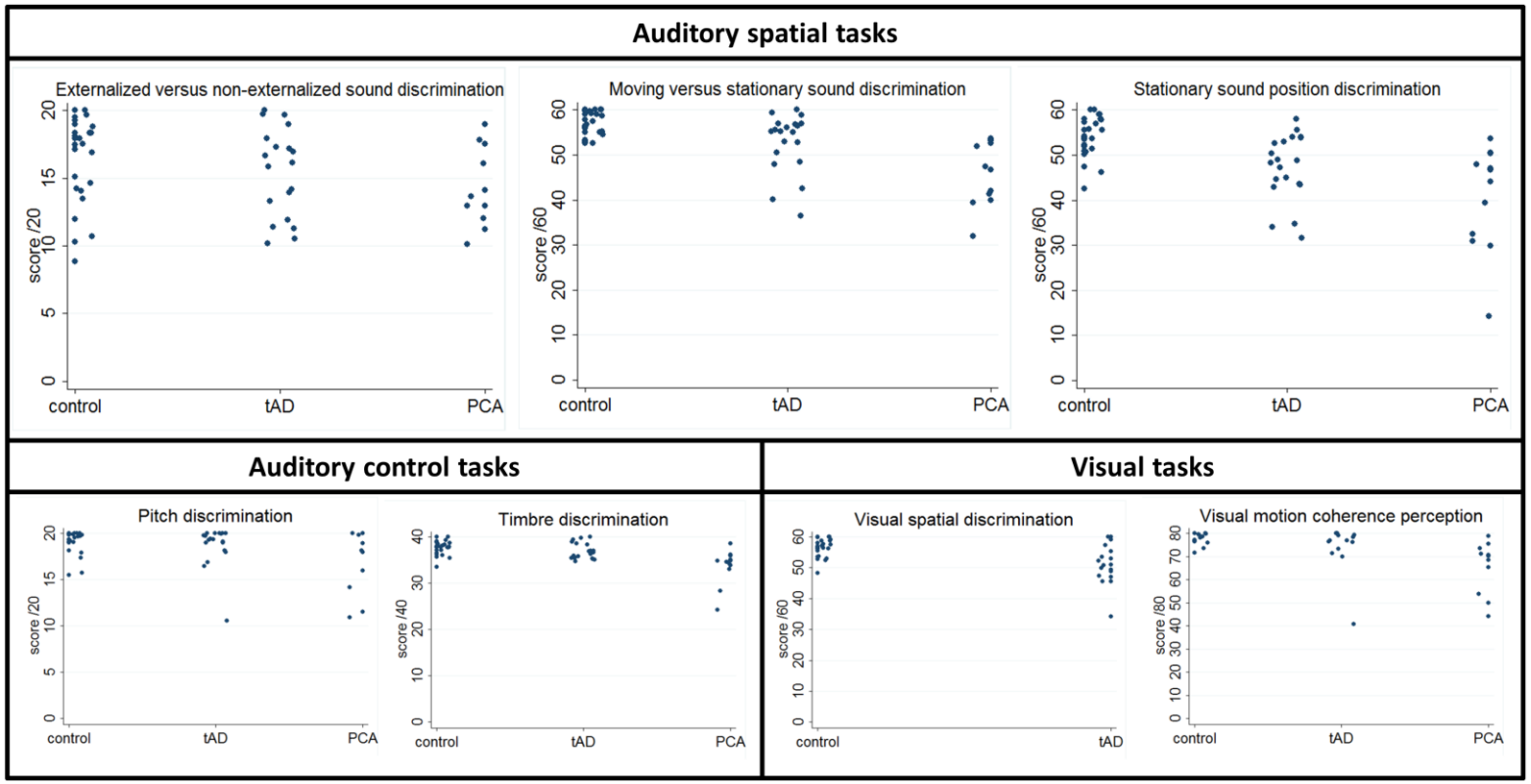
Table 3.2 – Summary of group performance on experimental tasks

Task	Perceptual step	Healthy controls	tAD	PCA
Auditory spatial discrimination				
Externalised vs. non-externalised sounds (/20)[a]		16.5(3.2)	15.3(3.4)	14.1(3.2)
Moving vs. stationary sounds (/60)		57.6(2.3)	52.2(6.5)*	45.4(6.7)**
d prime scores	3.93 radians/sec[b]	**4.5(0.4)**	**3.9(1.1)**	**3.3(1.3)**
	1.97 radians/sec	**4.5(0.4)**	**3.3(1.4)**	**1.9(1.4)**
	0.33 radians/sec[c]	**3.3(1.4)**	**2.4(1.2)**	**1.6(0.6)**
Stationary sound position (/60)		54.3(4.0)	46.7(7.7)*	39.9(11.8)*
d-prime scores	60 degrees gap	3.3(0.7)	2.3(1.1)	1.7(1.2)
	45 degrees gap[d]	3.7(0.8)	3.0(0.9)	2.6(0.6)
	30 degrees gap[d]	2.9(1.1)	2.2(0.8)	1.8(0.5)
Auditory control tasks				
Pitch discrimination (/20)		19.2(1.3)	18.6(2.3)	17.3(3.5)
Timbre discrimination (/40)[e]		37.9(1.5)	36.6(1.6)	33.3(4.0)**
d-prime scores	50% attenuation	**4.5(0.4)**	**4.3(0.7)**	**3.5(1.1)**
	10% attenuation	**3.2(0.7)**	**2.6(0.7)**	**1.8(1.1)**
Visual spatial tasks				
Spatial position discrimination (/60)[f]		57.0(2.8)	50.8(5.9)*	n/a
Motion coherence perception (/80)[g]		78.4(2.4)	73.9(10.1)*	65.5(12.2)*

Group raw scores on auditory and visual experimental tasks (total score in parentheses) are shown. For the auditory tasks, d prime scores for each perceptual step are also shown. Mean (standard deviation in parentheses) scores are presented. *significantly different from control group. **significantly different from control and other patient group ($p < 0.05$); scores in bold indicate a significant ($p < 0.05$) of perceptual step effect on task performance. Due

to time constraints or discontinuation of a particular block, subsets of participants completed particular blocks or tasks as follows: **a** 19 tAD and 11 PCA patients; **b** 24 healthy controls; **c** 19 tAD and nine PCA patients; **d** 17 tAD and eight PCA patients; **e** 19 tAD patients; **f** 18 tAD patients; **g** 14 healthy controls, 13 tAD and 11 PCA patients.

Figure 3.3 – Individual raw scores for each experimental task



Individual raw data are plotted for each experimental test for the healthy control, tAD and PCA patient groups.

3.4.3 Auditory control tasks

Due to time constraints, 1 tAD patient did not complete the timbre discrimination test. On both auditory control tasks, the healthy control and tAD groups performed comparably [pitch discrimination: OR = 0.65, CI 0.3 to 1.7, p = 0.38; timbre discrimination: OR = 0.78, CI 0.5 to 1.2, p = 0.25]; whereas the PCA group showed a trend toward inferior pitch discrimination performance relative to healthy controls [OR = 0.38, CI 0.1 to 1.1, p = 0.07] and a deficit of timbre discrimination relative both to healthy controls [OR = 0.41, CI 0.2 to 0.7, p = 0.003] and the tAD group [OR = 0.53, CI 0.3 to 0.8, p = 0.004].

3.4.4 Visual spatial control tasks

On experimental tests of visual spatial function, relative to the healthy control group the tAD group showed impaired visual spatial discrimination [OR = 0.37, CI 0.2 to 0.7, p = 0.001] (the PCA group was not assessed on this task due to the severity of visual spatial impairment in this group; see Table 3.1 and Table 3.2) and both patient groups showed impaired visual motion coherence perception [tAD: OR = 0.33, CI 0.1 to 1.0, p = 0.049; PCA: 0.15, CI 0.05 to 0.4, p < 0.001]; there were no differences between the tAD and PCA groups [OR = 0.44, CI 0.1 to 1.4, p = 0.16].

3.4.5 Correlations between parameters

Correlations between experimental task performance and general neuropsychological functions are summarised in Table 3.3. Performance on experimental tests in the patient groups was significantly positively correlated with a standard measure of general cognitive severity (MMSE score). There was also a significant positive correlation with pitch and moving vs. stationary sound discrimination for both patient groups, and between pitch and sound position discrimination in the tAD group only. Visual spatial discrimination performance correlated with moving vs stationary sound, sound position and pitch discrimination in the tAD

group. Performance on the visual motion coherence task correlated with moving vs stationary sound discrimination for both patient groups.

Table 3.3 – Summary of performance correlations (Spearman's rho) between experimental tasks and relevant general neuropsychological functions

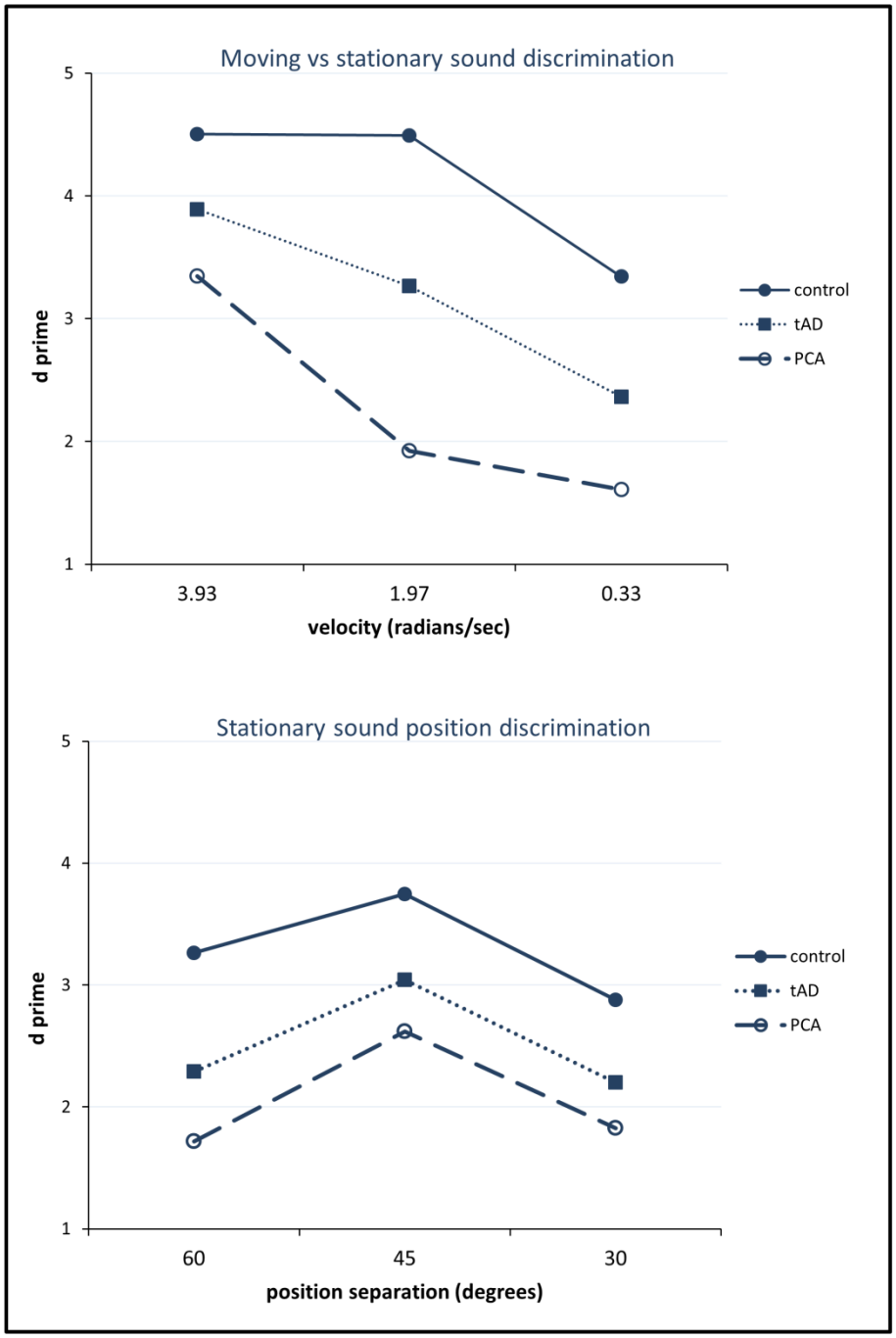
Task	Group	MMSE	Pitch discrimination	Digit span reverse	Visual spatial discrimination	Visual motion coherence
Auditory spatial discrimination						
Externalised vs. non-externalised sounds	*tAD*	0.24	0.28	0.12	0.24	0.57
	PCA	0.41	0.57	0.56	-	0.23
Moving vs. stationary sounds	*tAD*	0.68*	0.60*	0.25	0.65*	0.72*
	PCA	0.42	0.63*	0.04	-	0.69*
Stationary sound position	*tAD*	0.62*	0.55*	0.32	0.61*	0.87*
	PCA	0.26	0.42	0.08	-	0.23
Auditory control tasks						
Pitch discrimination	*tAD*	0.50*	-	0.52*	0.50*	-0.11
	PCA	0.32	-	0.36	-	0.53
Timbre discrimination	*tAD*	0.30	0.43	0.37	0.47	0.30
	PCA	0.08	0.14	0.17	-	0.29
Visual spatial tasks						
Visual spatial discrimination	*tAD*	0.81*	-0.29	0.56*	-	0.53
	PCA	-	-	-	-	-
Visual motion coherence perception	*tAD*	0.52	0.26	0.16	0.53	-
	PCA	0.16	0.53	-0.28	-	-

*significant at threshold $p < 0.05$

3.4.6 Effect of perceptual parameter

Mean d prime scores for all auditory experimental tasks are displayed in Table 3.2. Across groups, performance on the moving vs stationary sound discrimination was associated with magnitude of perceptual parameter for the healthy control [beta = -0.59, CI -0.8 to -0.4, $p < 0.001$], tAD [beta = -0.77, CI -1.1 to -0.4, $p < 0.001$] and PCA group [beta = -0.90, CI -1.4 to -0.4, $p = 0.001$]. The same was true for timbre discrimination [healthy control: beta = -1.29, CI -1.6 to -1.0, $p < 0.001$; tAD: beta = -1.65, CI -2.1 to -1.1, $p < 0.001$; PCA: beta = -1.71, CI -2.6 to -0.8, $p = 0.001$]. In contrast, performance on the stationary sound position discrimination test was not monotonically related to perceptual parameter level in any experimental group [healthy control: beta = -0.19, CI -0.4 to 0.1, $p = 0.13$; tAD: beta = -0.2, CI -0.4 to 0.3, $p = 0.88$; PCA: beta = 0.12, CI = -0.3 to 0.6, $p = 0.59$] but rather showed a falling off of discriminability at the largest spatial separation, shown in Figure 3.4.

Figure 3.4 – Group mean d prime scores



Mean d-prime scores are plotted for each perceptual parameter level/condition for the moving vs stationary and stationary sound position discrimination tasks. Unbroken lines represent healthy controls; dotted lines the tAD group; and dashed lines the PCA group.

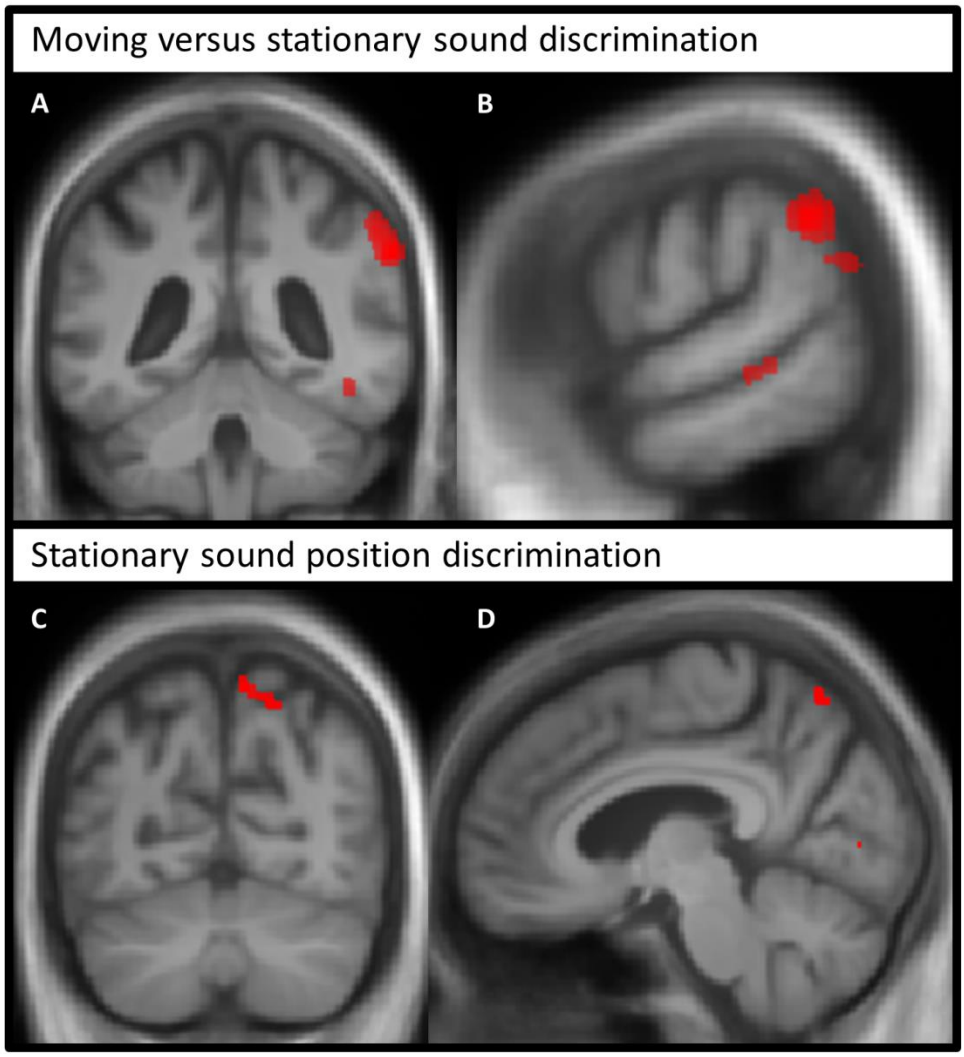
3.4.7 Neuroanatomical associations

In the voxel-based morphometry analysis, grey matter associations of performance on moving vs stationary sound discrimination and stationary sound position discrimination were assessed as these tasks showed disease-associated behavioural deficits (see Figure 3.5 and Table 3.4). In the combined patient cohort, performance on the moving vs stationary sound discrimination task was positively correlated with grey matter volume in right IPL (peak MNI stereotactic space coordinates [62 -45 36]), thresholded at $p < 0.05$ after FWE correction for multiple comparisons over the whole brain. No additional grey matter associations of moving vs stationary sound discrimination were identified at the prescribed threshold after correction within the small volumes of interest specified by our prior anatomical hypotheses; however, at a more lenient uncorrected threshold ($p < 0.001$ over the whole brain volume), additional cerebral correlates of moving vs stationary sound discrimination were identified in left temporo-parieto-occipital junction, right posterior STS, right fusiform gyrus and basal ganglia (Table 3.4). Performance on the stationary sound position discrimination task for the combined patient cohort was positively correlated with grey matter volume in right precuneus (peak MNI coordinates [8 -66 58]), thresholded at $p < 0.05$ after FWE correction for multiple comparisons within the small volume of interest specified by our prior anatomical hypotheses. No grey matter regions showing a significant inverse association with auditory spatial task performance were identified.

Assessed separately, the tAD and PCA groups showed no significant grey matter associations with performance on either spatial task at the prescribed threshold, nor were any significant inter-group differences in regional grey matter associations of auditory spatial performance identified at this corrected threshold. Visual spatial discrimination performance within the tAD group had a positive grey matter correlate in

right precuneus close to the region identified for auditory spatial discrimination in the combined patient cohort (peak MNI coordinates [9 -76 45]), at a lenient uncorrected threshold ($p < 0.001$ over the whole brain volume). Assessing visual motion coherence yielded no significant voxels at the prescribed threshold levels, however regions in left superior primary motor cortex, right IPL and left superior frontal gyrus were significant at a more lenient threshold of $p < 0.001$ uncorrected for multiple comparisons.

Figure 3.5 – Grey matter associations with auditory spatial task performance



Statistical parametric maps of associations of regional grey matter volume with performance on experimental auditory spatial tasks in the combined patient group. Maps are thresholded at an uncorrected whole-brain significance level $p < 0.001$ for display purposes. Maps are projected on coronal (A, C), and sagittal (B, D) sections of the mean patient cohort T1-weighted MR brain image; the right hemisphere is shown on the right in coronal sections.

Table 3.4 – Summary of neuroanatomical associations for experimental auditory spatial tasks in the patient groups

Region	Peak MNI coordinates (mm)			cluster size (voxels)	t-value	p-value
	x	y	z			
Moving vs stationary sound discrimination						
Right inferior parietal cortex	62	-45	36	657	6.81	0.038*
Left temporo-parieto-occipital junction	-48	-73	27	143	6.46	< 0.001
Right basal ganglia (lentiform nucleus)	27	2	-6	61	4.26	< 0.001
Right fusiform gyrus	45	-45	-15	56	4.21	< 0.001
Right mid superior temporal sulcus	60	-28	-5	121	4.16	< 0.001
Stationary sound position discrimination						
Right precuneus	8	-66	58	88	4.49	0.043**
Left cerebellum	-23	-42	-59	70	4.43	< 0.001

MNI coordinates of local maxima for all significant regional grey matter associations with performance on experimental auditory tasks, after adjusting for overall effect of syndromic group atrophy. Here significance has been thresholded at $p < 0.001$ uncorrected across the whole brain with coordinate inclusion criteria of 1) cluster encompassing a distinct anatomical region and 2) cluster size > 50 voxels. *survives at threshold $p < 0.05$ FWE correction for multiple comparisons across the whole brain; **survives at threshold $p < 0.05$ after FWE correction within pre-specified anatomical small volume.

3.5 Discussion

This study has shown that both clinically typical amnestic and posterior variant AD are associated with impairments in auditory spatial processing. In comparison to controls, both syndromic groups showed a relative sparing of the ability to make use of externalising cues, but a deficit in discriminating motion and static position in external space. The PCA group were more severely impaired at auditory motion discrimination when compared to the tAD group. With the caveat that power to detect weaker effects was relatively low, this is in the context of preserved non-spatial auditory control task performance for both nonverbal auditory working memory (pitch discrimination) and spectrotemporal processing (timbre discrimination) for the tAD group. In contrast, the PCA group showed impairment for timbre discrimination, with a trend towards a deficit for pitch discrimination. The auditory spatial deficits found in these two patient groups correlated with their performance in visual spatial location discrimination and motion coherence detection. Measures of working memory also correlated with performance, however analyses controlling for working memory ability still reveal an auditory spatial deficit. In terms of neuroanatomical associations with auditory spatial impairment, voxel based morphometry revealed correlations between these tasks and grey matter in right parietal regions.

Further examination of the behavioural results highlights a number of findings. When discriminability is broken down by perceptual step in the auditory tasks, effect of perceptual parameter on performance has the same effect for all experimental groups, suggesting that the tasks were accessing similar perceptual processes in all experimental groups. The non-monotonic relationship between perceptual step and discriminability for stationary sound position discrimination (shown in Figure 3.4) may be due to front-back confusions for larger spatial gaps (Blauert, 1997; Middlebrooks & Green, 1991). In this task, sound locations did not cross

the hemisphere between pairs to reduce detection based on lateralisation, therefore a 60 degree gap within a spatial hemifield would often result in a front-back discrimination; this was less likely for 45 and 30 degrees.

Comparing the tAD and PCA groups, greater posterior cortical involvement in the PCA group may have contributed to the greater impairment for moving vs. stationary sound discrimination; however sample sizes were too small to reliably accept any null result concerning anatomical differences between the two groups. The PCA group also showed deficits in spectrotemporal processing and a trend towards impairment in pitch processing. One explanation for this pattern could be that a primary deficit in auditory working memory is the basis for poor performance in all these tasks. Phonological working memory is a demonstrated weakness in this patient population (Crutch et al., 2013b), thus it may possible that this study paired with the findings in the current chapter stem from an inabitliy to hold sounds online. However, the analysis in this study controlled for working memory using backward digit span and the auditory spatial deficit remained. Further receptive linguistic functions have been revealed in PCA (Crutch et al., 2013b) with difficulties in abilities such as prosody processing. Therefore it may be the case that PCA patients suffer from complex spectrotemporal processing in addition to their spatial disabilities, exhibited here in timbre discrimination and in other studies by linguistic input processing functions.

The present findings touch on the possibility of a multi-modal spatial processing correlate. Here performance on visuospatial tasks correlated with auditory spatial tasks, suggesting possible commonality between the two modalities. In addition, the more severe auditory spatial impairment in a patient group characterised by visual spatial deficits (PCA) would also be consistent with similar if not the same brain regions contributing to

both functions. However, this must be qualified. The visual and auditory spatial tasks cannot be considered direct equivalents, as the auditory tasks were presented via egocentric space whereas the visual tasks were presented on a screen and therefore in allocentric space. Furthermore, with the caveat that sample sizes were not equivalent, neuroanatomical associations with auditory spatial and visual spatial tasks did not uniformly converge on the same regions in the current experimental cohort. Nevertheless, the finding that auditory motion discrimination correlates with atrophy in right IPL has uncovered a locus that is also commonly involved in visual spatial processing (Rizzolatti & Matelli, 2003) or multimodal interpretation of salient stimuli (Cohen, 2009; Singh-Curry & Husain, 2009). The parietal lobe may be critical for the formation of an egocentric spatial reference frame across sensory modalities (Karnath, 1997; Bellmann et al., 2001; Krumbholz et al., 2005). However, alternate findings have demonstrated that auditory spatial processing does not recruit identical regions implicated in visuospatial maps in inferior parietal regions (Kong et al., 2014). Of further interest is one study that found associations between auditory spatial working memory and inferior parietal lobe (Alain et al., 2008), which may hold particular relevance to the paradigms utilised here. There were also anatomical associations in the current study that were not in line with the idea that exclusively dorsal auditory areas contribute to the spatial processing of sounds. An area in right STS correlated significantly with performance on the moving vs stationary task, which may indicate the parallel role both streams play in auditory spatial processing (Cloutman, 2012), or perhaps the labelling of stimuli as ‘moving’ or ‘stationary’ (however the paradigm ensured that this was not necessary to complete the task successfully).

This study does not fully resolve the issue of whether auditory and visual spatial processing are governed by similar or the same regions, however the neuroanatomical findings of this study are in line with previous

evidence that dorsal auditory areas are responsible for the processing of auditory spatial cues (Alain et al., 2001; Arnott et al., 2004; Brunetti et al., 2005; Clarke et al., 2002; Krumbholz et al., 2005; Lewald et al., 2002; Warren & Griffiths, 2003; Warren et al., 2002; Zimmer et al., 2006; Zündorf et al., 2013). The findings further suggest that critical neuroanatomical substrates for processing sound motion and static sound location are separable. It remains unclear whether the cognitive mechanisms that process particular auditory spatial parameters can be differentiated (Blauert, 1997; Ducommun et al., 2002, 2004; Middlebrooks & Green, 1991), however the present neuroanatomical data accord with previous work in the healthy brain and in focal brain damage implicating temporo-parietal junction and PMC in the analysis of sound motion and static location, respectively (Ducommun et al., 2004; Krumbholz et al., 2005; Warren et al., 2002; Zündorf et al., 2013). This functional separation may arise from the relative dependence of auditory motion coding on fine-grained spectrotemporal analysis and auditory location discrimination on internally directed processes that integrate stored auditory representations (Griffiths & Warren, 2002; Warren et al., 2002; Zündorf et al., 2013; Zvyagintsev et al., 2013). It may also support previous evidence that sound motion detection is based on a velocity detection mechanism (Carlile & Best, 2002; Griffiths et al., 1996), however caution must be taken here in the light of impairment for both motion and location detection in these disease groups. The neuroanatomical regions implicated here are key posterior components of the DMN (Greicius et al., 2009; Seeley et al., 2009), and involvement of precuneus here further accords with previous work implicating PMC in AD (Goll et al., 2012).

A number of caveats should be taken into account. The externalised vs. non-externalised task produced a large range of performance in all groups, therefore factors such as task difficulty, hearing ability or head

movement (Brimijoin et al., 2013) may have been involved. Furthermore, as the best fitted model involved using odds of correct response as an outcome, the tests would have benefitted from the same number of items – for example detecting deficits is more likely for a 60-item task compared to a 20-item task. The power to detect weaker effects also influenced the neuroimaging findings: comparing associations between phenotypic variants, or modality was relatively underpowered to reveal differences with the current sample sizes. Despite these limitations, this study highlights an understudied symptom that may contribute to more general disorientation in patients with AD in everyday listening situations. Further investigation of how the AD brain is functionally altered along both the dorsal auditory pathway and the DMN regions may provide additional clues to the mechanistic changes behind the cognitive symptoms in this disease.

4 AUDITORY SPATIAL PROCESSING IN AD: AN FMRI INVESTIGATION

4.1 Introduction

The previous chapter outlined auditory spatial processing deficits in AD and their relationships with localised grey matter atrophy using structural MRI scans. This chapter aims to expand on these findings by assessing the pattern of functional MRI activation in AD patients when confronted with auditory spatial sounds. As discussed in section 1.6.7, lateral temporoparietal regions and dorsal auditory areas are thought to govern the preparation of behavioural response to sounds. PMC regions also seem to play a role in orienting attention to auditory spatial stimuli. In fMRI studies of the healthy brain, insular cortex has also been revealed to engage in processing aspects of auditory motion or integrating spatial with other sound characteristics (Altmann et al., 2008; Griffiths et al., 1994; Lewis et al., 2000). As indicated by the VBM findings in the preceding chapter and previous work in the healthy brain (see section 3.1), neuroanatomical substrates for auditory location and motion may dissociate.

Whilst behavioural studies indicate a deficit in auditory spatial processing in AD (Kurylo et al., 1993, Chapter 3), no studies have investigated any functional neuroanatomical alteration in this domain. fMRI studies of non-memory processes in AD are sparse, however investigation into DMN activation during memory tasks indicates that the relationship between structural grey matter loss and functional abnormalities in AD may not be straightforward. A series of studies has shown aberrant increase of activation in DMN regions during information encoding in AD patients compared to healthy controls (Celone et al., 2006; Pihlajamäki & DePeau, 2008; Pihlajamäki & Sperling, 2009; Sperling et al., 2003, 2010); therefore a simple reduction in activation across the brain does not seem to represent the disease profile of Alzheimer's dementia. One study

investigating neural activation in response to verbal memory encoding found that an AD group were less able to suppress activity in HG to successfully complete the task (Dhanjal et al., 2013). This indicates that network dysfunction in AD can also affect activity in widespread regions unrelated to its core neurodegenerative pattern, and that fMRI studies may contribute additional information about wider neural dysfunction in diseases such as AD. In this experiment, I aimed to investigate any functional neuroanatomical differences between patients with a diagnosis of typical AD and a healthy control group during auditory spatial processing to determine what non-amnestic impairments may be able to tell us about dysfunction in the AD brain.

This study investigated auditory spatial location and movement processing, using pitch as a non-spatial sound identity control stimulus and building on the well-established 'what-where' dichotomy in the healthy brain (see section 1.6.1). We made use of virtual space techniques to create a percept of sounds at a certain position around the head. The paradigm was motivated by previous work delineating distinct cortical substrates for processing pitch and spatial patterns in the healthy brain (Warren & Griffiths, 2003; Warren et al., 2002); making use of sound sequences that were either fixed or changing in pitch or spatial position, as well as creating auditory motion stimuli comprising spatially rotating sounds. Patterns of activation were assessed for a group of typical AD patients and a group of healthy age-matched controls, where the primary interest of the study was to investigate the functional neuroanatomical signature of auditory spatial processing in AD.

4.2 Hypotheses

This study rested on two main hypotheses: 1) AD will be associated with an altered cortical signature of auditory spatial analysis relative to healthy individuals. 2) This signature will include posterior auditory association and temporo-parietal regions previously implicated in auditory spatial

analysis and converging on DMN (Chapter 3; Goll et al., 2012; Lewis et al., 2000; Warren & Griffiths, 2003; Warren et al., 2002; Zündorf et al., 2013).

4.3 Methods

4.3.1 Participants

Fourteen consecutive typical AD patients (6 female) and 17 healthy older subjects (10 female) were recruited into the study. One control was excluded from the study after assessment due to a low MMSE score and generalised atrophy on structural MRI, leaving 16 (9 female) in the healthy control group. There was 1 left-handed participant in each experimental group; the remaining participants were right-handed (therefore matched for handedness). Demographic, clinical and neuropsychological details for the experimental groups are summarised in Table 4.1 and Table 4.2. All participants underwent peripheral hearing assessment in both ears as per the description in section 2.2. At the time of participation, 12/14 AD patients were receiving symptomatic treatment with an acetylcholinesterase inhibitor, with the remaining 2 patients receiving memantine. The diagnosis of AD was further corroborated by CSF examination (ratio total tau : beta-amyloid$_{1\text{-}42}$ >1 in 8/9 cases where CSF data were available).

Table 4.1 – Demographic and post-scan behavioural task data

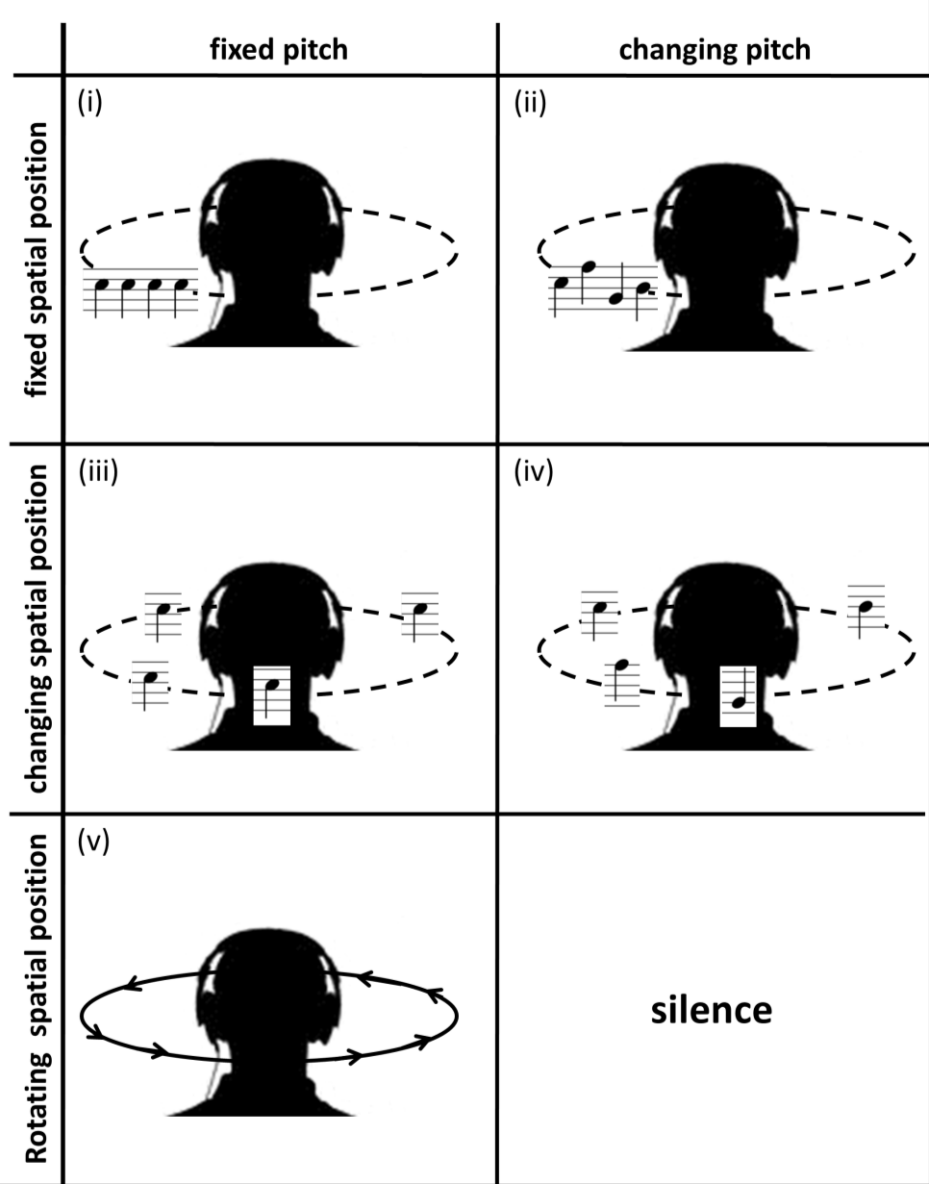
Characteristics	Healthy controls	AD
General		
No. (m:f)	8:8	8:6
Age (yrs)	70.1(5.0)	69.8(6.3)
Education (yrs)	16.0(2.3)	13.3(3.4)*
MMSE (/30)	29.3(1.1)	20.0(5.1)*
Symptom duration (yrs)	-	5.8(2.0)
Post-scan behavioural tasks		
Spatial sequence identification (% correct)	95.4(4.1)	81.0(15.8)*
Pitch sequence identification (% correct)	89.4(12.1)	78.2(17.8)*

Mean (standard deviation in parentheses) data are displayed unless otherwise specified. *significantly different from controls ($p < 0.05$).

4.3.2 Experimental design and stimuli

The stimuli here made use of convolving an IRN carrier sound with generic HRTFs, as described in section 2.6.1. The procedures for stimuli synthesis were adapted from previous work in the healthy brain (Warren & Griffiths, 2003; Warren et al., 2002), however will also be outlined here. For a schematic representation of all stimuli conditions presented in the scanner, see Figure 4.1. Six experimental conditions were created for presentation in the scanner: i) pitch fixed, spatial location fixed (PfSf); ii) pitch changing, spatial location fixed (PcSf); iii) pitch fixed, spatial location changing (PfSc); iv) pitch changing, spatial location changing (PcSc); v) pitch fixed, sound revolving around head (PfSr); and vi) silence. To create conditions (i) to (iv), individual IRN elements of duration 300ms were concatenated with inter-sound pauses of duration 75ms to generate sound sequences each containing 21 elements with overall duration 7.8s. For a given trial (sound sequence), pitch was either fixed or varied randomly between elements of the sequence with values 70, 85, 100, 115, 130 or 145 Hz, not corresponding to intervals in Western music; and spatial location was either fixed with starting position -90, 0, 90 or 180 degrees or randomly varied with spatial step size and direction ±30, 40 or 50 degrees in azimuth, such that the initial and final elements were always identical. To create condition (v), HRTFs were updated and interpolated over discrete positions around the azimuth (as described in section 2.6.1), corresponding to a constant angular velocity of ±100 degrees/s; initial position and IRN carrier pitch were randomly varied between trials at the same values used in conditions (i) to (iv). Conditions (i) to (iv) generated a percept of a sound source with constant or randomly varying pitch that either repeated at the same spatial location or jittered between locations around the head; condition (v) generated a percept of a sound source revolving smoothly around the head.

Figure 4.1 – Schematic representation of all conditions



Trials played during scanning are represented schematically. A total of six different conditions comprised the paradigm; the pitch and spatial positions sequences worked to form a factorial design, with the additional rotating stimuli and silence also included. This combination formed the following conditions: i) pitch fixed, spatial location fixed (PfSf); ii) pitch changing, spatial location fixed (PcSf); iii) pitch fixed, spatial location changing (PfSc); iv) pitch changing, spatial location changing (PcSc); v) pitch fixed, sound revolving around head (PfSr); and vi) silence. Dotted lines represent the azimuthal plane. The spatial steps and musical notation are used here purely for presentation purposes; stimuli used smaller spatial steps and frequencies that do not correspond to notes in traditional Western music.

4.3.3 Procedure

4.3.3.1 Stimulus presentation and brain image acquisition

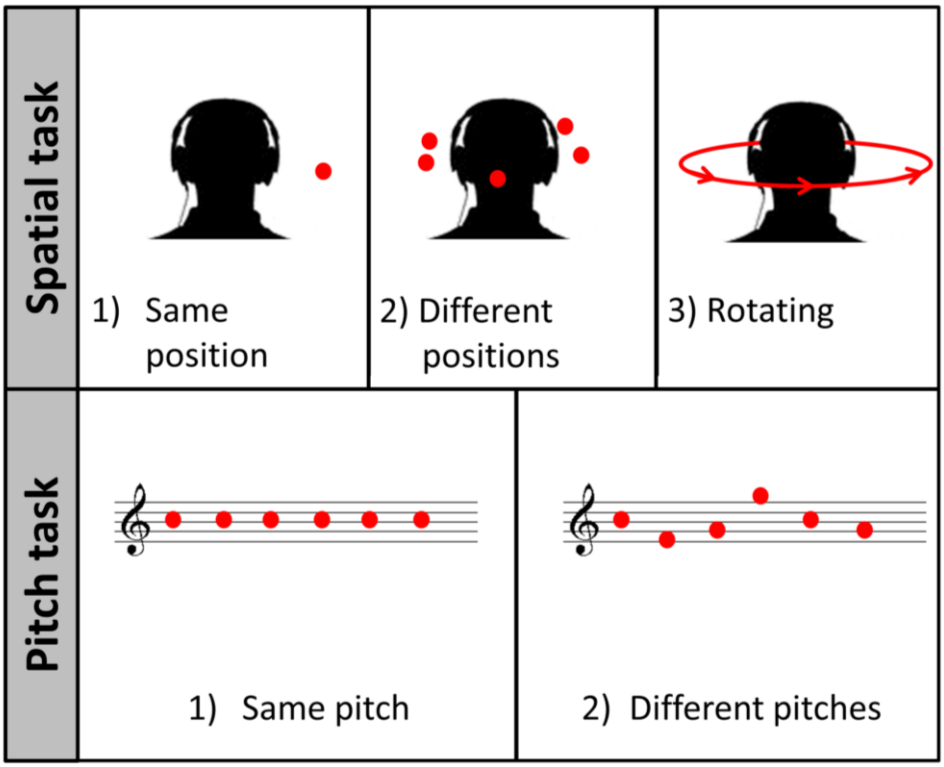
Stimuli were presented to participants using the method described in section 2.6. The initiation of the scanner pulse triggered a button press so as to synchronise stimuli presentation with the sparse acquisition protocol. Two identical scanning runs were administered, comprised of 16 trials per sound condition with an additional 8 silence trials, resulting in a total of 176 trials for the whole experiment. Stimuli were pseudo-randomised so that each participant heard the same pre-randomised order of stimuli. Participants were instructed to listen to the sound stimuli with their eyes open; there was no in-scanner output task and no behavioural responses were collected. Functional MR images were obtained using the methods described in section 2.7.2.

4.3.3.2 Post-scan behavioural task

Following the scanning session, each participant's ability to perceive and discriminate the experimental conditions presented during scanning was assessed using alternative forced choice psychoacoustic procedures that assessed pitch change detection and auditory spatial location change detection. For the spatial task, 30 stimuli from the scanning session (5 each of conditions (i)-(iv) and ten for condition (v)) were used. Participants were asked to identify whether sounds were fixed position, changing position or rotating. The pitch task used 20 stimuli from the scanning session (5 each of conditions (i)-(iv)); and required identification of sounds that were either fixed or changing pitch. For both tasks, participants were presented with visual representations of each condition. Responses were permitted either verbally or via pointing to the correct visual representation. It was established that all participants understood the tasks prior to commencing the tests; during the tests, no feedback about performance was given and no time limits were imposed.

All responses were recorded for off-line analysis. The visual guides used in this task can be found in Figure 4.2.

Figure 4.2 – Post-scan behavioural task visual guide



Participants were shown each task's visual guide on a single page and were able to refer to this throughout testing. Red circles represent sounds; red arrows represent the direction of movement.

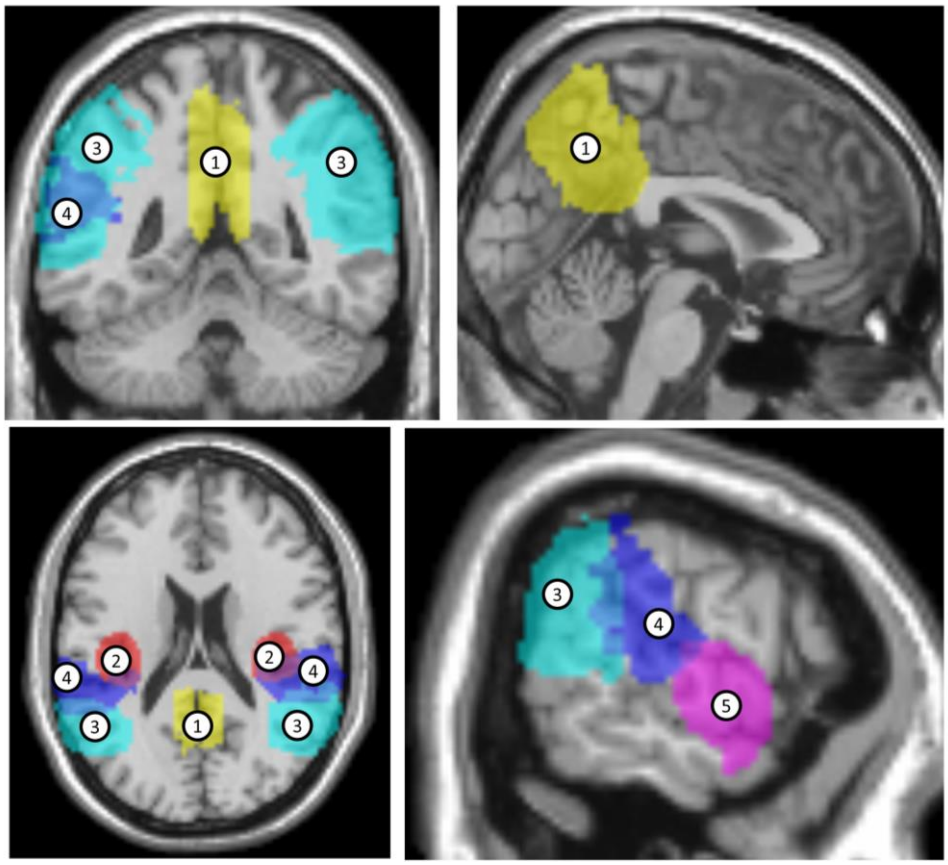
4.3.4 fMRI analysis

Images were pre-processed according to the procedure described in section 2.8.2, and were then entered into a first-level design matrix incorporating the five experimental conditions (PfSf, PfSc, PcSf, PcSc, PfSr and the baseline silence condition) as described in section 2.9.3.2. For each participant, first-level t-test contrast images were generated for the main effects of auditory stimulation [(PfSf + PfSc + PcSf + PcSc + PfSr) – silence], the factorial contrasts of changing spatial position [discrete spatial variation: (PcSc + PfSc) – (PcSf + PfSf)], changing pitch [(PcSc + PcSf) – (PfSc + PfSf)] as well as any interaction of these effects [(PcSc – PcSf) – (PfSc – PfSf)]. Using only conditions with fixed pitch, the effect of

continuous movement was assessed compared to sounds with fixed position [continuous spatial variation: PfSr – PfSf] and changing position [continuous vs. discrete spatial variation (PfSr – PfSc)]. Contrast images for each participant were entered into a second-level random-effects analysis in which effects within each experimental group and between the healthy control and AD groups were assessed using voxel-wise t-test contrasts.

Contrasts were assessed at a peak-level significance threshold $p < 0.05$ after FWE correction for multiple voxel-wise comparisons within neuroanatomical regions of interest pre-specified by our prior anatomical hypotheses. Regions previously implicated in the analysis of pitch patterns encompassed the anterior STG (Arnott et al., 2004; Patterson et al., 2002; Warren & Griffiths, 2003). Spatial regions included the temporoparietal junction (posterior STG and angular gyrus), PMC and insula (Arnott et al., 2004; Brunetti et al., 2005, 2008; Griffiths et al., 1994; Lewis et al., 2000; Shomstein & Yantis, 2006; Warren & Griffiths, 2003; Zündorf et al., 2013). A region that combined both anterior and posterior STG was used for the contrast assessing all sound activation. Anatomical regions were derived using the methods described in section 2.8.4. Representative sections illustrating the extent of these volumes can be found in Figure 4.3.

Figure 4.3 – Small volumes used for analysis of functional data



Representative slices illustrate the extent of the areas used to investigate voxel activity in small volumes. 1) PMC (edited Oxford-Harvard map); 2) insula (lg2 Jülich map); 3) angular gyrus (encompassing TPJ: Oxford-Harvard map); 4) posterior STG/PT (edited Oxford-Harvard map); 5) anterior STG (Oxford-Harvard map).

4.3.5 VBM analysis

Structural brain images were compared between the patient and healthy control groups in a VBM analysis (as described in sections 2.8.1 and 2.9.3.1) to obtain an AD-associated regional atrophy map. Statistical parametric maps of brain atrophy were thresholded leniently ($p < 0.01$ uncorrected over the whole brain volume) in order to capture any significant grey matter structural changes in relation to functional activation profiles from the fMRI analysis.

4.3.6 Analysis of behavioural data

In the analysis of post-scan behavioural data, a linear regression model incorporating robust, clustered standard error was utilised to test for the

main effects of disease and behavioural task on proportion of correct answers while also testing for any interaction between these two factors. The regression model controlled for years of education as a potential confounding factor.

4.4 Results

4.4.1 Demographic, neuropsychological and peripheral audiometry characteristics

The patient and healthy control groups were well matched for age and gender distribution, however the healthy control group had significantly more years of education (W = 547.77, z = 2.22, p = 0.03). Details of demographic information can be found in Table 4.1. Tone detection thresholds (in ms) on audiometry testing did not differ between the patient and healthy control groups (beta = 170, CI -4198 to 4540, p = 0.94), nor was there any significant interaction between group and sound frequency ($F_{(4,29)}$ = 1.11, p = 0.37) and was therefore not considered further in any analyses. Neuropsychological profiles (see Table 4.2) revealed significantly worse performance on all cognitive tasks in the AD group compared to controls, with the exception of forward spatial span. This profile likely reflects both the global cognitive impairment and lower educational level of the AD group, however an AD profile is corroborated by their specific weaknesses in tests of memory, executive function, naming and visuospatial working memory.

Table 4.2 – Neuropsychological profile of experimental groups

Neuropsychological assessment	Healthy controls	AD
General intellect: IQ		
WASI verbal IQ	120.3(8.9)	93.5(17.2)*
WASI performance IQ	120.8(15.7)	92.7(22.2)*
NART estimated premorbid IQ	121.7(5.5)	107.7(15.6)*
Episodic memory		
RMT words (/50)	47.4(2.2)	**31.4(7.4)***
RMT faces (/50)	42.6(4.2)	**33.6(6.9)***
Camden PAL (/24)	20.9(2.5)	**3.4(3.9)***
Executive skills		
WASI block design (/71)	43.1(16.0)	19.4(14.0)*
WASI matrices (/32)	28.2(12.5)	13.2(8.4)*
WMS-R digit span forward (/12)	8.6(1.9)	6.6(1.7)*
WMS-R digit span backward (/12)	7.2(2.2)	4.7(1.8)*
D-KEFS Stroop colour (s)[a]	31.4(7.3)	**52.5(21.0)***
D-KEFS Stroop word (s)[a]	21.4(4.2)	**35.0(18.1)***
D-KEFS Stroop interference (s)[a]	64.9(18.1)	**103.2(47.9)***
Letter fluency (F: total)	16.7(6.0)	9.4(4.9)*
Category fluency (animals: total)	20.9(5.1)	**11.1(5.0)***
Trails A (s)[b]	33.5(10.7)	**70.3(50.3)***
Trails B (s)[c]	77.9(20.1)	195.8(73.7)*
WAIS-R digit symbol (total)[d]	51.5(10.5)	**26.4(15.4)***
Verbal skills		
WASI vocabulary (/80)	70.1(4.6)	51.6(13.7)*
WASI similarities (/48)	39.6(6.9)	23.6(12.4)*
GNT (/30)	26.1(2.0)	**13.5(7.8)***
British picture vocabulary scale (/150)	147.1(1.9)	134.8(21.4)*
NART (/50)	42.8(4.5)	33.5(10.7)*
Posterior cortical skills		
GDA (/24)	15.9(4.2)	5.6(6.2)*
VOSP object decision (/20)	18.3(2.2)	15.1(3.7)*
Visuospatial ability		
VOSP dot counting (/10)	9.9(0.3)	8.6(1.9)*
WMS-III spatial span forward (/16)	6.8(1.7)	5.1(2.2)
WMS-III spatial span reverse (/16)	6.9(1.2)	**3.4(2.2)***

Mean (standard deviation in parentheses) performance scores are shown unless otherwise indicated. Maximum scores on neuropsychological tests are shown in parentheses. Results in bold indicate mean score < 5th percentile (no age appropriate norms were available for BPVS and letter fluency). *significantly different from control group ($p < 0.05$). **a** 13 ADs; **b** 12 ADs; **c** 9 ADs; **d** 11 ADs.

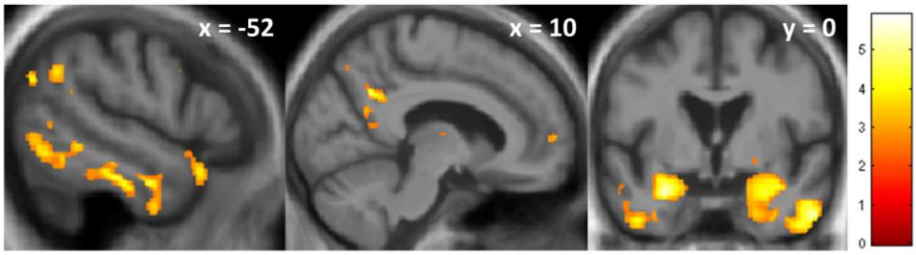
4.4.2 Post-scan behavioural task

Group performance data for the post-scan behavioural tests are presented in Table 4.1. There was a significant effect of group (beta = -0.12, CI -0.21 to -0.03, p = 0.01) and task type (spatial position/pitch change detection: beta = -0.06, CI -0.23 to -0.003, p = 0.04), however no significant interaction between group and test type ($F_{(1,29)}$ = 0.25, p = 0.62).

4.4.3 Structural neuroanatomy

Comparison of the AD and healthy control groups in the VBM analysis revealed the anticipated profile of AD-associated regional grey matter atrophy involving hippocampi, temporal, temporoparietal and posterior medial cortex; statistical parametric maps are presented in Figure 4.4, with further details of atrophic regions in Table 4.3

Figure 4.4 – Atrophy map of the AD group compared to healthy controls



Statistical parametric maps of regional grey matter atrophy in the AD group compared to the healthy control group based on a voxel-based morphometry analysis of structural brain MR images. Maps are presented on a group mean T1-weighted MR image in MNI space, thresholded leniently at an uncorrected threshold of p < 0.01 for display purposes. The colour side bar codes voxel-wise t-values of grey matter change. Planes of representative sections are indicated using the corresponding MNI coordinates.

Table 4.3 – Summary of AD group regional grey matter atrophy

Region	Side	Cluster (voxels)	Peak (mm)			*t*-value
			x	y	z	
Hipp/EC	R	1198	35	-12	-39	5.91
Hipp/amygdala	L	602	-29	2	-26	5.82
ITG	R	568	47	-4	-38	5.73
	L	158	-50	-28	-18	5.08
ITS/MTG	R	118	65	-33	-15	4.50
ITG	L	515	-60	-55	-11	5.01
	L	115	-48	-6	-38	4.17
lateral OPC	L	95	-20	-84	30	4.83
medial OPC	L	66	-8	-85	39	5.08
PCC	R	71	11	-55	33	4.98
dlPFC	R	65	46	30	27	4.79
TPJ	L	56	-45	-54	25	4.01
MTG/STS	R	54	52	-51	10	4.87

Regions of significant regional grey matter atrophy in the AD group compared with the healthy control group in the VBM analysis. Associations shown are significant at threshold $p < 0.001$ uncorrected for multiple comparisons over the whole brain; all significant clusters > 50 voxels are shown and peak (local maximum) coordinates are in MNI space. dlPFC, dorsolateral prefrontal cortex; EC, entorhinal cortex; Hipp, hippocampus; ITG/S, inferior temporal gyrus/sulcus; L, left; MTG, middle temporal gyrus; OPC, occipito-parietal cortex; PCC, posterior cingulate cortex; R, right; STS, superior temporal sulcus; TPJ, temporoparietal junction.

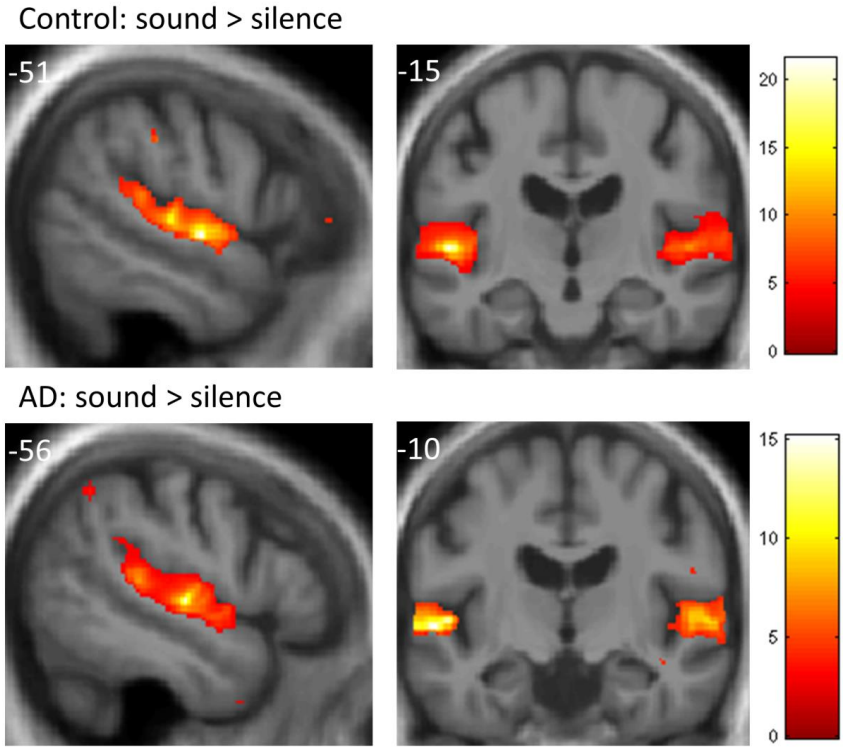
4.4.4 Functional neuroanatomy

Significant neuroanatomical findings from the fMRI analysis are summarised in Table 4.4 and statistical parametric maps for key contrasts and conditions are presented in Figure 4.6, Figure 4.7 and Figure 4.7. All reported contrasts were significant at $p < 0.05_{FWE}$ after multiple comparisons correction with pre-specified anatomical regions in clusters > 50 voxels.

Auditory stimulation (the contrast of all sound conditions over silence) produced as anticipated extensive bilateral activation of HG and STG, in both the healthy control and AD groups (Figure 4.5). Pitch variation (changing over fixed pitch) produced activation of right anterior STG and

STS in the healthy control group but no activation in the AD group at the prescribed threshold. Discrete auditory spatial variation (changing over fixed sound location) produced bilateral activation of posterior STG, PT and PCC in the healthy control group but no activation in the AD group at the prescribed threshold (Figure 4.6). No significant activations were identified for the 'reverse' contrasts of fixed over changing pitch or fixed over changing spatial location. The interaction of discrete spatial and pitch variation did not elicit significant activation in the healthy control group, however the AD group showed a significant interaction in right posterior insula.

Figure 4.5 – Functional neuroanatomy of auditory stimulation



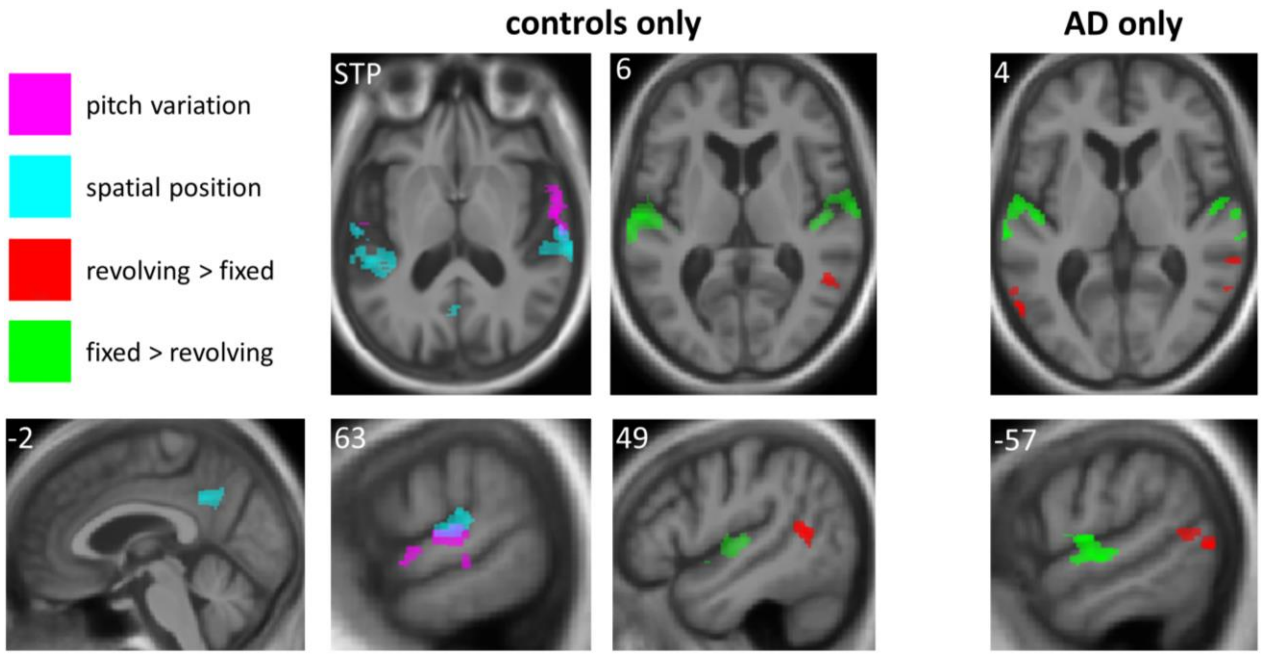
Statistical parametric maps show regions of greater activation for all sounds over silence [(PfSf + PfSc + PcSf + PcSc + PfSr) – silence] for the healthy control (top panels) and AD (bottom panels) groups. Clusters shown were significant at threshold $p < 0.05$ after correction for multiple comparisons within pre-specified anatomical regions of interest (see also Table 4.4); however maps have been thresholded at $p < 0.001$ uncorrected over whole brain for display purposes. The colour side bars code voxel-wise t-values of grey matter activation. Planes of representative sections are indicated using the corresponding MNI coordinates (mm).

Continuous auditory spatial variation (rotating over fixed sound location) produced activation in posterior MTG and STS in both the healthy control group and the AD group. The reverse contrast of fixed sound location over rotating sound produced bilateral activation of HG and anterior STG and STS in both groups (Figure 4.6). Comparing continuous with discrete spatial variation (rotating over changing sound location) revealed significant activation in left posterior MTG for the AD group whereas no significant peaks were found in the control group. For the reverse contrast of changing location over rotating sounds, both groups showed significant activation in bilateral posterior STG/HG.

When the AD and healthy control groups were compared directly, the effect of auditory spatial variation was significantly greater in the healthy control group than the AD group in posterior cingulate cortex (Figure 4.7). Post hoc analysis of condition beta weights revealed that this group-wise interaction was driven by significantly higher beta values in the control group for conditions with changing versus fixed auditory spatial location. Comparisons of activation yielded no significant voxels at the prescribed threshold when assessing contrasts pertaining to pitch variation or rotating sounds. The interaction of auditory spatial and pitch variation produced significantly greater activation of right posterior insula in the AD group versus the healthy control group (Figure 4.7); post hoc analysis of condition beta weights for this interaction revealed mirror beta profiles in the two groups but no significant pair-wise group or condition differences. Spearman's correlations were performed to assess any association between peak activation for specific contrast beta weights and performance on the out of scanner behavioural tasks in the patient group. There was a strong trend towards a significant correlation between peak activation in the posterior cingulate and performance in the spatial task ($r_{(s)}$ = 0.51, p = 0.06); however, no significant correlations were found

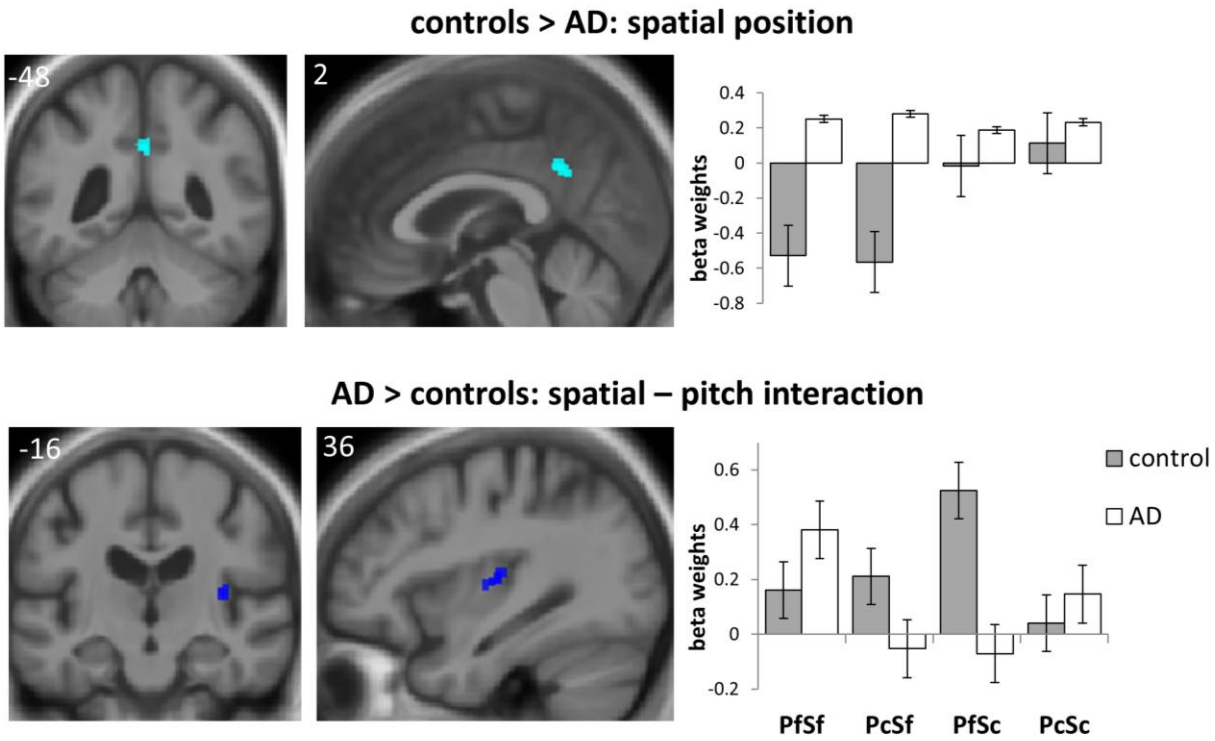
between the interaction contrast in the right posterior insula and performance on either the spatial ($r_{(s)}$ = -0.08, p = 0.78) or pitch ($r_{(s)}$ = -0.33, p = 0.24) tasks.

Figure 4.6 – Functional neuroanatomical data: within-group contrasts



Statistical parametric maps showing activation profiles for significant clusters in healthy control (left 5 panels) and AD (right 2 panels) groups. Clusters shown here were formed at an uncorrected whole-brain threshold of $p < 0.001$, but were significant after correction for multiple comparisons across the whole brain ($p < 0.05_{FWE}$). Maps are presented on a composite study specific mean image; the left hemisphere is shown on the left. For sagittal and coronal planes the slice is denoted by the relevant MNI coordinate. The axial slice shown here is tilted to best represent the activations seen along the superior temporal plane (STP). Significant clusters represented: magenta = changing pitch > fixed pitch [(PcSf + PcSc) – (PfSf + PfSc)]; cyan = changing position > fixed position [(PfSc + PcSc) – (PfSf + PcSf)]; red = rotating position > fixed position (rot – FpiFpo); green = fixed position > rotating position (PfSf – PfSr). PcSc, pitch changing, spatial location changing; PcSf, pitch changing, spatial location fixed; PfSc, pitch fixed, spatial location changing; PfSf, pitch fixed, spatial location fixed; PfSr, pitch fixed, spatial location rotating.

Figure 4.7 – Functional neuroanatomical data: between-group contrasts



Statistical parametric maps showing activation profiles for significant peak voxels after small volume correction comparing healthy control and AD groups. Clusters shown here incorporate these peak voxels. Maps are presented on a composite study specific mean image; the left hemisphere is shown on the left. For sagittal and coronal planes the slice is denoted by the relevant MNI coordinate. Top panels: control > AD activation for the contrast of changing position > fixed position [(PfSc + PcSc) – (PfSf + PcSf)], shown in cyan. Beta values at the peak voxel in PCC for each condition are shown top right. Bottom panels: AD > control for the *interaction* contrast of changing pitch vs changing position [(PcSc – PcSf) – (PfSc – PfSf)], shown in dark blue. Beta values at the peak voxel in right posterior insula for each condition are shown bottom right. PcSc, pitch changing, spatial location changing position; PcSf, pitch changing, spatial location fixed; PfSc, pitch fixed, spatial location changing; PfSf, pitch fixed, spatial location fixed.

Table 4.4 – Summary of fMRI data for experimental contrasts of interest in participant groups.

Group	Contrast	Region	Side	cluster (voxels)	Peak (mm)			t-value	p-value
					x	y	z		
HEALTHY CONTROLS	Sound > silence[a]	HG/STG	L	4236	-51	-15	1	21.51	<0.001
		HG/STG	R	2704	58	-27	12	9.96	<0.001
	Changing > fixed pitch[b]	Anterior STG/STS	R	477	59	2	-3	7.14	0.003
	Discrete changing > fixed location[c]	PT/posterior STG	L	933	-39	-37	15	8.69	0.001
		PT/posterior STG	R	584	66	-24	6	7.64	0.002
		PCC	L	318	0	-48	34	6.29	0.016
		PCC	R	109	2	-46	36	5.96	0.025
	Changing pitch vs. changing location[d]	Anterior STG/STS	L	53	-63	-12	4	6.34	0.008
	Revolving > fixed location[e]	Posterior MTG/STS	R	422	49	-51	9	6.69	0.019
	Fixed location > revolving[f]	Anterior STG/HG	L	781	-56	-18	3	11.12	<0.001
		Anterior STG/HG	R	1024	63	-7	1	9.37	<0.001
	Changing location > revolving[g]	Posterior STG	L	1141	-56	-16	4	12.89	<0.001
		Posterior STG	R	777	54	-18	3	9.36	<0.001
AD PATIENTS	Sound > silence[a]	HG/STG	L	3301	-56	-10	-2	14.72	<0.001
		HG/STG	R	2007	48	-16	4	10.18	<0.001
	Changing pitch vs. changing location[d]	Posterior insula	R	51	36	-16	7	7.52	0.005
	Revolving > fixed location[e]	Posterior MTG/STS	L	267	-65	-52	12	6.92	0.028
		Posterior STG/MTG	R	162	62	-40	12	7.67	0.014
	Fixed location > revolving[f]	Anterior STG/HG	L	541	-62	-15	0	6.82	0.010
		Anterior STG/HG	R	230	62	-10	-2	5.95	0.029
	Revolving > changing location[h]	Posterior MTG	L	59	-57	-58	1	8.40	0.005
	Changing location > revolving[g]	HG/STG	L	267	-48	-18	3	9.00	0.002

		posterior STG	R	368	54	-12	4	5.33	<0.001
CONTROLS >AD	Discrete changing > fixed location[c]	PCC	L	95	0	-48	34	4.51	0.049
		PCC	R	56	2	-48	34	4.51	0.049
AD > CONTROLS	Changing pitch vs. changing location[d]	Posterior insula	R	66	36	-16	9	4.77	0.016

Statistical parametric data summarising regional brain activations for contrasts between experimental conditions of interest, in each participant group and between groups. Contrasts shown within group represent significant peak voxels thresholded at a cluster-wise level across the whole brain ($p < 0.05_{FWE}$). No significant between group contrasts were found across the whole brain, but were further examined using small volumes of interest; these data are represented in bold. **a,** [(PfSf + PfSc + PcSf + PcSc + PfSr) – silence]; **b**, [(PcSc + PcSf) – (PfSc + PfSf)]; **c**, [(PcSc + PfSc) – (PcSf + PfSf)]; **d**, [(PcSc – PcSf) – (PfSc – PfSf)]; **e**, [PfSr – PfSf]; **f**, [PfSf – PfSr]; **g**, [PfSc – PfSr]; **h,** [PfSr – PfSc]. Conditions: PfSf = fixed pitch, fixed auditory spatial location; PcSf = changing pitch, fixed spatial location; PfSc = fixed pitch, changing spatial location; PcSc = changing pitch, changing spatial location.

4.5 Discussion

This study has revealed an altered functional neuroanatomical signature of auditory spatial processing in AD compared to the healthy older brain. Whilst no significant differences were found in neural response to pitch variation or continuous sound movement, discrete auditory spatial variation elicited altered patterns of activation in AD. In the healthy control group, the processing of pitch sequences activated anterior superior temporal cortex, consistent with previous evidence for pitch pattern analysis in the healthy younger brain (Patterson et al., 2002; Warren & Griffiths, 2003); while the processing of revolving sounds activated posterior temporal cortices in both the healthy control group and the AD group, also in line with normal functional neuroimaging work (Alho et al., 2014; Altmann et al., 2008). In contrast, the processing of sound location sequences activated right posterior lateral and medial temporoparietal junctional cortices in the healthy older group but not in the AD group, and this group activation difference was significant in PCC. Further altered activation compared with the healthy control group revealed a significantly greater interaction between pitch and spatial sequence processing in right posterior insula in the AD group. These functional neuroanatomical group differences were not associated with any disproportionate deficit in auditory spatial analysis in out-of-scanner behavioural testing. Furthermore, the functional neuroanatomical differences (in the case of the insular interaction effect) extended beyond the zone of disease-associated grey matter atrophy as characterised in a parallel structural neuroanatomical comparison between the groups. Taken together, these findings suggest that AD is associated with specific functional alterations in brain networks engaged in the processing of sound location.

As discussed in sections 1.3 and 1.6.7, PMC represents an area highly vulnerable to the pathological processes of AD and has been related to

auditory scene analysis involving both spatial and non-spatial components of ASA. The current findings build on work in chapter 3 where grey matter atrophy in right precuneus (one component of PMC) was associated with poorer performance on a task of spatial location discrimination, and further bolster the view that central auditory function is deficient in AD (see section 1.7.2).

Work on auditory spatial processing in the healthy brain has identified PMC in the reorienting of attention to particular locations (Mayer et al., 2006, 2007; Shomstein & Yantis, 2006), or more general attentional shifting control and self-awareness (Leech & Sharp, 2014; Vogt & Laureys, 2005). This may be particularly pertinent to the current stimuli as spatial position constantly shifted: as a passive listening paradigm was employed here this may also represent implicit tracking of a sound source or self-movement. As PMC is particularly vulnerable to both metabolic and structural insult in AD, generalised loss of grey matter in this region might plausibly account for the lack of activation in response to changing spatial location. However, when examining condition beta weights more closely, control activity in the peak voxel fell below baseline for fixed position sounds whereas there was no differentiation (and responses above or close to baseline) in the AD group. This pattern speaks to previous fMRI activation studies in AD, in which an inability to reduce activity in PMC was shown to influence memory task performance (Celone et al., 2006; Pihlajamäki & DePeau, 2008; Pihlajamäki & Sperling, 2009; Sperling et al., 2003, 2010). These results together would suggest that deactivation of PMC, coupled to activation of connected brain regions, may be essential for normal auditory spatial cognition.

Differential activation for the interaction of changing pitch and spatial sound components was also seen in the right posterior insula. The role of this region in auditory information processing continues to be defined.

Unlike PMC, the insula does not represent a core region of the DMN, but may act as a multimodal hub to integrate body state information with incoming external sensory input. It has been previously implicated in an alternate brain network (the 'salience network': Seeley et al., 2007) that acts to program behavioural responses to sensory stimuli, or may even mediate between default-mode and salience networks (Zhou & Seeley, 2014). Previous work assessing the auditory role of the insula has demonstrated involvement in the analysis of sound movement particularly motion relative to self (Griffiths et al., 1994, 1997; Lewis et al., 2000), however this multimodal region has functional subdivisions and a range of potentially relevant functions that have yet to be fully defined (Bamiou et al., 2003). It has been linked to fine-grained analysis of auditory timing cues (Bamiou et al., 2006) and the modulation of spatial by-nonspatial auditory object features (Altmann et al., 2008).

Insular activity is sensitive to cognitive load in the processing of musical and other sound patterns (Altmann et al., 2008; Nan et al., 2008) and to the detection of changes across sensory modalities (Downar et al., 2000): considered together with evidence that insula and its connections to DMN are affected relatively early in the course of AD (Xie et al., 2012), it is therefore plausible that the interaction of spatial and pitch pattern processing should engage this region more in the context of AD than in the healthy older brain, though the present study does not resolve whether this heightened activity is futile or compensatory. One account of AD has suggested a disruption of the equilibrium between the DMN and salience network (Seeley et al., 2009; Zhou & Seeley, 2014); a potentially unifying interpretation of the present findings might invoke a dysfunctional coupling between PCC and insular cortex in AD, leading to impaired ability to update mental representations of a sound source with shifting spatial and pitch trajectories. This would be consistent with a previously proposed role for PCC in tuning brain network activity between

internally and externally directed cognitive operations (Leech & Sharp, 2014).

Assessing auditory motion, no significant functional alterations in the AD group were found. This is in contrast to the strong behavioural and neuroanatomical signal shown in chapter 3. Both the healthy control and disease groups showed preferential processing for rotating sounds in posterior MTG, at the border with occipital cortex. Previous work, including the VBM findings of the previous chapter, indicate that IPL may be integral to auditory movement processing (Griffiths et al., 2000; Krumbholz et al., 2005; Lewis et al., 2000) contrary to the pattern observed here. However, some studies have highlighted the role of a visual motion processing region (V5) in auditory motion processing (Alink et al., 2012; Poirier et al., 2005). The 'reverse' contrast (fixed position sounds compared to rotating sounds) also activated predictably more anterior regions along the STG. Therefore despite the lack of STG/IPL activations, an anterior/posterior divide between revolving and non-revolving sounds was apparent. Within group contrasts also displayed differential activation between rotating and changing position sounds in MTG and STG regions. This could reflect either differential response to continuous versus intermittent sounds, or signify a difference between potential velocity processing and 'snapshot' processing (Blauert, 1997; Ducommun et al., 2004; Middlebrooks & Green, 1991). However, this study did not set out to directly test any hypothesis relating to such theories. A further caveat to these data relates to the conditions used in the study. Here we compared rotating, constant sound to intermittent sound. An ideal rotation control condition would be a constant sound matched for spectrotemporal properties in a fixed position (see the previous chapter and Warren et al., 2002). This in turn may also account for the apparent discrepancy between the current findings and previous work related to auditory motion processing.

Though this study's primary purpose was not to elucidate brain mechanisms of auditory 'what' and 'where' processing, support for this dichotomy can be found in the current results. In the control group, change in position elicited activity in bilateral posterior STG, posterior medial and motor cortices, whereas change in pitch saw greater activity in anterior STG, corroborating previous work (Arnott et al., 2004; Maeder et al., 2001; Rauschecker & Tian, 2000; Warren & Griffiths, 2003). Whilst the relatively small sample sizes reduce the power to detect weaker effects, there was no significant difference in activation between the AD and healthy control group in response to changing pitch. This may signify that the pathological process predominantly affects dorsal auditory stream neuroanatomy, in keeping with separable substrates for spatial and non-spatial auditory information. On the other hand, the data suggest that any separation of mechanisms is qualified: the reverse 'spatial' contrast between sound sequences with fixed location versus revolving sounds here produced activation extending anteriorly from Heschl's gyrus, perhaps reflecting temporal segmentation or a more stable pitch percept in the static 'baseline' sounds (Patterson et al., 2002). Ageing may itself reduce selectivity to spatial and nonspatial stimulus dimensions (Grady et al., 2011) and it is further possible that the enhanced interaction between pitch and spatial information in insula here reflects an amplification of this effect in AD.

This study has certain limitations that suggest directions for future work. Use of a passive listening paradigm was designed to address mechanisms of obligatory perceptual analysis. However, these mechanisms are likely to be modulated by output task, memory and attentional demands (Warren et al., 2005) and by mechanisms for coding behavioural stimulus salience that may also be altered in AD (Fletcher et al., 2015). Such factors should be investigated explicitly, especially in the context of successful

and unsuccessful perceptual discrimination, which would aid in separating compensatory from futile activation patterns. Additionally, auditory spatial processing is not the only auditory function affected in AD (see section 1.7.2). These two chapters have focussed on the spatial aspects of central auditory function, however this comprises just one facet of ASA. fMRI has provided a useful tool in assessing auditory dysfunction in the AD brain. As generic ASA segregation and grouping ability appears to be deficient in AD (Goll et al., 2012), the next chapter seeks to investigate non-spatial ASA cognition at a neuroanatomical functional level.

5 AUDITORY MASKING IN AD: AN FMRI INVESTIGATION

5.1 Introduction

As discussed in section 1.6.2, ASA is a formidable computational process. Applying these principles to the everyday situations our auditory system encounters, segregating auditory 'foreground' from 'background' often requires matching of incoming spectrotemporal cues to previously learned templates (Billig et al., 2013; Bregman, 1990; Griffiths & Warren, 2002; Kumar et al., 2007). The 'cocktail party effect' (Cherry, 1953; Moray, 1959) exemplifies the use of a well learned auditory template (own name) over 'background', representing the processing of salient stimuli when 'masked' by other information that can compete for resources both peripherally and cortically (Scott & McGettigan, 2013). However, the precise neuroanatomical substrates underpinning this process have yet to be clearly defined. Previous work in healthy populations has implicated a distributed, dorsally directed cortical network including PT and posterior STG, supramarginal gyrus (SMG), IPS and prefrontal projection targets (Dykstra et al., 2011; Gutschalk et al., 2007; Hill & Miller, 2010; Kondo & Kashino, 2009; Overath & Kumar, 2010; Wilson et al., 2007; Wong et al., 2009). The role of frontal and parietal inputs into this network range from primary labelling of salient events (Cohen, 2009; Downar et al., 2000), integration of signal representations for programming behavioural responses (Cusack, 2005; Lee et al., 2014a) or attentional modulation (Hill & Miller, 2010; Nakai et al., 2005). Cocktail party processing frequently involves speech, which in turn may mediate the involvement of particular brain regions (Billig et al., 2013; Davis et al., 2011; Scott & McGettigan, 2013a; Scott et al., 2000, 2004, 2009).

The involvement of ASA and masking in AD can be predicted on both behavioural and neuroanatomical grounds. Previous evidence discussed in section 1.7 illustrates generic central auditory and specific ASA deficits

in AD; this combined with clinical observations of patients' difficulties in noisy situations and impairments of attention and working memory (Stopford et al., 2012) would suggest that AD affects brain mechanisms required for successful cocktail party processing. This is further supported by the overlap in regions linked to successful ASA and the DMN regions particularly targeted in AD. In particular, temporoparietal junction has been associated with hearing speech in noise in elderly subjects using fMRI (Wong et al., 2009); a PET study elicited mPFC (Salvi et al., 2002).

This study set out to use a realistic ASA paradigm in the context of fMRI, in order to probe functional brain mechanisms associated with both the segregation of auditory foreground from background and the processing of intelligible speech. This was motivated by the idea that we use previous knowledge to match incoming acoustic signals to spectrotemporal templates/schema and that this aids in the parsing of auditory scenes (Bregman, 1990; Griffiths & Warren, 2002). Participants' own names were used as highly salient acoustic targets (Moray, 1959; Wood & Cowan, 1995) with naturalistic multi-speaker babble as background. The crucial effect of processing own name over background in relation to the stimuli in question is therefore interpreted as an interaction between segregation of auditory foreground from background, and sound identity representation. This study made use of a passive listening paradigm, aiming to reduce any confounding effects of task output in cognitively impaired patients.

5.2 Hypotheses

Two main hypotheses arise for this investigation: 1) patients with AD and healthy older individuals will show similar profiles of auditory cortex activation in response to sound and representation of name identity; 2) ASA functions requiring template matching alongside object segregation will show differences between patients and controls, specifically in

temporoparietal regions associated with altered metabolism in AD and also one of the key substrates for ASA.

5.3 Methods

5.3.1 Participants

13 consecutive typical AD patients (5 female) and 17 age-matched healthy controls (7 female) participated in the study. All participants were right-handed and none were professional musicians. Demographic, clinical and neuropsychological data for the experimental groups are summarised in Table 5.1. Peripheral hearing ability was assessed in the right ear for each participant. At the time of participation, 12 patients were receiving symptomatic treatment with an acetylcholinesterase inhibitor (one was also receiving memantine). CSF examination was undertaken in 6 patients with AD and revealed a total tau: beta-amyloid$_{1-42}$ ratio > 1 (compatible with underlying AD pathology) in all cases.

Table 5.1 – General demographic, clinical, neuropsychological and behavioural data for participant groups

Characteristics	Healthy controls	AD
General		
No. (m:f)	17 (8:9)	13 (8:5)
Age (yrs)	68.3 (3.9)	65.7 (5.6)
Education (yrs)	15.8 (3.0)	13.4 (3.2)*
Musical training (yrs)	1.5 (2.6)	3.0 (2.8)
MMSE	28.8 (0.9)	19.7 (6.5)*
Symptom duration (yrs)	-	4.9 (1.7)
Neuropsychological assessment		
General intellect: IQ		
WASI verbal IQ	118.6 (8.1)	87.1(22.3)*
WASI performance IQ	118.1(15.1)	83.5(17.4)*
NART estimated premorbid IQ	119.7 (5.7)	103.9(16.5)*
Episodic memory		
RMT words (/50)	46.2 (2.8)	**30.6 (6.9)***
RMT faces (/50)	43.1 (4.6)	**33.5 (7.1)***
Executive skills		
WASI block design (/71)	42.4(16.6)	12.6(13.7)*
WASI matrices (/32)	29.4(14.9)	12.8 (9.6)*
WMS-R digit span forward (/12)	8.6 (1.8)	6.1 (2.1)*
WMS-R digit span backward (/12)	6.6 (2.2)	4.5 (2.8)*
D-KEFS Stroop colour (s) [a]	33.0 (7.1)	**53.3(18.0)***
D-KEFS Stroop word (s) [a]	22.4 (4.5)	**41.4(25.6)***
D-KEFS Stroop interference (s)[a]	62.2(16.7)	**102.1(32.9)***
Verbal skills		
WASI vocabulary (/80)	68.1 (4.5)	45.2(20.2)*
WASI similarities (/48)	41.1 (9.0)	23.1(12.8)*
GNT (/30)	24.9 (3.2)	**12.9 (8.5)***
BPVS (/150)	146.8 (3.0)	123.8(28.8)*
NART (/50)[b]	41.2 (4.6)	30.2(12.2)*
Posterior cortical skills		
GDA (/24)[c]	15.6 (3.5)	6.4 (4.9)*
VOSP object decision (/20)	18.2 (1.5)	14.8 (2.9)*
Post-scan behavioural tasks		
Name detection (/20)	19.9 (0.3)	19.0 (1.5)
Segregation detection (/20) [b]	17.1 (2.7)	12.2 (4.1)*

Values are mean (standard deviation) unless otherwise stated. Raw data are shown for neuropsychological tests (maximum score in parentheses); results in bold indicate mean score < 5th percentile for normative data according to mean group age (not available for BPVS). * significantly different to healthy control group ($p < 0.05$); **a** 10 ADs; **b** 12 ADs; **c** 9 ADs.

5.3.2 Experimental design and stimuli

Stimuli were created by manipulating two key components of ASA: template processing and sound object segregation. Auditory templates ('foreground' stimuli) were manipulated by presenting participants' own name either in its raw or spectrally rotated form. Spectral inversion preserves the acoustic complexity of the sound, but renders it unintelligible (Blesser, 1972; Scott et al., 2000). These foreground targets were then either superimposed over, or interleaved with acoustic background stimulus (multi-speaker babble) to control the requirement for object segregation. The interaction of processes that mediate auditory object segregation and template matching indexes the detection of own name in a busy auditory scene. These manipulations gave rise to four experimental conditions in a factorial design:

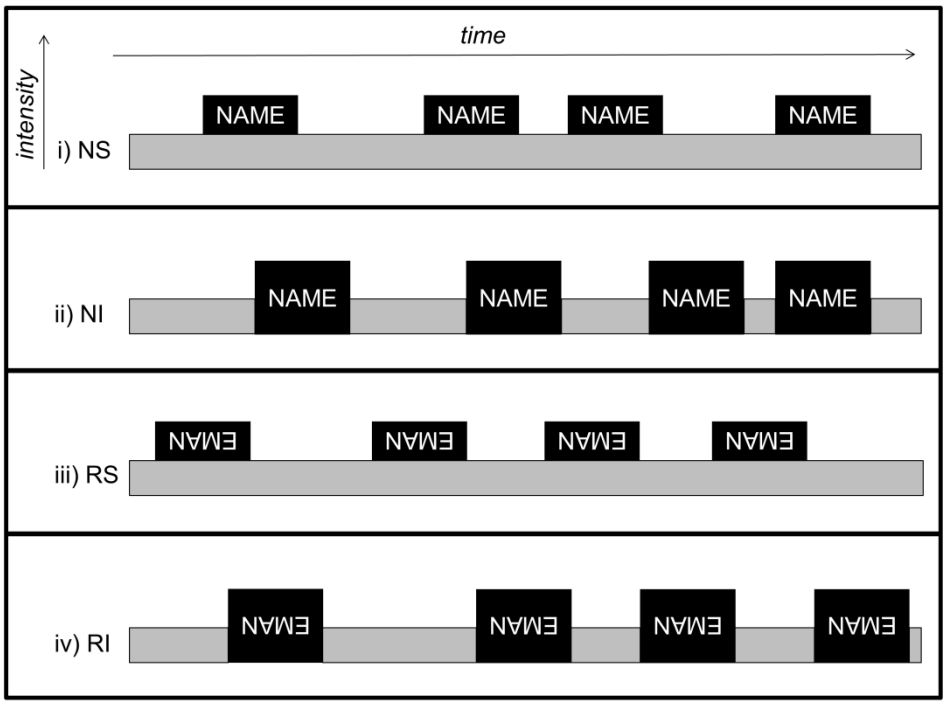
1) NS: own natural name superimposed on babble
2) NI: own natural name interleaved with babble
3) RS: spectrally rotated name superimposed on (spectrally rotated) babble
4) RI: spectrally rotated name interleaved with (spectrally rotated) babble

Each participant's own first name was recorded in a sound-proof room, by the same young adult female speaker using a Standard Southern English accent. Recorded name sounds were spectrally rotated using a previously described procedure that preserves spectral and temporal complexity but renders speech content unintelligible (Blesser, 1972). An acoustic 'background' of speech babble was created by superimposing recordings of 16 different female speakers reading passages of English from the EUROM database of English speech (Chan et al., 1995) using a previously described method (Rosen et al., 2013); no words were intelligible from the sound mixture. Babble samples were spectrally rotated in order to provide an acoustic background for the spectrally rotated name sounds

that reduced any spectral 'pop-out' effects. The signal-to-noise ratio of names to background babble was fixed at 17 dB, corresponding to a moderately noisy (e.g., cocktail party) environment (International Telecommunication Union, 1986). This ratio is much higher than conventional speech-in-noise studies; however it maintains perceptual stability in a passive listening paradigm lacking behavioural output.

To create experimental trials, name and rotated name sounds were added to corresponding (raw or spectrally rotated) babble samples by either superimposing on or interleaving with babble; name sounds were repeated four times within a single trial and the total duration of each trial was fixed at 8s (duration of individual name exemplars 0.6s to 0.9s; experimental trials schematised in Figure 5.1). 20 unique trials were created for each condition by randomly varying the onsets of the target within the 8s sound trial. An additional rest baseline condition comprising 8s silent intervals was included in the scanning protocol.

Figure 5.1 – Schematic representation of fMRI stimulus conditions



Dark grey boxes signify presentations of participant's own name, in either natural or spectrally rotated (inverted) form; light grey boxes represent the acoustic background (multi-talker babble). Onsets of name exemplars were varied randomly between trials; each trial was 8s in total duration.

5.3.3 Procedure

5.3.3.1 Stimulus presentation

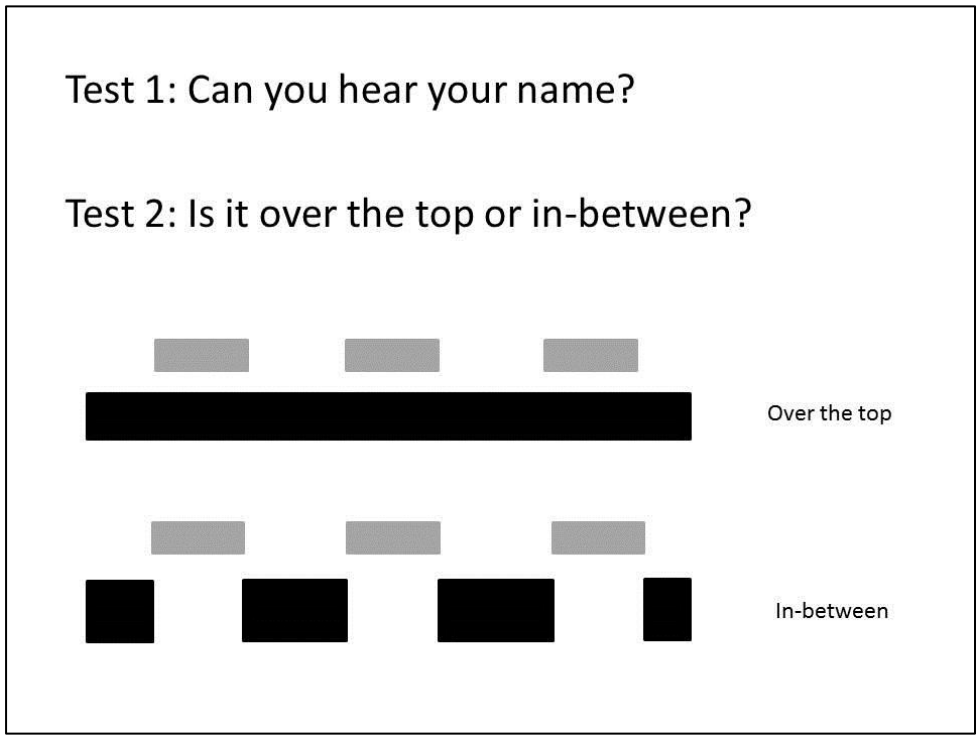
In the fMRI session, experimental trials were each triggered by the MR scanner on completion of the previous image acquisition in a 'sparse' acquisition protocol. 2 identical scanning runs were administered, each comprising 20 trials for each sound condition plus 10 silence trials, yielding a total of 180 trials for the experiment. Participants were instructed to listen to the sound stimuli with their eyes open; there was no in-scanner output task and no behavioural responses were collected.

5.3.3.2 Post-scan behavioural task

Following the scanning session, each participant's ability to perceive and discriminate the experimental conditions presented during scanning was assessed using a two alternative forced choice psychoacoustic procedure. 20 auditory stimuli representing all sound conditions (5 each of NS, NI, RS

and RI) were derived from the same component stimuli used in the scanner, but with a duration of 4s with two foreground 'targets' per trial. In the first test, the task (name detection) was to determine whether or not the participant's own name was present (discrimination of NS/NI from RS/RI conditions); in the second test, the task (segregation detection) was to determine whether the two kinds of sounds (name and babble) were superimposed or interleaved ('Are the sounds over the top or in-between?'; discrimination of NS/RS from NI/RI conditions), assisted by a visual guide (see Figure 5.2). It was established that participants understood the tasks prior to commencing the tests; during the tests, no feedback about performance was given and no time limits were imposed. All participant responses were recorded for off-line analysis. 2 of the AD patients could not demonstrate an understanding of the segregation detection task therefore did not complete this section.

Figure 5.2 – Visual guide shown to participants in post-scan behavioural testing



For the segregation detection task, the 'foreground' sound (grey) was either the participant's natural spoken name or its spectrally rotated (unintelligible) analogue; the 'background' sound (black) was either 16-talker babble or its spectrally rotated analogue. The task instruction on each trial was to decide whether the two kinds of sounds ('grey' and 'black') were 'over the top' (superimposed) or 'in-between' (interleaved).

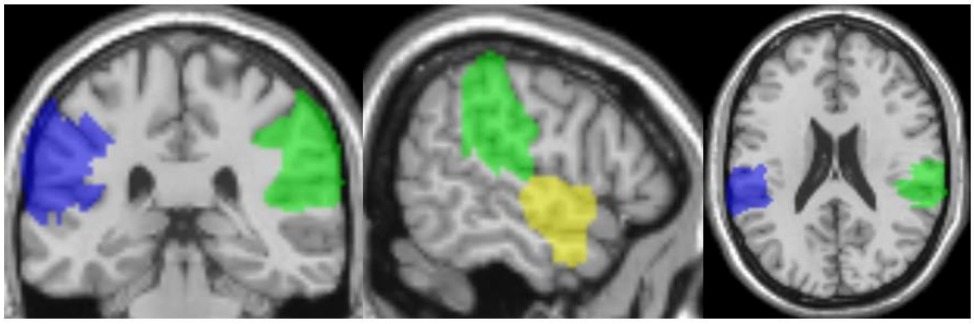
5.3.4 fMRI analysis

Pre-processed functional images (see section 2.8.2) were entered into a first-level design matrix incorporating the 5 experimental conditions (NS, NI, RS, RI and the baseline silence condition) as described in section 2.9.3.2. For each participant, first-level t-test contrast images were generated for the main effects of auditory stimulation [(NS + NI + RS + RI) – silence], identification of own name [(NS + NI) – (RS + RI)] (in the absence of a specific output task during scanning, we use 'identification' here to indicate specific processing of own-name identity in relation to an acoustically similar perceptual baseline), and segregation of auditory foreground from background [(NS + RS) – (NI + RI)]. In addition, contrast

images were generated for the interaction of identification and segregation processes [(NS - RS) – (NI - RI)], representing the overall effect of processing name over background ('name-segregation interaction'). Both 'forward' and 'reverse' contrasts were assessed in each case. Contrast images for each participant were entered into a second-level random-effects analysis in which effects within each experimental group and between the healthy control and AD groups were assessed using voxel-wise t-test contrasts.

Contrasts were assessed at peak voxel statistical significance in two anatomical small volumes of interest, specified by the prior hypotheses (Dykstra et al., 2011; Goll et al., 2012; Overath & Kumar, 2010; Scott et al., 2000, 2009; Wong et al., 2009) These regional volumes comprised temporoparietal junction (including superior temporal and adjacent IPL posterior to HG; previously suggested to be involved in ASA) and STG anterior and lateral to HG (the putative substrate for name identity coding); a combined regional volume with addition of HG was used to assess the overall effect of auditory stimulation (e.g. (NS + NI + RS + RI) – silence). These regions are shown in Figure 5.3.

Figure 5.3 – Small volumes used for analysis of functional data



Representative slices illustrate the extent of the areas used to investigate voxel activity in small volumes. Green (right) and blue (left) areas indicate the small volume posterior to HG and yellow represents the volume anterior to HG.

5.3.5 Voxel-based morphometry analysis

Statistical parametric maps (see sections 2.8.1 and 2.9.3.1) of brain atrophy were thresholded leniently ($p < 0.01$ uncorrected over the whole brain volume) in order to capture any significant grey matter structural changes in relation to functional activation profiles from the fMRI analysis.

5.3.6 Behavioural analysis

In the analysis of post-scan behavioural data, a 'name-segregation interaction' measure was generated as the d-prime of name detection in the superimposed and interleaved conditions; the main effect of group and any interactions between test type and group were assessed for all test measures (name detection score/segregation detection score/name-segregation interaction d-prime). In the AD group, correlations between individual post-scan test performance measures and peak effect sizes (beta estimates) for fMRI contrasts of interest were assessed using linear regression with robust, cluster-adjusted standard error: name detection performance was correlated with peak activation in the name identification contrast; segregation detection performance with the segregation contrast; and d-prime with the name-segregation interaction contrast.

5.4 Results

5.4.1 Demographic, neuropsychological and peripheral audiometry characteristics

The patient and healthy control groups did not differ significantly in age ($t_{(28)} = 1.51$, $p = 0.14$), gender distribution ($\chi^2_{(1)} = 0.62$, $p = 0.43$) or years of musical training ($t_{(28)} = -1.48$, $p = 0.15$); the healthy control group had on average significantly more years of education ($t_{(28)} = 2.08$, $p = 0.048$), though participants in both groups overall were relatively highly educated (see Table 5.1). Tone detection thresholds (in ms) on audiometry testing did not differ between the patient and healthy control groups (beta =

3420, CI -673 to 7514, p = 0.10). There was a significant interaction between group and frequency [$F_{(4,30)}$ = 3.14, p = 0.03] however this was driven by the effect of frequency type within group and tests for each frequency revealed no differences between AD and healthy control groups. Neuropsychological profiles (see Table 5.1) revealed significantly worse performance on all cognitive tasks in the AD group compared to controls. This profile likely reflects both the global cognitive impairment and perhaps the lower educational level of the AD group, however an AD profile is corroborated by their specific weaknesses in tests of memory, executive function and naming.

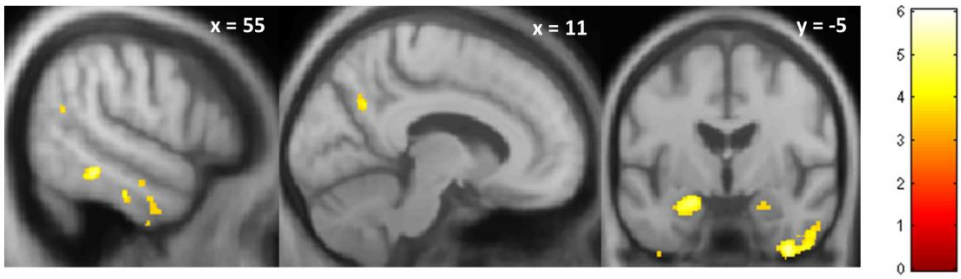
5.4.2 Post-scan behavioural task

Group performance data for the post-scan behavioural tests are presented in Table 5.1. There was a significant main effect of test type (name detection/segregation detection: beta = -2.82, CI -4.24 to -1.41, p < 0.001) and a strong trend to a main effect of group (beta = -0.88, CI -1.77 to 0.003, p = 0.051). There was a significant interaction between group and test type (F(1,29) = 9.29, p = 0.005): these results were driven by poorer performance of the AD group than the healthy control group on the auditory segregation detection task (t = 3.61, p = 0.001). Wald tests also revealed significantly superior performance on name than segregation detection in both healthy individuals (t = 4.09, p < 0.001) and patients (t = 6.11, p < 0.001). There was no significant interaction between group and name-segregation interaction d-prime ($F_{(1,29)}$ = 2.75, p = 0.11).

5.4.3 Structural neuroanatomy

Comparison of the AD and healthy control groups in the VBM analysis revealed the anticipated profile of AD-associated regional grey matter atrophy involving hippocampi, temporal and posterior medial cortex; statistical parametric maps are presented in Figure 5.4 with further details of regional atrophy shown in Table 5.2 .

Figure 5.4 – Atrophy map of the AD group compared to healthy controls



Statistical parametric maps of regional grey matter atrophy in the Alzheimer's disease group compared to the healthy control group based on a voxel-based morphometry analysis of structural brain MR images. Maps are presented on a group mean T1-weighted MR image in MNI space, thresholded leniently at $p < 0.01$ uncorrected for multiple comparisons over whole brain. The colour side bar codes voxel-wise t-values of grey matter change. Planes of representative sections are indicated using the corresponding MNI coordinates.

Table 5.2 – Summary of AD group regional grey matter atrophy

Region	**Side**	**Cluster** (voxels)	**Peak** (mm)			***t*-value**
			x	y	z	
Posterior MTG	R	2187	60	-36	-15	6.03
MTG	L	566	-65	-21	-23	4.10
Hippocampus	L	395	-23	-4	-20	4.06
ITG	L	276	-47	-33	-24	4.81
Posterior ITG	L	574	-57	-34	-20	4.70
PCC	R	54	11	-60	33	4.51
Posterior ITG	L	57	-48	-61	-15	4.15

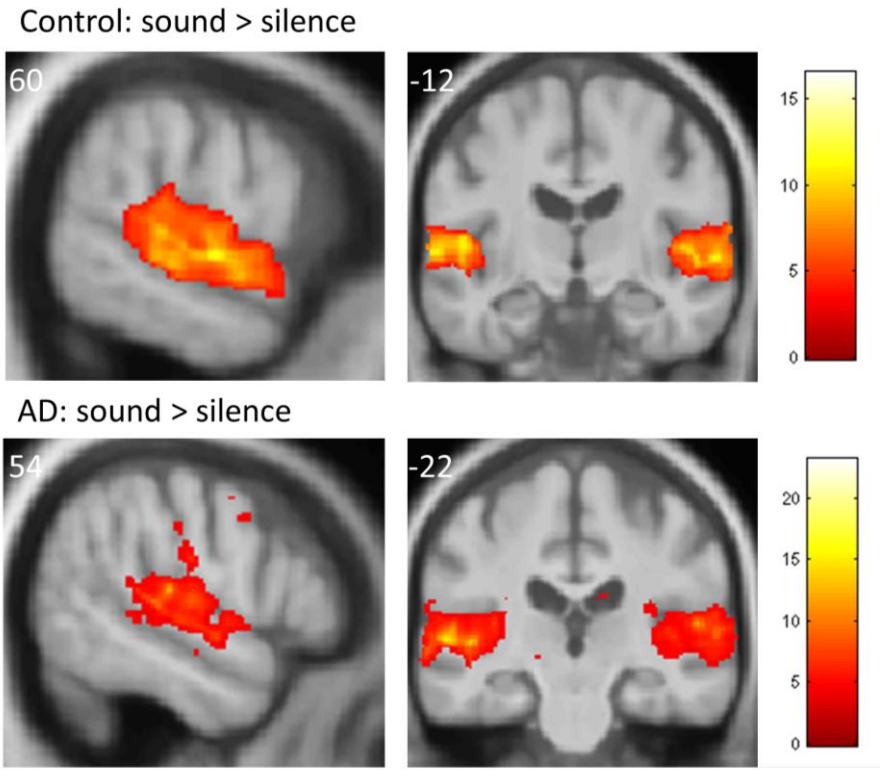
Regions of significant regional grey matter atrophy in the Alzheimer's disease group compared with the healthy control group in the VBM analysis. Associations shown were significant at threshold $p < 0.01$ uncorrected for multiple comparisons over the whole brain; all significant clusters > 50 voxels are shown and peak (local maximum) coordinates are in MNI space. ITG, inferior temporal gyrus; L, left; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; R, right.

5.4.4 Functional neuroanatomy

Significant neuroanatomical findings from the fMRI analysis are summarised in Table 5.3 and statistical parametric maps for key contrasts

and conditions are presented in Figure 5.5, Figure 5.6 and Figure 5.7. All reported contrasts were significant at threshold $p < 0.05_{FWE}$, corrected for multiple voxel-wise comparisons within anatomical regions of interest specified by our prior experimental hypotheses. Auditory stimulation (the contrast of all sound conditions versus silence) was associated, as anticipated, with extensive bilateral activation involving STG in both the AD and healthy control groups (Figure 5.5); no significant differences between groups were identified and there was no significant activation associated with the reverse contrast.

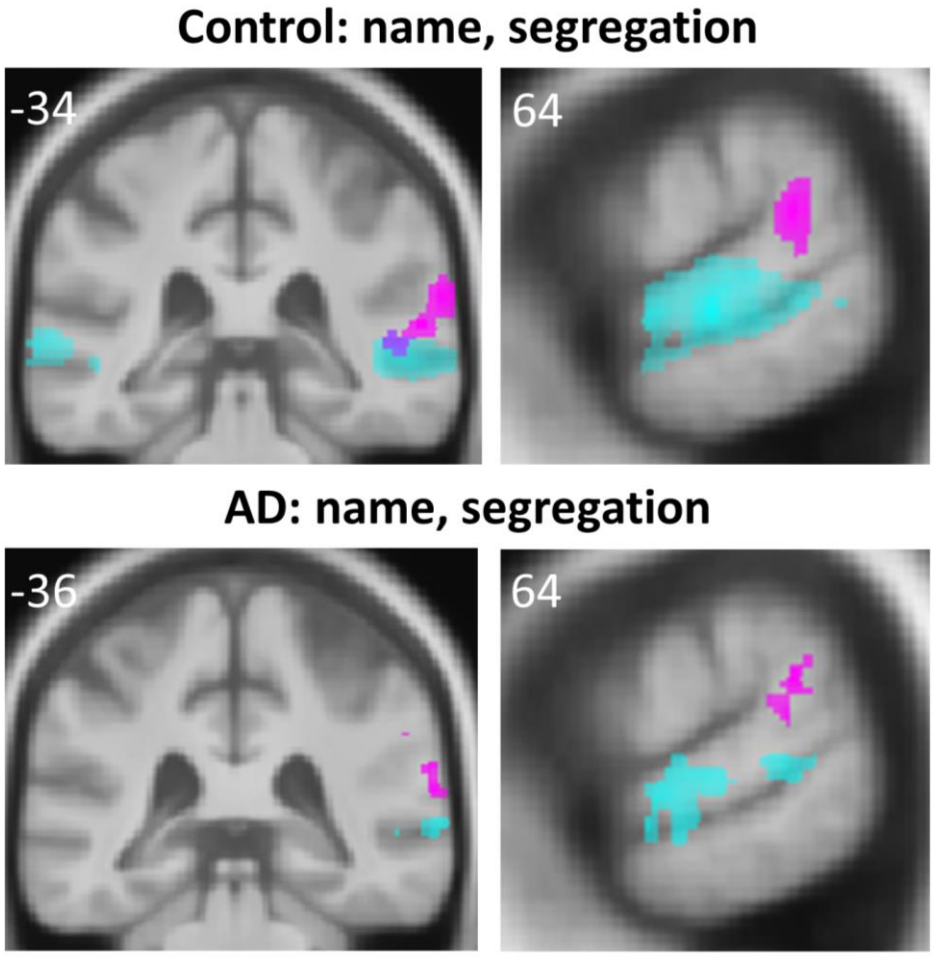
Figure 5.5 – Functional neuroanatomy of auditory stimulation



Statistical parametric maps show regions of greater activation for all sounds over silence [(NI + NS + RI + RS) – silence] for the healthy control (top panels) and AD (bottom panels) groups. Clusters shown were significant at threshold $p < 0.05$ after correction for multiple comparisons within pre-specified anatomical regions of interest (see also Table 5.3); however maps have been thresholded at $p < 0.001$ uncorrected over whole brain for display purposes. The colour side bars code voxel-wise t-values of grey matter activation. Planes of representative sections are indicated using the corresponding MNI coordinates (mm).

Identification of own name compared with spectrally rotated analogues produced extensive bilateral activation of STG and STS in both the AD and the healthy control groups (Figure 5.6); no significant activations were associated with the 'reverse' contrast in either group. In the contrast assessing auditory object segregation processing, no significant activations were found in either group for the 'forward' contrast, however right PT and posterior STG were more activated in the interleaved than superimposed sound conditions (i.e., in the 'reverse' contrast: [(NI + RI) – (NS + RS)]) in both the AD and the healthy control groups; healthy individuals showed additional activation in an inferior parietal junctional area (SMG), also show in Figure 5.6. The contrast to assess the interaction of own name identification with auditory segregation processing produced no significant activations in the healthy control group but significant activation of right SMG in the AD group.

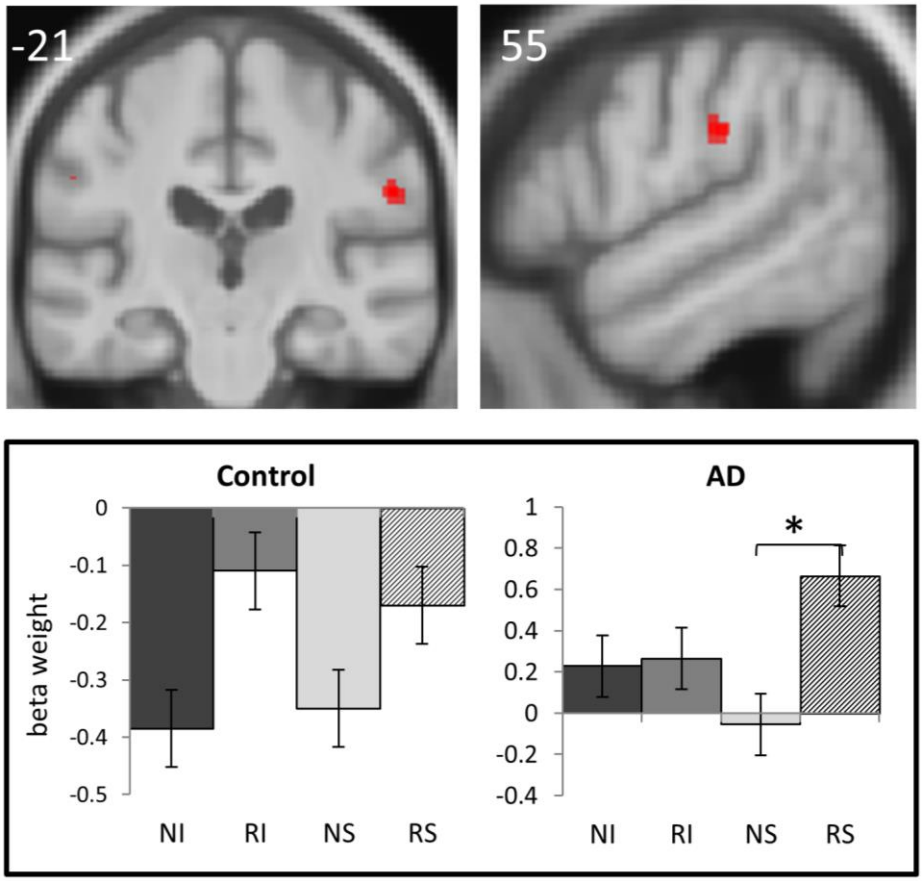
Figure 5.6 – Functional neuroanatomical data – within group contrasts



Statistical parametric maps of regional brain activation for contrasts of interest in the healthy control (top) and AD (bottom) groups, rendered on coronal and sagittal sections of the study-specific group mean T1-weighted structural MR image in MNI space. The coordinate of each section plane is indicated and the right hemisphere is shown on the right in all coronal sections. Maps have been thresholded at $p < 0.001$ uncorrected over whole brain for display purposes; activations shown were significant at $p < 0.05$ after FWE correction for multiple comparisons over an anatomical small volume of interest. Contrasts were composed as follows: name identification (cyan), [(NS + NI) – (RS + RI)]; auditory object segregation processing (magenta: reverse contrast), [(NI + RI) – (NS + RS)].

When comparing activation between the healthy control and AD groups, no significant differences were found in the conditions assessing name or object segregation processing. However, there was a significant difference between groups for this contrast in right SMG (see Table 5.3 and Figure 5.7). To further investigate this disease-associated modulation of name-segregation interaction in SMG, we conducted an exploratory post hoc analysis of condition effects for both the AD and healthy control groups. Beta parameter estimates in each sound condition relative to the baseline silence condition were compared using pair-wise t-tests (bonferroni corrected) at the peak voxel of activation for the name-segregation interaction contrast. In the AD group, activation in the RS condition was significantly greater than both the NS condition ($t(12) = 3.01$, $p = 0.03$) and the RS condition in the healthy control group ($t(28) = 3.47$, $p = 0.02$); there were no other significant sound condition differences within or between groups. The correlation analysis of peak-voxel beta contrast estimates and post-scan behavioural performance in the AD group revealed no significant relation for name identification (left anterior STG: $r = -0.23$, $p = 0.45$; right anterior STG: $r = 0.22$, $p = 0.48$) but a near-significant trend for segregation processing (right posterior STG: $r = -0.56$, $p = 0.06$). Beta estimates for the name-segregation interaction contrast were significantly correlated with name-segregation interaction d-prime ($r = -0.66$, $p = 0.01$).

Figure 5.7 – Functional neuroanatomical data – between group contrasts



Statistical parametric maps (panels top row, bottom left) of regional brain activation for the between-group name-segregation interaction; beta weights (group mean ±1 standard error peak voxel beta parameter estimates) for each experimental condition at the right SMG peak from the name-segregation interaction are also shown (*indicates significant difference in effect size between conditions, $p < 0.01$). Maps are rendered on coronal and sagittal sections of the study-specific group mean T1-weighted structural MR image in MNI space and thresholded at $p < 0.001$ uncorrected over whole brain for display purposes; activations shown were significant at $p < 0.05$ after FWE correction for multiple comparisons over an anatomical small volume of interest. The contrast here indicates the interaction of auditory object and segregation processing [(NI – RI) – (NS – RS)]. The coordinate of each section plane is indicated and the right hemisphere is shown on the right in all coronal sections.

Table 5.3 – Summary of fMRI data for experimental contrasts of interest in participant groups.

Group	Contrast	Region	Side	cluster (voxels)	Peak (mm)			*t*-value	*p*-value
					x	y	z		
HEALTHY CONTROLS	Sound versus silence	HG	L	4344	-44	-21	4	12.10	<0.001
		Mid STG	R	4635	60	-12	-2	11.56	<0.001
	Name identification*	Mid STG/STS	L	1788	-56	-13	-2	10.31	<0.001
			R	1989	66	-16	-5	11.38	<0.001
		Post STG	L	219	-62	-24	1	8.22	0.001
			R	35	65	-18	6	5.46	0.039
	Segregation processing**	PT/ SMG	R	172	65	-36	19	5.68	0.028
AD PATIENTS	Sound versus silence	Mid STG	L	3639	-56	-21	3	23.14	<0.001
		Post STG	R	3990	54	-22	10	11.79	<0.001
	Name identification	Ant STG/STS	L	652	-59	0	-15	8.34	0.003
			R	1073	62	-1	-6	8.34	0.003
	Segregation processing	Post STG/PT	R	67	65	-37	24	6.48	0.047
	Name-segregation interaction	SMG	R	39	55	-22	28	6.47	0.048
PATIENTS > CONTROLS	Name-segregation interaction	SMG	R	57	55	-21	28	6.06	0.002

Statistical parametric data summarising regional brain activations for contrasts between experimental conditions of interest, in each participant group and between groups. All contrasts shown are thresholded at $p<0.05_{FWE}$ after multiple comparisons correction in pre-specified anatomical small volumes. *contrast [(NS + NI) – (RS + RI)]; **contrast [(NI + RI) - (NS + RS)]; ***contrast [(NI – RI) – (NS – RS)] where NI is own natural name interleaved with babble, NS own natural name superimposed on babble, RI spectrally rotated name interleaved with babble, RS spectrally rotated name superimposed on babble; no significant activations were identified for the 'forward' segregation contrast [(NS + RS) - (NI + RI)] in either participant group, for the name-segregation interaction contrast in the healthy control group or for auditory stimulation, name identification or segregation processing between groups. AD, Alzheimer's

disease; Ant, anterior; HG, Heschl's gyrus; Post, posterior; PT, planum temporale; SMG, supramarginal gyrus; STG, superior temporal gyrus; STS, superior temporal sulcus.

5.5 Discussion

To highlight the main findings, this study has demonstrated differentiable activation in the context of interaction between sound segregation and name processing in AD. However, this interaction is difficult to unpick when considering the significant reverse contrasts found. Within the temporoparietal area of interest, a region in right IPL showed altered activation for the interaction of sound template and segregation processing. Higher-order ASA functions (Dykstra et al., 2011; Kondo & Kashino, 2009; Kong et al., 2014; Linden et al., 1999) and metabolic abnormality in AD (Buckner et al., 2005; Matsuda, 2001) converge on this neuroanatomical locus, which suggests that dysfunction of DMN areas such as IPL affects the processing of auditory scenes. The neural dysfunction exhibited in this study builds on previous work indicating central auditory deficits in the AD population by demonstrating a functional impairment, confirming hypotheses that complex auditory scene perception suffers from cortical alterations. This work also utilises relatively ecologically valid stimuli, illustrating how generic deficits can translate into neural processing dysfunction for real life auditory situations.

Returning to more general findings, both the AD and control group showed similar patterns of activation in right anterior STG and STS for template (name) processing. This is in line with previous work showing greater activity in superior temporal areas beyond HG for intelligible speech (Davis et al., 2011; Meyer et al., 2005; Obleser et al., 2008; Scott et al., 2000), perhaps reflecting both spectrotemporal template matching and lexical access. Using the same stimuli as in the scanner, the behavioural findings in the current study indicate that both patient and control groups could adequately identify their own name, suggesting that the activation pattern observed reflects adequate perceptual processing. One drawback of the current paradigm is that the contrasts compared

naturally presented name with its spectrally rotated version, as well as the inclusion of both interleaved and superimposed trials; therefore spectrally rotated name was also concurrent with spectrally rotated background. The stimuli were constructed this way to prevent spectral 'pop out' of rotated template over naturally presented babble, however future work could clarify the effects of spectral rotation itself versus template-matching processes, using alternative speech degradation methods or auditory target objects.

A somewhat less intuitive finding was that of segregation processing. Here the *reverse* contrast yielded significant activation in right posterior STG in both patient and control groups. Interleaved trials elicited greater activity than superimposed in an area highly linked to template processing and auditory stream segregation, contradictory to the idea that superimposed sounds should place greater computational demand on these regions (Deike et al., 2004, 2010; Gutschalk et al., 2007; Nakai et al., 2005; Smith et al., 2010; Wilson et al., 2007; Zatorre et al., 2002a). There are a number of possible explanations for this unusual finding. Firstly, the signal-to-noise ratio was much higher than in conventional studies of speech-in-noise processing, which may not have taxed posterior STG to the same degree in the superimposed conditions. However some studies have also found enhanced activation in temporal regions for speech in quiet compared to speech in noise at lower ratios than the in the current study (Hwang et al., 2007, 2006). Repeated name stimuli may have led to habituation of posterior STG over the 8s sound period. There is also the possibility that reduced intelligibility of the superimposed trials induced less activation (Scott & McGettigan, 2013a), however the high performance on the name detection task performed outside of the scanner would suggest otherwise. One final suggestion is that the way the stimuli were constructed gave rise to certain expectancies over trials. Drawing on the theory that our auditory system makes use of 'glimpses'

(Cooke, 2006; Festen & Plomp, 1990; Vestergaard et al., 2011) – moments when the background noise is less intense – the clearer templates presented in the interleaved trials may have elicited greater sensitivity for template matching in posterior STG. Posterior temporal and temporoparietal cortex may be particularly sensitive to expectancies of this kind in sound scenes (Mustovic et al., 2003; Voisin et al., 2006).

Given the poor performance of the AD group on the segregation detection task, it is notable that no differences in functional neuroanatomy were found for this contrast. This may be due to the relatively small case numbers holding a reduced power to detect effects, but may also have resulted from aspects of the study design. For example, the stimuli used here were intended to reflect everyday auditory scenes. The use of babble for background noise is likely to have entailed elements of both energetic and informational masking of superimposed speech sounds (Scott & McGettigan, 2013a) – the process of disambiguating target sounds from maskers may vary with masker type in AD. Even though the current stimuli aimed to reflect realistic situations, the relative demands from each masker type is likely to be more variable over time in a 'real' cocktail party scenario. Furthermore, signal to noise ratio may have varying effects even on the ageing brain (Wong et al., 2009); future work assessing the effect of masker level relative to targets may elucidate separable neural effects. A final point to make regarding this issue is the use of a passive listening paradigm. While employed to reduce separable task strategies or difficulty effects with cognitively impaired participants, sound mixtures requiring a behavioural output may reveal further disease-related neuroanatomical signatures.

Although this study did not set out to investigate lateralisation of response to the sounds presented, it is of interest that regions in the right hemisphere respond preferably to both name and segregation demands

for both experimental groups. The use of rotated speech in this contrast may have been relevant: for example Scott et al. (2009) found greater activation in right STG for speech presented over rotated speech compared to when it was presented over speech modulated noise. Right posterior STG also correlated with performance in the out of scanner segregation task in the AD group, suggesting that activity in this area is strongly implicated in auditory object segregation. Right temporoparietal cortex has also been implicated in spatial analysis of auditory scenes (Arnott et al., 2004; Krumbholz et al., 2005; Zimmer et al., 2003; Zündorf et al., 2013). These findings paired with those of the current study and chapter 3, suggest a multi-process role of this region in auditory scene analysis.

Despite the lack of AD-specific neural signatures for segregation processing per se, the interaction of this with template processing exhibited a distinct pattern of activation in right SMG for the AD group compared to controls. This region has been previously implicated in ASA in the healthy brain as well as network pathophysiology in AD (see sections 1.3 and 1.6.7). Previous work has highlighted the role of SMG in auditory target detection, spatial attention, streaming and phonological processing (Dykstra et al., 2011; Kondo & Kashino, 2009; Kong et al., 2014; Linden et al., 1999; Meyer et al., 2005; Nakai et al., 2005; Scott & McGettigan, 2013a), indicating that it may work to prepare orienting and behavioural responses to the auditory environment (Hickok & Poeppel, 2007; Warren et al., 2005). This may be particularly pertinent to the current stimuli, as hearing one's own name may elicit preparation for action (e.g., responding to a social signal or locating the speaker). Studies assessing attentional responses to this type of stimulus suggest that own name can be processed implicitly as a target (Moray, 1959; Perrin et al., 1999; Wood & Cowan, 1995). Deconstructing the complex interaction of between-group comparisons in name-segregation interaction (see Figure

5.7) revealed that response in the peak voxel particularly differentiated between spectrally rotated and naturally presented name when superimposed over background in the AD group. Activation in relation to silent trials was also generally enhanced compared to controls. Although not statistically significant, the results point towards a trend in the control group for a relative deactivation in response to all sound stimuli in this region. Together these profiles suggests that AD may induce abnormally enhanced activation (or conversely a failure in deactivation) of IPL in the analysis of incoming sound streams. Whereas deactivation of DMN in the healthy older brain may work to maximise processing efficiency in order to prepare for less predictable stimuli (Chiang et al., 2013; Newman & Twieg, 2001), inefficiency and therefore inability to inhibit DMN regions in AD may be the cause of the interaction seen in this study. This idea is in keeping with the proposed broad attentional spotlight ('sentinel') function of DMN (Buckner et al., 2008; Gilbert et al., 2007; Gusnard & Raichle, 2001; Hahn et al., 2009; Shulman et al., 1997). Furthermore, self-referential stimuli are similarly linked to DMN (Gusnard et al., 2001; Molnar-Szakacs & Uddin, 2013; Northoff et al., 2006) which ties in with the use of participants own name as an auditory template in the current study. If representation of self extends to neural response to one's own name, this may further explain the altered processing of our stimuli in the AD group.

When arguing for generalised deterioration of IPL in AD, one possible explanation for the current results could be that the functional alteration in this area is a mere artefact of atrophy. However, there are two arguments to counter this. Firstly, the leniently thresholded VBM results do not indicate disproportionate atrophy in the IPL; although this area is highly unlikely to be entirely intact in the current AD cohort, this does suggest that volume loss alone does not account for the AD-associated functional alteration observed. Secondly, the direction of activation

alteration suggests that the AD group had a higher level of neural response to most of the sound stimuli which counter the proposal that lower volume would induce less activity.

The activity in the peak voxel found for the name-segregation interaction contrast in the AD group also significantly correlated with its behavioural measure (name-segregation d-prime). This was a negative correlation, suggesting that increased activity in this region reflects poorer performance on the task. While a direct link between behavioural output and neural activation cannot be derived from the current passive listening paradigm, the association between in-scanner response and out-of-scanner performance does support the suggestion that increased activity in IPL reflects inefficiency of auditory processing in AD. Disambiguating compensatory processing from a generalised aberrant increase of cerebral activity is a key question in neurodegenerative disease (Elman et al., 2014). The focus in the current study was to assess AD-related alteration in brain mechanisms that may not require any task to reflect processing. However, further investigation of task effects may reveal additional pathophysiology.

There are several limitations to highlight in this study. The case numbers here were relatively small, especially to detect between-group effects. Larger patient cohorts with a broader phenotypic spectrum would be useful to develop our understanding of how temporoparietal dysfunction affects auditory processing (for example lvPPA). Furthermore, larger case numbers would justify the assessment of functional neuroanatomy across the whole brain. The auditory paradigm employed in this study raises unresolved issues that should be investigated in more detail: these include perceptual difficulty effects on the processing of sound conditions within healthy control and patient cohorts; target, masking stimulus, and signal-to-noise effects; and the potential impact of explicit task

requirements. Experiments that could develop on the paradigm presented here include the presentation of non-name information (or indeed other names), perhaps tracking a whole sentence as well as systematic investigation of the effects of signal-to-noise ratio. Nevertheless, this study could be thought of as a base on which to build further investigation into real-world auditory scenes and their effect on the AD brain. One of the main goals of this thesis is to investigate the functional impact that ASA dysfunction may have in AD; stimuli that mirror everyday listening situations may demonstrate how generic processing deficits translate to tangible symptoms.

6 ASSESSING PITCH, TEMPORAL, STREAMING AND KEY FUNCTIONS AS 'MUSICAL SCENE' ELEMENTS IN AD: A NEUROPSYCHOLOGICAL INVESTIGATION

6.1 Introduction

Music is arguably one of the most enjoyable ways we use our auditory system. Consequently a great deal of research into music processing in typical AD (tAD) focuses on the beneficial impact of music on mood and even memory performance in this patient group (see section 1.7.3). However, more detailed investigation has shown that musical processing is also susceptible to the generalised cognitive difficulties that accompany tAD. For example, tAD groups are impaired at learning new melodies (Bartlett et al., 1995; Halpern & O'Connor, 2000; Vanstone et al., 2012), with conflicting evidence around the preservation of familiar melody recognition (Baird & Samson, 2009; Bartlett et al., 1995; Cuddy & Duffin, 2005; Johnson et al., 2011; Vanstone & Cuddy, 2010; Vanstone et al., 2012). Whilst a number of case studies in patients with premorbid musical expertise have documented relatively preserved ability for certain components of music (Beatty et al., 1999; Cuddy & Duffin, 2005; Omar et al., 2010), little is known about how the broader disease population process musical sounds. This chapter seeks to investigate generalizable patterns of function in the wider AD population, using music as a rule-based nonverbal stimulus that creates complex auditory scenes. As discussed in section 1.6.6.2, 'musical scenes' require the coding of a number of separable components. This chapter will focus on aspects of pitch pattern (melody), key (tonality), temporal (rhythm and metre) processing as well as assessing the recognition of famous tunes in polyphonic compositions (musical streaming).

6.1.1 Pitch and melody perception

Melodies are comprised of patterns of pitch that can be analysed at two levels. Pitch direction determines the pattern of 'up' and 'down' to create a global contour, while pitch interval can vary locally within this contour

(Peretz, 1990; Peretz & Coltheart, 2003). A functional hierarchy, with global contour acting as a framework on which to hang local intervals, was first suggested by findings in healthy individuals. Dowling & Fujitani (1970) used transposed novel melodies to show that contour, but not interval violations alone could be detected if a tune had changed key. Peretz & Morais (1989) found that participants were more likely to successfully discriminate melodies that changed in contour compared to interval. This may relate to Gestalt principles drawn on by Bregman (1990) with regard to music processing: sequences of notes provide more meaning than one note in isolation, which may be why such groupings of melodic 'up' and 'down' are given psychological preference. Neuropsychological studies have confirmed this proposed hierarchy by showing an isolated deficit in interval processing with preserved contour discrimination, whilst impairment in global processing also results in local deficits (Peretz, 1990). However, localisation of these functions has proven more problematic. One previous study indicated that left hemispheric regions subserve local processing and right hemispheric regions global contour (Peretz, 1990); a subsequent study with more detailed lesion information showed that lesions to more posterior right temporal lobe were most likely to lead to melody discrimination impairment (Liégeois-Chauvel et al., 1998). In contrast, functional neuroimaging in the healthy brain observed left posterior STS in response to global violations in melodies, whereas local violations activated bilateral posterior STS regions (Stewart et al., 2008). Using a machine learning fMRI technique, Lee et al. (2011) found a network of regions including left STS, right IPL and anterior cingulate cortex were involved in processing melodic contour.

While previous work on how AD may affect global or local processing of pitch patterns is lacking, a number of studies have revealed a reduction or misbalance between global and local processing of visuospatial

information (Delis et al., 1992; Filoteo et al., 2001; Massman et al., 1993; Matsumoto et al., 2000; Slavin et al., 2002), however a number of caveats must be taken into account. Divided attention played a large role, as well as a patient's individual neuropsychological profile: it may be the case that those with younger onset or particular deficits in the performance domain are disproportionately affected. Work in the healthy brain as well as hemispatial neglect has implicated temporoparietal regions in global spatial processing (Fink et al., 1997; Robertson & Lamb, 1991), which along with the findings of Liégeois-Chauvel et al. (1998) may indicate that AD patients would be particularly vulnerable to processing pitch patterns at a global level. Though limited, pitch pattern processing in AD cohorts has been more frequently studied compared to temporal or streaming function. As detailed previously in section 1.7, many researchers have found that pitch discrimination is intact in AD (Goll et al., 2012; Johnson et al., 2011; Kurylo et al., 1993; Strouse et al., 1995; White & Murphy, 1998). Unfamiliar melody discrimination based on scale (scale subtest of the Montreal Battery for the Evaluation of Amusia [MBEA]: Peretz et al., 2003) is preserved (Hsieh et al., 2011; Johnson et al., 2011), however this discrimination can be accomplished using scale knowledge and assessing whether a note sounds 'out of key': contour or interval subtests have not been conducted at a group level. One case study indicated that an AD patient performed similarly to controls on the contour subsection of the MBEA (Omar et al., 2010) but the context of this individual's high level of musical experience makes any generalisation to the wider population difficult.

6.1.2 Key perception

Relationships between particular pitches enable a tonal structure, also known as 'scale' or 'key'. In Western classical music, relationships between the 12-note pitch chroma form a certain hierarchy related to a reference tone, also known as the 'tonic' (Krumhansl, 2000; McDermott & Oxenham, 2008). Work using unfamiliar melodies in healthy individuals

has shown that tones that do not fit with the established key are coded as 'unexpected' (Janata & Reisberg, 1988; Janata et al., 2003); functional imaging of these processes indicates the involvement of frontal regions such as mPFC (Janata et al., 2002). However, IFG has also been implicated in violating tonal expectancies, albeit in stimuli involving harmonies (Brown & Martinez, 2007; Koelsch, 2006; Koelsch et al., 2003, 2005, 2006; Tillmann et al., 2003). Tonality and contour have also been shown to doubly dissociate. Peretz (1993) documented a patient with right IFG and left temporal lobe damage who was able to make use of contour to discriminate melodies, however displayed an inability to use tonality to decide whether tunes had finished, or to make pleasantness judgements. Conversely, Satoh et al. (2007) described a patient who after bilateral temporal lobe infarction was able to make tonality and pitch judgements in the context of impaired contour discrimination and auditory agnosia. Considering the temporoparietal and medial prefrontal atrophy present in AD patients, the encoding of tonality may be affected.

6.1.3 Rhythm and metre perception

A local-global dichotomy can also be applied to temporal aspects of music processing. Using this viewpoint, metre (placing of stress or accents to determine the beat of music) can be conceived as a global structure whereas rhythmic patterns (the relative length of notes within a beat) require a form of local processing (Schuppert et al., 2000), however influential theories hold that these two processes are dealt with in parallel (Peretz, 1990; Peretz & Coltheart, 2003; Peretz et al., 2003). In an fMRI study with nonmusicians, Chen et al. (2008) found that STG, PT and dorsal premotor regions were activated for passive listening to rhythms. In an active fMRI task, rhythm encoding elicited IPL, IFG, supplementary motor area and cerebellum (Konoike et al., 2012). When investigating brain areas involved in metre processing, premotor and basal ganglia are implicated (Grahn & Rowe, 2009; 2013). Therefore regions responsible for repeating and producing rhythm are closely linked to its perception.

However, when assessing regions necessary for rhythmic processing, temporoparietal damage has led to both rhythm and metre deficits (Di Pietro et al., 2004; Robin et al., 1990; Wilson et al., 2002). Dissociations between pitch and rhythmic processing occur frequently (Ayotte et al., 2000; Peretz, 1990; Peretz & Kolinsky, 1993; Di Pietro et al., 2004; Samson et al., 2001), indicating the modular nature of music cognition. A large review of neuropsychological studies found rhythm processing more commonly linked to left hemispheric areas (Vignolo, 2003), with a number of studies exhibiting dissociations between rhythm and metre (Fries & Swihart, 1990; Wilson et al., 2002). However, a bias towards reporting temporal lobe lesions in reference to auditory processing may mask the involvement of other regions connected to temporal processing in the healthy brain.

Few studies of musical temporal processing have been conducted in AD. More general work in central auditory processing has demonstrated a deficit in duration pattern identification (Hellström & Almkvist, 1997; Strouse et al., 1995), which may predict difficulties in local rhythm processing. Whilst difficult to compare premorbidly expert musicians with untrained groups, one case study shows preserved rhythmic discrimination and metre perception (Cowles et al., 2003), while another amateur musician patient exhibited impairments in these domains (Beatty et al., 1999). Considering the proposed high temporal resolution of the left temporal lobe (Scott & McGettigan, 2013b; Zatorre et al., 2002b), rhythmic processing may be particularly affected by dementia phenotypes such as lvPPA with disproportionate atrophy in dominant temporoparietal cortex.

6.1.4 Musical streaming

A large body of previous work outside the domain of music (and much of the tenet of this thesis) would suggest, as in other stimuli, that generic processes contributing to streaming are impaired in AD (see in particular

section 1.7.2). This may be compounded by any potential deficits in processing the long-term structure of melodies. Musical streaming also provides one opportunity to assess nonverbal schema-based segregation of sounds by making use of well-known auditory templates such as familiar tunes. Whilst recognition of familiar melodies in tAD has produced varying results between studies (Cuddy & Duffin, 2005; Cuddy et al., 2012; Hsieh et al., 2011; Johnson et al., 2011; Vanstone & Cuddy, 2010; Vanstone et al., 2012), patients have often performed above chance in these tasks. Tasks that utilise individual playlists may be of use here to comply with personal knowledge and intact musical lexicon. Musical streaming represents the culmination of many processing modules, thus it has not been studied in as great a detail compared to pitch or temporal patterns, either in the healthy brain or in AD. Priming or familiarity aids the recognition of melodies interleaved with distractor tones (Bey & McAdams, 2002; Dowling, 1973; Dowling et al., 1987; Szalárdy et al., 2014). Bey & Zatorre (2003) document fMRI activation in bilateral HG, STG, thalamus and IFG when listening to interleaved melodies in healthy subjects. In a self-report after right temporoparietal stroke, McDonald (2006) describes 'an unusual emphasis on the inner parts of the performance', with another right temporoparietal case detailing a difficulty perceiving the whole in the context of preserved ability to perceive individual instruments (Mazzoni et al., 1993). These accounts, paired with evidence that tAD patients are impaired on tests of generic ASA (Goll et al., 2012) along with their neurodegenerative signature, would suggest that AD patients may find musical streaming difficult.

6.1.5 Designing a dementia-specific musical scene battery

This chapter aims to investigate in detail certain aspects of musical processing, to determine the processing deficits that may lead to impairment in the cognition of musical 'scenes'. Patients with a diagnosis of typical, memory-led AD along with lvPPA patients were investigated, as

two AD phenotypic classes that affect temporoparietal regions (Chételat et al., 2008; Henry & Gorno-Tempini, 2010; Herholz, 1995; Minoshima et al., 1997; Rohrer et al., 2010). An additional naPPA disease group was also tested as a group likely to possess early auditory perceptual deficits (Goll et al., 2010, 2011). However, one significant drawback of investigating music in this particular population is that musical stimuli necessarily unfold over time, thus current available tests assessing music perception often involve working memory to a relatively high degree. Working memory for tone patterns is impaired in tAD compared to control groups (Ménard & Belleville, 2009; White & Murphy, 1998), whilst impaired working memory is central to lvPPA (although predominantly in the verbal domain: Goll et al., 2011; Gorno-Tempini et al., 2008, 2011, 2004; Rohrer et al., 2010); therefore asking patients to compare relatively lengthy tune excerpts may confound working memory ability with the musical function of interest. One prominent test of music perception (MBEA: Peretz et al., 2003) investigates scale, interval, contour, and rhythm discrimination via a two-alternative-forced-choice paradigm using tunes of length 3.8 – 6.4s, requiring a relatively high degree of working memory capacity.

The tests devised in the current battery aimed to minimise as far as possible any working memory components; therefore novel paradigms were developed that make use of continuous sound presentation. For local-global pitch deviance detection, participants were required to detect deviant notes from one continuous arpeggio-like stream, rather than discriminating between two tunes. Key deviance detection also required on-line responses to target 'wrong' notes within a monophonic melody. The paradigm for local-global temporal deviance detection made use of previous methods utilised in an electrophysiological study (Geiser et al., 2009), whereby a constant rhythmic pattern altered in either local rhythm or global metre. Whilst many of these tasks increased the demand for sustained attention, this attentional domain is likely to be less affected

than working memory or divided attention in tAD (Baddeley et al., 1991, 2001; Stopford et al., 2012). For the streaming task, participants made a yes/no response to whether they detected a familiar tune embedded in a polyphonic musical texture.

6.2 Hypotheses

Given the neuroanatomical profile of the three disease groups, each test warrants its own predictions: 1) in the pitch task, AD phenotypes (tAD and lvPPA) would exhibit greater difficulty with global aspects of pitch pattern processing compared to controls; naPPA would show a less specific impairment. 2) in the tonality (key) task, temporoparietal and perisylvian damage will lead to impairment in all three disease groups. 3) in the temporal task, due to relatively preserved motor regions, both AD phenotypic groups would perform similarly to controls; in light of early auditory perceptual difficulties, naPPA patients will however display a deficit in temporal deviance detection. 4) in the embedded tunes task, musical streaming will be impaired in all patient groups.

6.3 Methods

6.3.1 Participants

Sixteen consecutive patients (6 female) with a diagnosis of tAD, 5 patients (2 female) with lvPPA and 9 patients (6 female) fulfilling criteria for naPPA were recruited. 20 healthy controls (10 female) matched as far as possible to the patient groups for age and musical training, with no history of significant neurological or psychiatric disorders also participated. Each participant underwent peripheral audiometry testing in the right ear and the pitch discrimination screening task (see sections 2.2 and 2.3). Syndromic diagnoses in the patient groups were corroborated with a comprehensive general neuropsychological assessment (summarised in Table 6.1). Brain MRI scans were available for review for 13 patients in the tAD group, 1 patient in the lvPPA group and 7 patients in the naPPA group and reviewed by an experienced neurologist blinded to diagnosis: all of

the tAD patients displayed bilateral hippocampal atrophy, with 2 patients showing asymmetrical atrophy in temporoparietal regions; 1 disproportionately left sided and 1 right sided. The lvPPA patient exhibited asymmetric left hemispheric atrophy, predominantly in perisylvian cortex; 2 of the naPPA showed diffuse cerebral atrophy with the remaining 5 displaying asymmetric left perisylvian atrophy. No brain MRIs showed a significant cerebrovascular burden. Where information was available, lumbar punctures in 12/13 patients with tAD and 3/4 patients with lvPPA showed a total CSF tau: beta-amyloid$_{1-42}$ ratio >1, compatible with underlying AD pathology. 5/6 of the nPPA patients displayed a CSF profile suggesting non-AD pathology. The naPPA patient with a CSF profile consistent with AD (total tau = 713, beta-amyloid$_{1-42}$ = 344) did not show an amyloid positive profile in an 8F-amyloid (Florbetapir) PET imaging study; while the remaining lvPPA patient who did not undergo a lumbar puncture did show an amyloid imaging profile supportive of underlying AD pathology. At the time of testing, 13 tAD patients were receiving symptomatic treatment with donepezil, 2 memantine and one was receiving no medication; in the lvPPA group, 4 patients were receiving donepezil and 2 memantine (one in addition to acetylcholinesterase inhibitor); in the naPPA group 1 patient was receiving donepezil. Clinical examinations in 8/9 of the naPPA patients revealed a range of motor slowness (3 absent, 4 mild and 1 moderate). Demographic, neuropsychological and clinical details of the experimental groups are summarised in Table 6.1; the musical background questionnaire (see section 2.4) was summarised by 2 measures: years of musical training and hours per week listening to music.

Table 6.1 – General demographic, clinical and neuropsychological profiles

Characteristic	Healthy controls	tAD	lvPPA	naPPA
Demographic and clinical				
No. (m:f)	10:10	10:6	3:2	2:7
Age (yrs)	69.9(4.6)	68.9(6.4)	63.6(6.2)	71.9(7.8)
Musical training (yrs)	4.8(3.7)	4.1(2.9)	3.2(4.0)	2.7(2.6)
Musical listening (hrs/week)	10.4(9.9)	8.8(11.0)	5.2(3.1)	4.9(7.2)
Education (yrs)	17.0(2.2)	15.3(2.7)	14.4(3.0)	16.3(2.6)
MMSE (/30)[a]	29.3(1.0)	20.6(4.7)*	15.8(9.6)*	20.1(11.2)*
Symptom duration (yrs)	-	6.4(2.1)	5.8(3.1)	6.8(3.7)
Neuropsychological assessment				
General intellect: IQ				
WASI verbal IQ[a,b]	118.9(7.2)	98.4(13.6)*	**69.3(12.4)****	84.1(19.0)*
WASI performance IQ[b]	119.7(13.1)	90.8(20.0)*	94.0(20.6)	100.0(20.0)
NART estimated premorbid IQ[c]	121.9(5.1)	113.5(8.7)*	88.0(12.2)**	106.0(15.8)*
Episodic memory				
RMT words (/50)[d,e,f]	48.1(2.1)	**29.7(6.1)*****	**32.4(6.0)***	45.1(6.3)
RMT faces (/50)[d,e]	42.8(3.9)	**32.9(6.1)***	**33.6(7.2)**	36.1(5.5)*
Camden PAL (/24)	19.7(2.5)	**3.5(3.8)*****	**2.6(2.5)*****	17.3(4.5)
Executive skills				
WASI Block Design (/71)[b]	43.4(15.9)	18.8(13.2)*	25.5(21.8)	19.3(17.7)*
WASI Matrices (/32)[b]	24.9(4.2)	12.8(7.3)*	17.0(9.0)	18.4(8.3)

WMS-R digit span forward (/12)	8.7(2.0)	6.8(2.3)	**3.0(2.5)***	6.1(2.4)
WMS-R digit span reverse (/12)[a,b]	7.4(2.0)	4.9(1.8)*	**2.0(1.4)****	3.1(2.3)*
D-KEFS Stroop colour (s)[b,e,g]	30.4(5.1)	**51.9(21.9)***	**62.3(19.0)***	**67.4(20.9)***
D-KEFS Stroop word (s) [b,e,g]	21.4(3.5)	**34.2(19.0)**	**34.5(12.7)**	**51.8(24.6)***
D-KEFS Stroop interference (s)[g,h,i]	60.0(16.9)	**105.8(49.3)***	**115.0(17.0)**	**149.0(37.3)***
Letter fluency (F: total)[g]	16.0(5.4)	11.1(4.8)	6.8(1.5)*	3.8(2.7)**
Category fluency (animals: total)[g]	22.9(5.7)	**11.9(5.0)***	**9.2(5.2)***	**10.4(3.4)***
Trails A (s) [b,f,j]	32.2(10.1)	**69.6(45.4)***	**83.8(38.5)***	69.0(37.2)*
Trails B (s)[f,k]	80.1(38.6)	**198.5(74.5)***	**232.3(73.0)***	233.3(67.4)*
WAIS-R Digit Symbol (total)[f,h]	54.3(10.9	**23.6(14.8)***	38.0(11.1)	**27.1(12.0)***
Language skills				
WASI Vocabulary (/80)[b]	70.2(2.8)	56.4(9.5)*	**23.0(19.8)****	35.0(20.5)**
WASI Similarities (/48)[b]	38(5.0)	26.4(10.6)*	**13.0(7.3)***	24.8(12.0)*
GNT (/30)[a]	26.1(2.4)	15.1(6.7)*	**7.4(7.9)***	14.8(8.8)*
BPVS (/150)	148.0(1.5)	144.9(2.9)*	140.8(6.8)	139.3(13.3)*
NART (/50)[b,c]	42.9(4.0)	36.1(6.9)*	16.8(10.8)**	30.2(12.8)*
Word repetition (/45)	-	-	40.0(3.5)	32.9(15.4)
Sentence repetition (/10)	-	-	6.6(3.4)	5.7(4.4)
Posterior cortical skills				
GDA (/24)[a]	14.8(5.3)	5.4(6.1)*	4.4(5.0)*	4.0(4.1)*
VOSP Object Decision (/20)[a]	18.9(1.3)	15.8(3.3)*	17.8(2.2)	15.8(5.2)

Mean (standard deviation in parentheses) performance scores are shown unless otherwise indicated. Maximum scores on neuropsychological tests are shown in parentheses. Results in bold indicate mean score < 5th percentile for normative data according to mean group age (not available for BPVS, letter

fluency, word or sentence repetition). * significantly different from control group ** significantly different from control and AD group *** significantly different from control and naPPA group ($p < 0.05$). **a** 8 naPPA; **b** 4 lvPPA; **c** 6 naPPA; **d** 19 controls; **e** 15 tAD; **f** 7 naPPA; **g** 5 naPPA; **h** 13 tADs; **i** 2 lvPPA; **j** 14 tADs; **k** 10 tADs.

6.3.2 General structure of experimental battery

Four main tasks were devised to assess musical 'scene' analysis:

1) Detection of local or global deviants in pitch (melodic) patterns
2) Detection of key deviants in unfamiliar melodies
3) Detection of local or global deviants in temporal patterns
4) Detection of famous tunes embedded in unfamiliar distractor tunes.

In order to minimise the working memory demands of such tasks, paradigms assessing deviance detection made use of continuous presentation of a pattern with a number of deviants occurring for each trial. Participants were therefore required to attend to the pattern and respond via a button press when they heard a deviant note. A control task was devised to assess the ability to comply with the attentional demands of these tasks, whereby participants were required to detect timbre deviants presented in a continuous carrier scale. The embedded tunes task assessed whether participants could identify highly famous tunes either alone or with concurrent distractor tunes; they were therefore able to answer at any point during each trial presentation, again minimising working memory demands. A schematic diagram representing each task is shown in Figure 6.1. All tasks used a synthetic musical note carrier either created in MATLAB® (global versus local tasks and the timbral control task) or MuseScore (guitar timbre for key deviance detection and piano timbre for embedded tunes and tune recognition task).

6.3.3 Local-global pitch deviance detection

6.3.3.1 Main task

This task aimed to access both global and local pitch pattern (melody) processing. Stimuli consisted of three different keys, all comprising the same pattern of tonic-dominant-tonic (interval of 5 then 4 tones) over two octaves, note range F2 to C5. A simple up-down global pattern was

consistent across all stimuli and repeated for a number of cycles over each trial. Each trial contained 5 deviants that differed in one of 3 ways: 1) local deviant – global direction was preserved, with the local interval violated; 2) global deviant – global direction was violated; 3) global-direction-only deviant – global direction was disrupted, but only using notes previously heard in the pattern (i.e. only the order of notes was altered). All deviant notes adhered to the diatonic scale of each trial. Notes were presented isochronously at either 120 or 150 beats per minute (bpm), with 4 trials for each deviant type presented in a blocked fashion (local; global; global-direction-only); 20 potential deviants occurred for each deviant type. Deviants occurred at a pseudo-randomised onset (each participant was played the same sounds and intervals between deviants were required to be at least 1.5s). Participants were instructed to press the spacebar as quickly as possible whenever they heard a 'wrong note'; presses within 1.5s after deviant onset were counted as a correct response. Stimuli were between 33.12 and 41.4s in duration, with no deviants occurring before the second 'cycle' of global up and down. Participants were initially presented with an example pattern containing no deviants, then practice trials for each deviant type. Instructions explained that a number of deviants would occur for each trial, and that they would hear the pattern at least once at the beginning before any deviants occurred.

6.3.3.2 Easy version

If participants did not correctly detect more than 50% of the deviants for any of the blocks (local; global; global direction only), they completed half of all subsequent blocks and continued to an easier version of the task. Here the pattern presented varied only between 2 notes; local deviants changed the interval and global deviants the direction (both notes not heard in the pattern and notes heard in the pattern an octave lower) with two trials per condition. A small subset of controls scoring adequately also completed this task.

6.3.4 Key deviance detection

This task was designed in order to assess participants' key knowledge. 5 stimuli were presented, comprised of unfamiliar melodies grounded in the rules of Western classical music, derived from unfamiliar folk tunes (a subset of those used previously by Warker & Halpern, 2005) and composed by an experienced musician. Melodies were created in MuseScore® and converted to wav files with a synthetic guitar carrier. A different major key was used for each melody (A, G, D, F, B-flat), with duration of between 33.5s and 39.6s. 4 key deviants were presented in each melody; these deviants fitted with the melody's global contour, but did not 'belong' to the established key (the set of 8 notes that comply with a diatonic scale); this created a perception of 'wrong' or 'out-of-key' notes. No deviants occurred before the fourth bar of the melody so as to establish the key. Participants were instructed to press the spacebar as soon as they heard a note that didn't fit with the key, or 'wrong note'; presses within 1.5s of the deviant onset were counted as a correct detection. This paradigm therefore aligns closely with the method presented in a previous study (Janata et al., 2003). Participants were also told that the melodies adhered to the rules of Western classical music (with the exception of the deviants), and that the melodies did not change key at any point.

6.3.5 Local-global temporal deviance detection

Patterns consisted of a repeated rhythmic motif with a consistent metre (time signature), similar to the stimuli used in Geiser et al. (2009). 5 different patterns were presented, repeated so that the same patterns were used for both local and global deviant trials. The metre/time signature alternated between three or four beats per cycle (3/4 or 4/4), emphasising the first note of the cycle (or bar) with increased sound intensity. Each of the first 5 trials contained 4 local deviants; deviants were created by altering the rhythm so that it disrupted the established pattern. The next 5 trials created global deviants (4 per trial) by altering

the metre: the position of the louder note disrupted the established pattern, creating the perception of an 'early' or 'late' beat. Here there were 20 potential deviants to detect per condition (local or global). A larger time window was given for this task to allow for duration judgements, therefore a correct response was determined by any button press that was within 2s after the onset of a deviant note. Trials were between 22.5 and 38.4s in duration, with notes presented at a rate of either 120 or 150 bpm. No deviants occurred before the third repeat of the rhythmic pattern and occurred at a pseudo-randomised onset (each participant was played the same sounds and intervals between deviants were required to be at least 2s). All participants were presented with 2 example patterns and practices for each block. Instructions explained that a number of deviants would occur for each trial, and that they would hear the pattern at least twice at the beginning before any deviants occurred.

6.3.6 Timbre deviance detection control

This task manipulated the timbre of carrier notes during a continuously ascending and descending melodic scale in a major key. The spectral envelope of the carrier was varied to produce two different timbres. 5 timbral deviants were presented during each trial, whereby a correct button press was coded if response was within 1.5s of the deviant timbre. Notes were presented at a rate of 100bpm with a trial duration of 32.4s. All participants were presented with 1 example and at least 1 practice.

6.3.7 Embedded tune detection

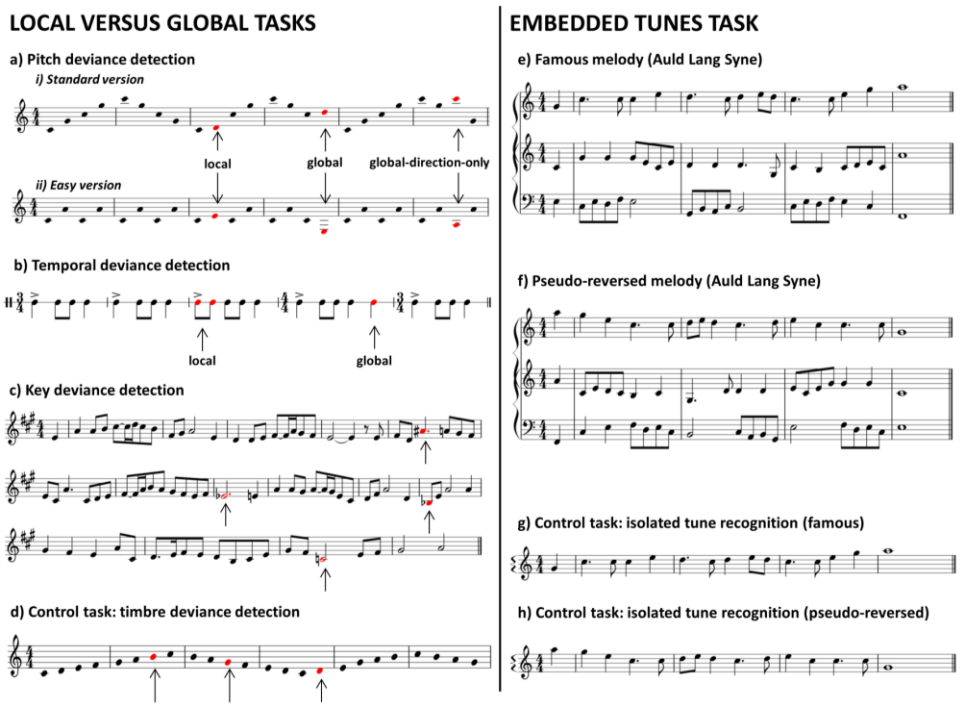
This task was devised to assess 'musical streaming' by making use of very familiar tunes (a list can be found in Appendix 3) as auditory objects, and novel harmonious distractor tunes as background. Stimuli gave the percept of a three-part harmony; the top line carried the tune for all trials. 10 trials contained famous tunes and 10 contained the same tunes pseudo-reversed (dotted rhythms were not reversed and tunes were altered so that the phrase ended on a long tonic or dominant note).

Duration of the stimuli was between 7s and 13s. Participants were instructed to respond 'yes' if they recognised a tune and 'no' if they did not. All participants were presented with 2 examples.

6.3.7.1 Tune recognition control

This task was designed to check and confirm that participants could recognise the previously embedded tunes, and was administered after the embedded tune detection task to prevent any priming effects. Each of the 20 tunes (half famous, half pseudo-reversed) was presented in isolation; participants were again asked to discriminate between familiar, famous tunes and those they did not recognise.

Figure 6.1 – Schematic representation of musical task stimuli



Musical notation of exemplar stimuli. Deviant notes are shown in red; for timbre deviance detection the red notes also represent a change in spectral envelope (timbre). For the embedded tunes task, each example represents 'Auld Lang Syne' in its raw and pseudo-reversed forms.

6.3.8 Behavioural analysis

6.3.8.1 Deviance detection tasks

As participants were free to respond at any time, it was necessary to account for potentially varying strategies: for example if only assessing 'correct' presses, a participant who only pressed in response to all the deviants (and never pressed outside the correct time windows) would be equally as correct as a participant who pressed continuously and indiscriminately throughout a trial. Therefore an individual's proportion of correct presses (the proportion of one or more presses for each 'correct' time window) was corrected by subtracting the probability of pressing by chance, predicted using a Poisson distribution of each participant's incorrect presses. This can be represented by the following equation:

$$S = P - (1 - e^{-\lambda})$$

where S = score

P = proportion correct presses

λ = rate of incorrect presses x correct time window.

This transformation resulted in a 'corrected-detection-score' for each participant for each condition (e.g. local; global). This analysis method was utilised for the local-global pitch, key, local-global temporal and timbre control deviance detection tasks. As these data did not conform to normality assumptions, I first performed a Kruskal-Wallis test analysis of variance, then any significant effects were further examined via a multiple linear regression model using bias corrected & accelerated CIs calculated from 2000 bootstrap replications. CIs were bonferroni-corrected to account for multiple comparisons, and the combinations of coefficients were calculated to analyse (where appropriate) effects of condition and patient group. An effect was therefore considered significant if the CI did not include zero. A cluster-adjusted Poisson regression was also

conducted for the pitch, key and temporal pattern deviant detection tasks to determine whether there was any difference in the incidence risk ratio (IRR) of incorrect presses between groups. Spearman's correlation coefficient was used to assess associations between task performance and measures of disease severity such as MMSE and disease duration. Task-specific analyses are detailed below:

6.3.8.1.1 Pitch deviance detection

The regression models for this task were corrected for performance in the pitch discrimination task, as this significantly associated with corrected-detection-score. The effects of condition (local; global; global-direction-only) and patient group (control; tAD; lvPPA; naPPA) as well as any interaction between these 2 factors were tested. Bias corrected and accelerated CIs were assessed at the 99.8% level to correct for the multiple comparisons made.

6.3.8.1.2 Key deviance detection

This analysis controlled for digit span forwards (a measure of auditory working memory) performance and CIs were assessed at the usual 95% level.

6.3.8.1.3 Temporal deviance detection

The regression model corrected for digit span forwards and CIs were assessed at the 99% level, again correcting for multiple comparisons. The effects of condition (local; global) and patient group (control; tAD; lvPPA; naPPA) as well as any interaction between these 2 effects were tested.

6.3.8.1.4 Timbre control task

This analysis also controlled for digit span forwards performance and CIs were assessed at the usual 95% level.

6.3.8.1.5 Embedded tunes

Responses from the isolated tune recognition task dictated the analysis of this task. If a participant was unable to correctly identify a famous tune as

famous in isolation, this item was excluded from the analysis of their embedded tunes responses. This resulted in varying numbers of famous and reversed items for each participant, therefore cluster adjusted logistic regression that made use of signal detection theory was utilised. Odds of responding 'famous' when the tune was famous (i.e. a correct 'famous' response) was modelled to produce odds ratios (ORs) for each patient group, whilst also controlling for performance on the digit span forward task. The Wald criterion was used to test for any interaction effect, or specific patient group differences. Recognition performance was analysed using linear regression with robust standard error to determine whether total score differed between patient groups.

6.4 Results

6.4.1 Demographic, neuropsychological and peripheral audiometry characteristics

Results of the analysis of demographic and clinical data are summarised in Table 6.1. The patient and healthy control groups were well matched for age ($\chi^2_{(3)}$ = 6.53, p = 0.09), education ($\chi^2_{(3)}$ = 6.03, p = 0.11) musical training ($\chi^2_{(3)}$ =3.00, p = 0.39), musical listening ($\chi^2_{(3)}$ = 3.19, p = 0.36) and gender distribution ($\chi^2_{(3)}$ =2.91, p = 0.41). As expected, MMSE differed between all groups ($\chi^2_{(3)}$ = 30.46, p < 0.0001) but not between patient groups ($\chi^2_{(2)}$ = 1.68, p = 0.43). The patient groups were also well matched for disease duration ($\chi^2_{(2)}$ = 0.28, p = 0.87). As anticipated, all patient groups performed worse than controls on many standard neuropsychological measures, with the tAD group showing particular weaknesses in areas of memory and executive function, the lvPPA also displayed poor memory as well as particular deficits in verbal working memory, executive function and verbal tasks, whilst the naPPA group showed relatively preserved memory with predominant impairment in tasks requiring a speeded verbal output. Whilst data were not available for either a normative sample or the current control group, both the

lvPPA and naPPA show reduced word and sentence repetition (most healthy individuals would score at ceiling for this task).

Assessing peripheral audiometry performance, the tAD group did not differ significantly from controls (beta = -1604, p = 0.44, CI -5702 to 2495), however there was a significant difference between both the lvPPA (beta = 13001, p = 0.03, CI 1263 to 24739) and naPPA (beta = 11925, p = 0.002, CI 4585 to 19265) groups and the control group. A significant interaction between group and frequency was found ($F_{(12,49)}$ = 2.78, p = 0.006), however for simplicity a combined audiometry score using the sum of detection thresholds for all frequencies was used as a measure when assessing its relationship with experimental task performance. When tested, this audiometry score did not significantly associate with any of the musical tasks.

6.4.2 Local-global pitch deviance detection

Three tAD and 1 naPPA patient did not pass the pitch screening task, therefore 20 controls, 13 tAD, 5 lvPPA and 8 naPPA participants took part in the main pitch task. A summary of performance for each group and each experimental task is presented in Table 6.2; individual scores are shown in Figure 6.2. 6 controls, 5 tAD, 2 lvPPA and 6 naPPA went on to complete the easy version of the task. Comparing the subset that every participant completed with the partially complete subset revealed a systematic difference (beta = -0.04, CI -0.10 to -0.001), therefore subsequent analyses only deal with items that all participants completed (10 deviants for each condition). A Poisson regression indicated that the naPPA group (IRR = 3.21, p = 0.001, CI 1.66 to 6.20) pressed incorrectly significantly more frequently compared to controls, but not the lvPPA group (IRR = 1.21, p = 0.57, CI 0.62 to 2.39) or the AD group (IRR = 2.16, p = 0.05, CI 0.99 to 4.69). There was no significant difference between conditions ($\chi^2_{(2)}$ = 1.93, p = 0.38), however a significant interaction between condition and patient group was found ($\chi^2_{(6)}$ = 23.01, p = 0.0008).

Turning to corrected-detection-scores, a significant effect of combined patient cohort was apparent for local ($\chi^2_{(3)}$ = 15.58, p = 0.001), global ($\chi^2_{(3)}$ = 20.52, p = 0.0001) and global-direction-only deviants ($\chi^2_{(3)}$ = 22.51, p = 0.0001). A trend was noted for the effect of condition ($\chi^2_{(2)}$ = 5.69, p = 0.06), however this did not reach significance. Estimations of linear coefficients to determine patterns between groups within conditions indicated that compared to controls, each patient group exhibited a different pattern: the tAD group showed significantly poorer performance in the global condition (beta = -0.26, CI -0.52 to -0.03) but not the local (beta = -0.12, CI -0.30 to 0.08) or the global-direction-only (beta = -0.26, CI -0.46 to 0.02) conditions. The lvPPA group performed significantly worse in the global-direction-only condition (beta = -0.46, CI -0.84 to -0.22) with not significant differences for local (beta = -0.24, CI -0.50 to 0.02) or global (beta = -0.46, CI -0.84 to -0.22) conditions. The naPPA group performed significantly worse for all three conditions (local: beta = -0.45, CI -0.91 to -0.12; global: beta = -0.43, CI -0.76 to -0.21; global-direction-only: beta = -0.54, CI -0.88 to -0.21). The naPPA group also performed worse than the AD group for local (beta = -0.33, CI -0.76 to -0.01) and global-direction-only deviants (beta = -0.28, CI -0.76 to -0.05). No significant correlations between disease severity (MMSE or disease duration) and task performance were found.

6.4.2.1 Easy version

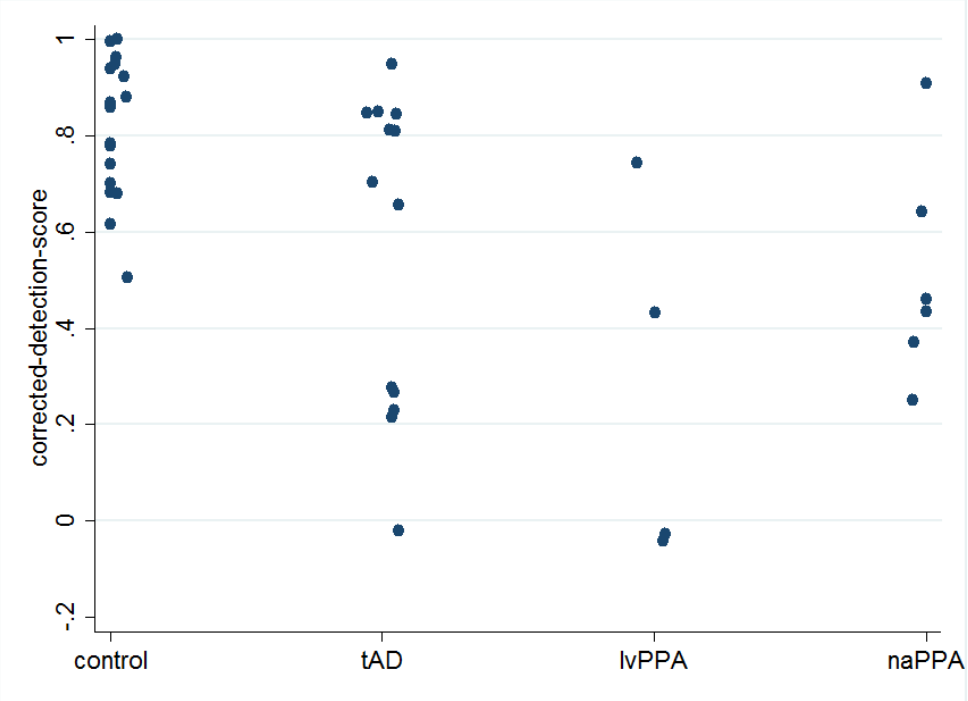
No significant differences in performance related to group or condition were found; no significant interaction between these factors was found.

Figure 6.2 – Individual corrected-detection-scores for local-global pitch deviance detection

6.4.3 Key deviance detection

Twenty controls, 13 tAD, 4 lvPPA and 6 naPPA patients undertook this task. Omissions were due failure of the pitch discrimination screening task (3 tADs and 1 naPPA) or experimenter error in completing this subtest (1 lvPPA and 2 naPPAs). A summary of corrected-detection-scores can be found in Table 6.2; individual corrected-detection-scores are shown in Figure 6.3. The Poisson regression revealed a significant difference in the frequency of incorrect presses between both the lvPPA (IRR = 3.47, $p < 0.001$, CI 2.0 to 6.0) and naPPA (IRR = 3.88, $p < 0.001$, CI 1.9 to 8.0) groups compared to the healthy control group; this was not the case for the tAD group (IRR = 1.01, $p = 0.96$, CI 0.63 to 1.6). The main linear regression indicated that all patient groups detected fewer key deviants compared to controls (tAD: beta = -0.22, CI -0.4 to -0.1; lvPPA: -0.50, CI -0.8 to -0.2; naPPA: -0.26, CI -0.4 to -0.02). There were no significant differences between any of the patient groups. Corrected-detection-scores did not correlate significantly with MMSE, disease duration or forwards digit span in the combined patient group.

Figure 6.3 – Individual corrected-detection-scores for key deviance detection



6.4.4 Local-global temporal deviance detection

One tAD patient did not complete this task due to time constraints; 2 tAD and 1 naPPA patient were not able to comply with the task demands, therefore 13 tAD and 8 naPPA patients (with 5 lvPPA and 20 control participants) undertook this task. A summary of performance for each group and each experimental task is presented in Table 6.2; individual scores are shown in Figure 6.4. A Poisson regression indicated that both the tAD (IRR = 2.79, p = 0.022, CI 1.16 to 6.74) and the naPPA (IRR = 6.28, p < 0.0001, CI 2.31 to 17.12) patient groups pressed incorrectly significantly more frequently than the control group; this was not significant in the lvPPA group (IRR = 1.93, p = 0.559, CI 0.21 to 17.32). The global condition also elicited more incorrect presses compared to the local condition (IRR = 2.70, p < 0.001, CI 1.64 to 4.44), with an additional significant interaction between patient group and condition ($\chi^2_{(3)}$ = 12.24, p = 0.007), driven by a significant difference between the naPPA and control group in the local (beta = -1.82, p < 0.0001, CI -2.84 to -0.84) in contrast to the global condition (beta = -0.86, p = 0.048, CI -2.10 to 0.39).

Assessing corrected-detection-scores, across conditions the naPPA (beta = -0.33, CI -0.72 to -0.08) had significantly lower scores compared to the control group; this was not the case for the lvPPA (beta = -0.21, CI -0.53 to 0.20) or the tAD groups (beta = 0.10, CI -0.20 to 0.01). Across all groups, correction detection scores were lower for the global deviants compared to the local condition (beta = -0.11, CI -0.17 to -0.06). No significant interaction between group and condition was found. A significant correlation between MMSE and corrected detection score in the global condition was found ($r_s(26) = 0.52$, $p = 0.0008$); no other correlations between either the local condition or disease duration were significant.

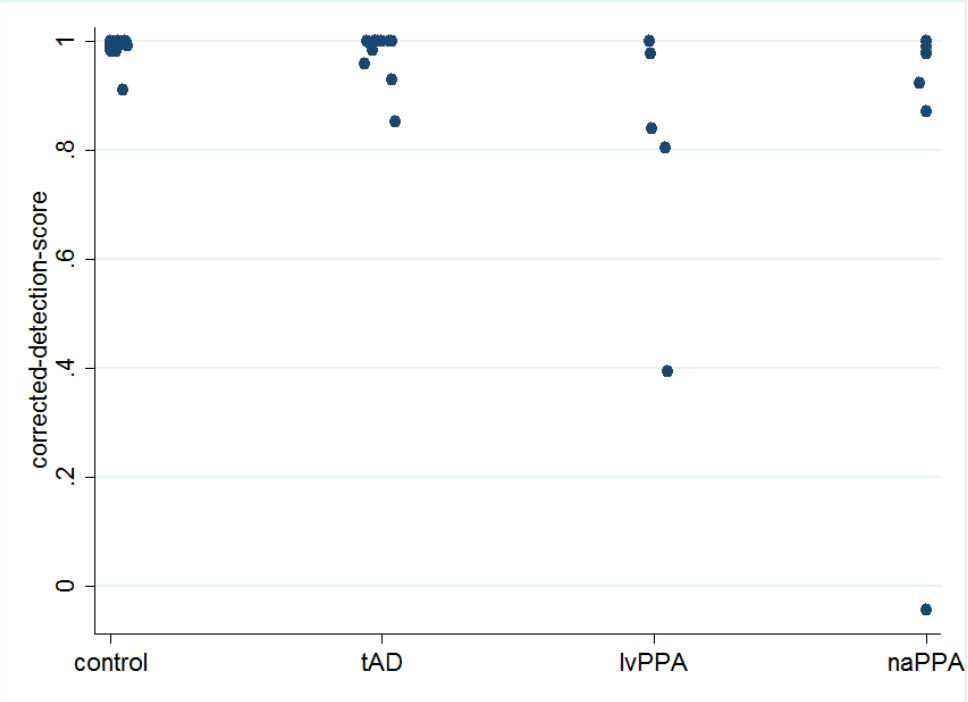
Figure 6.4 – Individual corrected-detection-scores for local-global temporal deviance detection

6.4.5 Timbre deviance detection control

A summary of performance for each group is presented in Table 6.2; individual scores are shown in Figure 6.5. All patient groups pressed

incorrectly significantly more frequently compared to the healthy control group (tAD: IRR = 9.39, p = 0.03, CI 1.3 to 67.3; lvPPA: IRR = 20.45, p = 0.002, CI 3.0 to 141.7; naPPA: 31.65, p < 0.001, CI 4.9 to 203.9). However there was no significant difference between corrected-detection-scores in the tAD and healthy control groups (beta = -0.01, CI -0.05 to 0.03), however both lvPPA (beta = -0.17, CI -0.5 to -0.02) and nAPPA (beta = -0.18, CI -0.6 to -0.01) groups performed significantly worse than controls.

Figure 6.5 – Individual corrected-detection-scores for timbre deviance detection control



6.4.6 Embedded tune detection

6.4.6.1 Recognition task

Due to an error where administration of the recognition task was omitted, 1 control, 1 lvPPA and 1 naPPA participant did not complete this task, therefore 19 controls, 16 tAD, 4 lvPPA and 8 naPPA participants took part in both this and the main task. For the recognition task, a linear regression showed that both the tAD (beta = -0.5, p = 0.028, CI -0.94 to -0.06) and lvPPA (beta = -2.35, p = 0.019, CI -4.30 to -0.40) groups recognised significantly fewer tunes compared to the control group. The naPPA group

did not perform significantly differently to controls (beta = -1.38, p = 0.234, CI -3.67 to 0.92).

6.4.6.2 Main task

A summary of performance for each group and each experimental task is presented in Table 6.2; individual scores are shown in Figure 6.6. Assessing only items that were successfully recognised in isolation, all patient groups showed reduced odds of a correct familiar response compared to controls (tAD: OR = 0.13, p = 0.038, CI 0.02 to 0.89; lvPPA: OR = 0.10, p = 0.048, CI 0.009 to 0.98; naPPA: OR = 0.08, p = 0.008, CI 0.01 to 0.52). No significant differences between patient groups were found. A significant correlation between odds of correct response and disease duration was found ($r_s(28) = 0.45$, p = 0.02) but not for MMSE (($r_s(28) = 0.09$, p = 0.65).

Figure 6.6 – Individual proportion correct scores for embedded tune detection

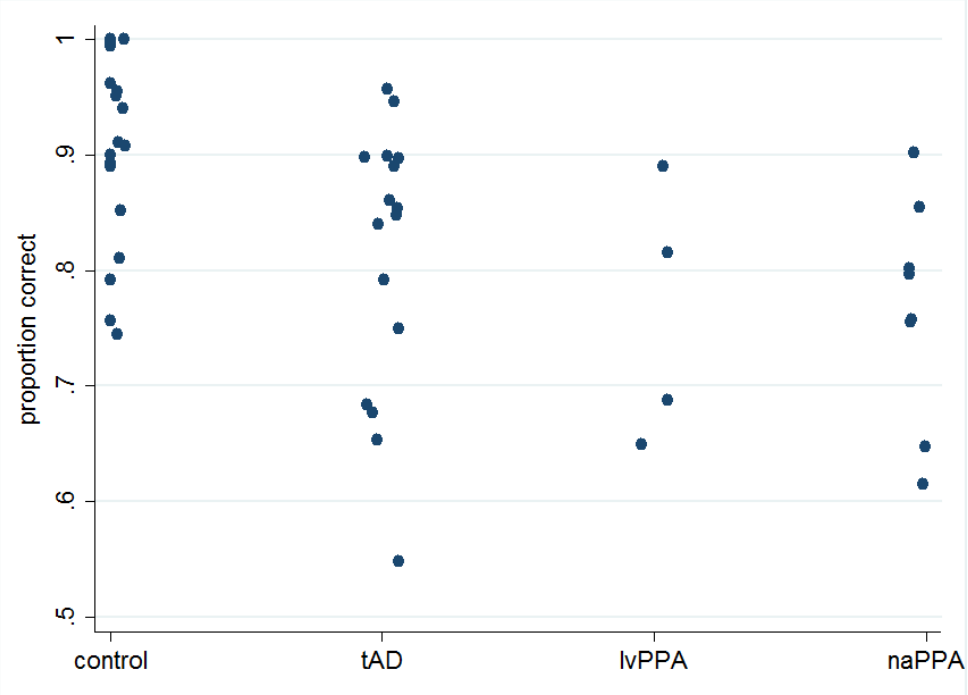


Table 6.2 – Summary of group level performance for each experimental task

Task	Controls	tAD	lvPPA	naPPA
Timbre deviance detection (n)	20	15	5	9
Corrected-detection-score	0.99(0.02)	0.98(0.04)	0.81(0.25)[a]	0.84(0.36)[a]
Pitch deviance detection (n)	20	13	5	8
Local (corrected-detection-score)	0.90(0.17)	0.74(0.25)	0.59(0.25)	0.37(0.43)[a,b]
Global (corrected-detection-score)	0.91(0.13)	0.60(0.32)[a]	0.37(0.44)	0.40(0.30)[a]
Global direction only (corrected-detection-score)	0.82(0.19)	0.53(0.29)	0.30(0.34)[a]	0.21(0.24)[a,b]
Key deviance detection (n)	20	13	4	6
Corrected-detection-score	0.81(0.13)	0.58(0.33)[a]	0.28(0.39)[a]	0.51(0.22)[a]
Temporal deviance detection (n)	20	13	5	9
Local (corrected-detection-score)	0.92(0.07)	0.75(0.15)	0.51 (0.33)	0.52(0.36)[a]
Global (corrected-detection-score)[c]	0.81(0.17)	0.59(0.17)	0.31(0.22)	0.35(0.29)[a]
Embedded tune detection (n)	19	16	4	8
Odds ratio	154.83	20.63[a]	9.21[a]	8.24[a]
95% Confidence interval	35.12 – 682.52	6.58 – 64.64	2.38 – 35.69	3.29 – 10.63
Recognition (total /20)	19.75(0.44)	19.25(0.77)[a]	17.40(2.30)[a]	18.38(3.29)

Group scores on musical experimental tasks are shown (number of participants are indicated for each task). Mean (standard deviation in parentheses) scores are presented; underneath each task the measure used (corrected-detection-score/odds ratio) is noted. **a** = significantly different from control group, **b** = significantly different from tAD group, **c** = significantly different from the local condition.

6.5 Discussion

This novel battery assessing aspects of musical scene processing has revealed distinct patterns of deficits in typical AD, its language variant (lvPPA) and a non-AD language-led dementia (naPPA). Local-global pitch deviance detection showed varying profiles of impairment between all three patient groups. Particular conditions where patient groups detected significantly fewer deviants were global (contour) for the tAD group, global-direction-only (contour) for the lvPPA group and all three conditions (interval and contour) for the naPPA group. For key deviance detection, all patient groups performed worse compared to the healthy control group. The local-global temporal pattern task showed that all experimental groups detected fewer deviants in the global (metre) compared to the local (rhythm) condition. When comparing patient groups' performance to controls, only the naPPA group showed impairment in detecting temporal deviants and this involved both classes of deviants. When assessing timbre deviance detection, the tAD and control group performed similarly, however the lvPPA and naPPA groups detected significantly fewer timbre deviants compared to controls. With regard to streaming using highly familiar melodies, after taking tune recognition *per se* into account, all patient groups showed impairment in detecting famous tunes embedded in harmonious distractor tunes.

The current findings in local-global pitch deviance detection are suggestive of a diminished ability to process one form of global auditory information in tAD patients. This is in line with some previous findings that visual global processing is reduced in tAD (Matsumoto et al., 2000; Slavin et al., 2002). Whilst previous studies have not found such a clear cut dissociation (Delis et al., 1992; Filoteo et al., 2001; Massman et al., 1993), the current results lend support to the idea that tAD patients may possess a weakness in forming coherent global representation of stimuli, or are at least misbalanced between local and global processing abilities.

What is difficult to resolve is the differential reduction in global and global-direction-only deviance detection between the tAD and lvPPA groups, however the reliability of such results may be variable considering the small sample sizes in this study. Global-direction-only deviants changed only the order of the notes, therefore would be predicted to be harder than detecting contour as well as novel note deviants, however the tAD group were only impaired in the global condition. Mechanisms for pitch height and chroma may dissociate (Warren et al., 2003), therefore more detailed behavioural assessment (and replication) paired with structural associations may go some way towards untangling such processes in these phenotypes.

The neurodegenerative signature of AD reveals particular vulnerability of (amongst others) temporoparietal regions. This paired with studies in both the healthy brain and neuropsychological cohorts of visuospatial attention (Fink et al., 1996, 1997; Lamb et al., 1990; Robertson & Lamb, 1991) points towards the idea that temporoparietal atrophy may contribute to the cognitive signature seen in the present study. The dorsal auditory stream has also been suggested as the primary substrate for processing pitch changes over long time periods (one conceptualisation of 'global' information: Sanders & Poeppel, 2007). The finding that patients at the language-led, disproportionately temporoparietal end of the AD phenotypic spectrum were also deficit in one aspect of global pitch pattern processing lends further support to this notion. Of particular interest here is how melodic contour may mirror the ability to process prosody, which forms one component of sentence processing (Friederici, 2002); a function that is disproportionately affected in lvPPA, However, definite conclusions are hard to draw with current sample sizes. Whilst some work has implicated divided attention in local-global processing in AD and more generally (Filoteo et al., 2001; Fink et al., 1997; Lux et al., 2006; Slavin et al., 2002; Weissman et al., 2002), the current paradigm

only required participants to respond to one element at a time. Issues of attention cannot be excluded as contributing to the pattern of deficits seen in this study; however reduced ability to detect only global (contour) deviants here may indicate a processing style that is not simply related to divided attention deficits.

The current findings do not support previous models suggesting that a global melodic processing deficit should necessarily lead to a local deficit (Liégeois-Chauvel et al., 1998; Peretz, 1990; Peretz et al., 1994). One study in healthy individuals may shed some light on the reasons for these findings. Lee et al. (2014b) found that participants were more accurate in encoding a 2-note interval if this was embedded in a 3-note sequence (i.e. preceded by another note). The authors suggest a relationship with tonality is made with greater melodic context (Krumhansl, 1990). Therefore it may be the case that our stimuli (consisting of tonic and dominant notes), following a predictable (arpeggio) pattern, served to assist more accurate encoding of local interval deviants compared to the unpredictable novel tunes used in previous methods. This idea could also explain the pattern of results regarding differences between conditions; local deviants were not detected less frequently than global deviants in the control group. However, this framework does not resolve the greater difficulty for detecting global deviants that was found in both AD variant groups; predictable contour patterns should make contour as well as interval deviants relatively easy to detect. Furthermore, the global deviants also violated the tonal hierarchy similarly to the local deviants. Assessing pitch patterns with varying tonal hierarchies may help resolve some of these issues. The overall pattern of results indicates that both AD phenotype groups performed similarly to controls on an easier version of the test and another paradigm-matched task assessing temporal deviance detection. This counters any suggestion that the two AD variant groups were simply unable to comply with the task demands.

Local-global temporal deviance detection did not show any specific deficits in the AD variant groups compared to controls. These findings support evidence that pitch and temporal pattern analysis can dissociate (Liégeois-Chauvel et al., 1998; Peretz, 1990; Peretz & Kolinsky, 1993; Peretz et al., 1994; Samson et al., 2001; Schuppert et al., 2000). The current findings do not lend support to a generalizable bias in global processing in AD when considering the auditory temporal domain, however some previous work has indicated a rhythm processing deficit in naPPA (Vandenberghe et al., 2012). However these classifications are incommensurate; relations between local and global elements in the pitch and temporal domains may be processed via different mechanisms. The current findings may be considered more surprising when noting the previous link between temporoparietal cortex and rhythmic processing in neuropsychological work (Fries & Swihart, 1990; Fujii et al., 1990; Griffiths et al., 1997; Robin et al., 1990). As mentioned above, both typical AD and lvPPA patients show neuropathological vulnerability in these regions; further work assessing both anatomical correlations and varying behavioural methods such as shorter patterns with final 'probe' notes may be needed to resolve these issues. Further neuroanatomical investigations assessing loci involved in both pitch and rhythmic pattern analysis are warranted. Nevertheless, the potentially preserved processing of musical rhythm and metre may provide one way in which AD patients are able to access the beneficial parts of music. Considering the wider theoretical implications of this work, our results are in line with previous work using very similar stimuli where young healthy participants were worse at detecting metre compared to rhythm alterations (Geiser et al., 2009). This would counteract the tenet that metre serves as a global component in a hierarchical manner before rhythm is encoded (Schuppert et al., 2000) and would lend further support to parallel processing theories (Peretz, 1990; Peretz & Coltheart, 2003).

Turning to key/tonality processing, all patient groups displayed a reduced ability to detect tones that did not fit with an established key. As key is a dimension that is necessarily formed over time, it could be argued that a certain degree of working memory ability is required to represent tonal structure. However, backward digit span (as an independent index of working memory) had no significant relationship with performance on key deviance detection. Whilst it is tempting to suggest that the poor performance in key deviance detection may stem from melodic contour processing deficits, previous work in brain damaged patients suggests that the representation of tonal relationships between pitch may dissociate from the coding of pitch direction (Peretz, 1993; Satoh et al., 2007). Therefore despite on occasion working together (see above), any impairment in key processing may be the result of atrophy in substrates separable from those involved in pitch contour processing. Further work with larger cohorts and additional brain imaging analysis could contribute to such an idea. Work in the healthy brain has implicated temporoparietal and medial prefrontal regions in tonality expectation (Janata et al., 2002; Koelsch et al., 2005; Tillmann et al., 2003); particular focus on these areas in the future might reveal abnormalities that associate with deficits in tonality processing in AD. Additionally, as a non-DMN region, IFG has been implicated in tonal processing in the healthy brain (Brown & Martinez, 2007; Koelsch, 2006; Koelsch et al., 2003, 2005, 2006; Tillmann et al., 2003) which may be particularly pertinent to naPPA and to a lesser extent lvPPA.

The typical AD group were able to detect timbral deviants and comply with the task demands of the current paradigm. Therefore for this patient subgroup, it is likely that any deficits revealed in other experimental tasks are related to the perceptual demands of the stimuli. The lvPPA group were able to comply with a number of task elements in the pitch and

temporal pattern tasks, however they performed worse than controls in timbre deviance detection. Deficient processing of timbre in both lvPPA and naPPA has been shown in previous work (Goll et al., 2010, 2011). The pattern of performance in the naPPA group showed impairment in all domains (including timbre deviance detection). Thus, it is difficult to exclude the possibility that this group found the demands of this particular paradigm difficult to comply with – for example responding with a button press, or meeting the sustained attentional demands of the tasks. Many of the patients in the naPPA group were also inclined to press more frequently (and indiscriminately) rather than a total absence of detection; this poor performance may point towards particular difficulty in encoding auditory input, or towards a general behavioural bias to over-respond in such paradigms. The mild levels of motor slowing in the naPPA group are unlikely to account for such a response profile where more presses are evident. Nevertheless, subsets of all patient groups (including naPPA patients) were able to perform comparably to controls in an easy two-note version of the local-global pitch pattern task.

A primary deficit of processing spectrotemporally complex sounds is corroborated via music in this study, in line with previous work indicating perceptual deficits in both speech and nonverbal sounds in naPPA (Goll et al., 2010, 2011; Hailstone et al., 2012; Maruta et al., 2014; Rohrer et al., 2012b). This paired with the defining features of working memory and syntax processing deficits (Gorno-Tempini et al., 2011; Grossman, 2012; Libon et al., 2007), may indicate a more generalised difficulty in integrating auditory signals over long time periods in naPPA. However, this suggestion is at odds with preserved familiar melody recognition in our naPPA sample; therefore the processing of novel versus well learned auditory signals seems to diverge. One suggestion that may account for such results is based on previous work showing that non musicians need on average 5 notes to recognise a tune as familiar (Dalla Bella et al.,

2003). It may be that the naPPA auditory system can cope with recognition of short familiar excerpts in isolation, however breaks down when either detecting such musical templates amongst distractors, or actively tracking and integrating novel auditory information over a longer time period. Regardless, further work to define any separation in pathways for familiar and unfamiliar sounds may facilitate our understanding of music processing in both dementia and the healthy brain.

Performance on the embedded tunes task signifies a difficulty with streaming of melodic stimuli in both AD variants as well as naPPA. This supports the hypothesis that deficiency in generic ASA in AD also applies to musical stimuli. As the analysis only included items that were recognised in isolation, the results would suggest the addition of distracting auditory information as the main culprit for poor performance, rather than inability to either integrate tune elements over time, or impaired access to semantic representations. Everyday situations often require the processing of salient sounds over background noise and evidence for other nonverbal auditory processing deficits in these patient cohorts (Cope et al., 2014; Gates et al., 1995, 2011; Goll et al., 2010, 2011; Golob et al., 2001; Kurylo et al., 1993; Strouse et al., 1995) suggest that auditory input dysfunction represents an understudied symptom that would benefit from further investigation. The current task utilised the 'highest voice effect' – whereby preference is afforded to the top line in any polyphonic mixture (Crawley et al., 2002; Fujioka et al., 2005, 2008; Palmer & Holleran, 1994). More subtle deficits of attention might be detected if this were tapped explicitly. Additional work to decipher whether temporoparietal atrophy contributes to the musical streaming deficit seen in these patients, as well as any potentially distinct dysfunction between disease phenotypes, would also be of use.

There are a number of caveats to be taken into account when considering the approach of this study. The use of such a novel task in assessing elements of pitch and temporal pattern processing was, as mentioned, designed to minimise working memory demands. However, this method did place extra demand on patients' sustained attention, and integration of elements over time was still required. Conversely, such processing demands are unavoidable for stimuli that in their very nature unfold over time; in fact the current paradigm represents naturalistic listening situations more closely than alternative forced choice methods. Patient groups may have been using different strategies in their responses – the naPPA group in particular pressed much more frequently than the control group; therefore tasks that require a button press may not be as suitable for this patient group. Although both lvPPA and naPPA tend to affect individuals predominantly at younger age (Rogalski et al., 2007), the tAD group here represented relatively younger onset patients. Whilst advantages are lower incidence of other pathologies (i.e. vascular damage) and lower likelihood of peripheral hearing loss, this may have influenced the current results. Previous work in the visual domain has suggested that younger onset AD patients are more inclined to exhibit a global processing impairment compared to older onset patients (Matsumoto et al., 2000). Further work is needed to determine whether this is corroborated in the auditory domain. The present findings require replication. Nevertheless, these findings may form a starting point on which subsequent studies of musical scene processing can expand, and the use of music as a valuable nonverbal tool to assess nonverbal auditory cognition in dementia is widened.

7 GENERAL DISCUSSION

7.1 Summary of findings

This thesis sought to characterise specific deficits in ASA processing in AD that were applicable to everyday listening situations, and how these relate to the disease's neuropathological profile. Specific deficits in the processing of spatial sound, tracking of pitch contour, musical template segregation and tonal perception were found. Where tested, rarer phenotypes showed a similar ASA profile; furthermore a PCA group exhibited a greater impairment in one aspect of auditory spatial processing. Neuroanatomical associations point towards posterior DMN regions as the most likely brain bases for these behavioural difficulties; this was demonstrated in both regional atrophy and altered patterns of neural activation.

Chapter 3 confirmed the previous findings of Kurylo et al. (1993), and using virtual spatial sounds presented through headphones documented impairments in motion detection and location discrimination in typical AD. This deficit also extended to the visual variant of AD (PCA) and was more pronounced in this subgroup with respect to auditory motion detection. Atrophy in DMN regions such as right IPL and PMC correlated with performance in auditory motion detection and location discrimination respectively.

Using similar stimuli, an inability to modulate PMC activity in response to change in the spatial location of sounds was apparent for a typical AD cohort in chapter 4. Differential activation for the interaction of change in spatial and non-spatial auditory components was also displayed in a region that whilst not attributed to the DMN, may act as a link between DMN and the salience network non-DMN region (right posterior insula).

In chapter 5 a region in the right IPL exhibited altered activation in a typical AD group in response to the interaction of template (own name) and auditory stream segregation. This stemmed from an inability to deactivate this region in a similar way to the healthy control group and negatively correlated with name-over-babble detection in an out of scanner task.

The behavioural findings of chapter 6 indicate selective deficits in relation to music processing. Compared to naPPA patients who showed a pervasive difficulty on all tasks assessing musical scene processing, both typical and language variant (lvPPA) AD groups found the detection of global pitch contour deviants disproportionately harder to detect than local changes; they also were less likely to detect tonal deviants in unfamiliar melodies. This was not the case for rhythm and metre, where the two groups performed similarly to controls. Assessing 'musical streaming' through the use of familiar auditory templates presented in distractor tunes exemplified how generic concepts of ASA can be applied to common listening situations, and consequently displayed a deficit in both AD phenotypes.

7.2 ASA and neural networks in AD

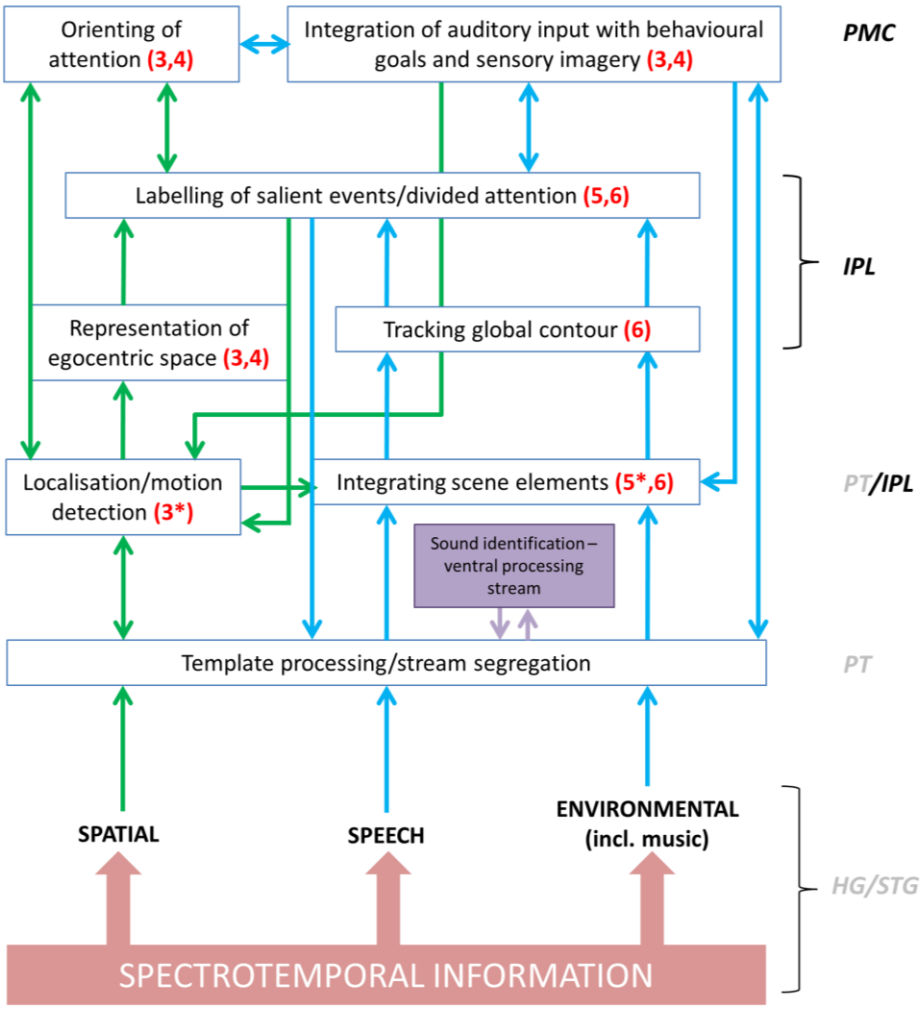
This thesis demonstrated how both structure and function of posterior DMN neuroanatomical regions contribute towards behavioural ASA deficits in AD. Arguably the strongest connection was between auditory spatial processing, a function that taxes the dorsal auditory stream, and parietal DMN loci (PMC and IPL). Convergence of both grey matter volume loss and functional alterations on the PMC during spatial sound localisation indicates the utility of auditory spatial processing in accessing this 'hub' region. Tracking sound sources in space requires updating of an internal sensory image with incoming sensory information and precise dynamic coding of sensory signals: neural operations that are likely to be vulnerable to the anatomical topography of AD (Leech & Sharp, 2014;

Vogt & Laureys, 2005) and to the effects of neurodegenerative pathology on essential electrophysiological properties of cortical neurons (Ahveninen et al., 2014; Cancelli et al., 2006; Jessen et al., 2001). As suggested in section 1.4, DMN breakdown in AD may contribute to loss of multiple processes, as all its nodes are likely to engage in more than one function. For example, PMC dysfunction in AD has been previously shown to correlate with memory and visuospatial function (Bokde et al., 2010; Celone et al., 2006; Desgranges et al., 2002; Jacobs et al., 2012; Pihlajamäki & DePeau, 2008; Pihlajamäki & Sperling, 2009; Sperling et al., 2003, 2010; Thiyagesh et al., 2009; Vannini et al., 2008). Spatial imagery may be one unifying process that cuts across all three functions. These elements may also tie in with and extend the general proposed 'internally-directed' cognition of the DMN (Buckner & Carroll, 2007; Buckner et al., 2008). One caveat to this proposal is the utility of DMN reduction in response to *any* task (Gusnard & Raichle, 2001; Raichle et al., 2001; Shulman et al., 1997). As functional studies in AD have tended to focus on memory tasks, it is still difficult to rule out aberrant PMC/DMN activity as a generic processing defect in response to general external stimuli in AD.

These conjectures remain to be tested in future work. Nevertheless, the functional MRI studies in this thesis also highlight the need to look beyond neural deactivation in AD. Chapter 5 showed a difference in how right SMG responded to auditory templates processing over babble: this stemmed from an inability to reduce its activity in the AD group. The interaction between spatial location change and disease group in chapter 4 also resulted from a lack of PCC differentiation between conditions in AD. This exemplifies how imaging modalities that assess function rather than structure contribute to the holistic picture of disease in AD. Figure 7.1 attempts to draw together the neuropsychological and neuroanatomical findings found in this thesis by referring back to the

schematic diagram (Figure 1.3) of how DMN dysfunction may contribute to ASA impairment in AD. It is notable how there is little evidence from the studies in this thesis for lower-level template and stream segregation deficits *per se*; it is when these two aspects combine, or when spatial elements are involved, that the current findings are better characterised. This could also be viewed as ASA in more ecological settings. What this thesis did not find was links between ASA and the DMN as a whole (i.e. dysfunction in all nodes concurrently). However, ASA may provide a useful means of assessing posterior DMN function. As suggested previously, it is these posterior DMN regions that may serve as a link between different phenotypes of (especially young onset) AD (Lehmann et al., 2010, 2013; Migliaccio et al., 2009; Warren et al., 2012). Therefore further investigation into how and why posterior DMN nodes affect ASA may also inform us about what leads AD neuropathology to diverge into asymmetric or posterior variants.

Figure 7.1 - Schematic representation of proposed associations between DMN and ASA in AD: integration with findings of current investigations



Reproduction of Figure 1.3 with additional support from findings in this thesis. Numbers (bold, red) indicate which chapters provide support for the implication of either function or neuroanatomical region in AD. * direct evidence for an association between function and neuroanatomy

7.3 ASA processing in AD phenotypic variants

In addition to assessing ASA in typical, amnestic AD, I also investigated auditory spatial processing in PCA and musical scene analysis in lvPPA. The PCA group were similarly impaired at sound location discrimination, but showed a greater deficit in detecting auditory motion. This index of ASA processing correlated with right posterior IPL; therefore the greater

involvement of posterior cortical areas in PCA may explain this disproportionate impairment. While vision is the most salient symptom for this disease group, the findings in chapter 3 highlight how multi-modal spatial impairments may contribute to environmental disorientation in PCA. The similar level of sound localisation impairment between PCA and AD speaks to a tentative suggestion that PMC may be similarly affected in both groups; this region may therefore provide a unifying neuroanatomical feature between phenotypes (Lehmann et al., 2010, 2013) with spatial sound localisation as a behavioural index of its degeneration.

Small sample sizes prevented description of neuroanatomical relationships between musical scene performance and AD phenotypes in chapter 6, however behavioural evidence indicates similar profiles in memory- and language-led AD. The impairment of embedded tune detection signifies difficulty in segregating auditory templates from background, extending the findings of generic ASA impairment in AD (Goll et al., 2012) to real-world auditory stimuli. Caution must be taken interpreting such a novel paradigm, but the additional impairment of global rather than local pitch deviance detection warrants attention. This cannot be simply attributed to inability to integrate auditory events over time as both groups performed similarly to healthy controls in temporal deviance detection. In section 6.1.1 I drew parallels with global and local dichotomies in visuospatial processing in AD; pitch may be perceived as a visuospatial image, especially when considering musical notation and the conceptualisation of pitch contour. Thus, relationships between auditory and visuospatial imagery and perception may go towards explaining the findings of chapter 6. Examination of anatomical relationships with such functions may uncover generic processing biases that inform us about the AD brain. In combination, chapters 3 and 6 signify how ASA may be similarly affected across AD variants. Future work should address this with

concurrent assessment of ASA processes both behaviourally and neuroanatomically for all phenotypes in direct comparison.

7.4 Top down and executive factors

This thesis focused on ASA processes that require integration of bottom-up signals with auditory templates such as spatial location cues, one's own name and familiar melodies. However, none of the studies sought to unpick the various contributions of these processes from attentional and executive deficits also seen in AD. Control tasks with similar demands as the test of interest were devised to rule out low-level auditory input difficulties and demonstrate ability to comply with the task itself – for example timbre and pitch discrimination attempted to match working memory demands of the auditory spatial tasks, or timbre deviance detection mirrored sustained attention demand in the musical tasks. Backward digit span was also commonly used as a covariate to account for working memory and executive function. The fact that many of the deficits persisted after controlling for this factor suggests that the deficits seen throughout this thesis cannot be simply attributed to a reduction in working memory capacity. However, tasks that systematically vary the attentional demands in ASA may provide further information about how bottom-up and top-down processes interact. Techniques such as priming, changing the voice (top/middle/bottom) in musical streaming and use of bistable percepts may provide such a source.

7.5 Can ASA aid diagnosis of AD?

In a study using a prospective cohort of older adults, Gates et al. (2011) suggested that deficits in central auditory function may be a 'harbinger' of AD. Combined with visual spatial processing, auditory spatial localisation may contribute to detecting an early weakening of posterior DMN nodes. In the current studies, this dimension also correlated with indices of disease severity, indicating its impairment may track disease progression. However, longitudinal studies are required to confirm this suggestion.

Practically speaking, difficulty in processing multiple streams of auditory information may be easier and more salient for an individual to detect. As Gates et al. (2011) remark, simple and short tests of ASA could be devised that provide a general health screen for which greater attention can then be given if scoring poorly on a particular dimension. Similar ideas have been proposed regarding the early olfactory impairment in AD (Mesholam et al., 1998; Wilson et al., 2009). Characterising ASA as a biomarker for AD may not supersede indices such as brain imaging or CSF profiles, as these are commonly abnormal a number of years before any cognitive symptom onset (Jack et al., 2013; Sperling et al., 2011). One further issue surrounding ASA is that ageing cohorts concurrently experience peripheral hearing loss (Davis, 1990). One of the exclusion criteria for recruitment into all current studies was peripheral hearing loss, therefore despite its use in considering how neural networks in AD affect ASA, blanket assessments would likely be confounded by presbycusis in the general population. There is also growing evidence that peripheral hearing loss may associate with later cognitive decline (Lin et al., 2011); peripheral and central auditory functions and their relative predictive power for AD onset will need further attention before any definitive statements can be made.

7.6 ASA and naturalistic listening situations in AD

The findings of this thesis have a number of implications for the everyday experience of AD patients. Emphasising difficulties in processing concurrent auditory streams and determining the spatial location of sounds speaks to a number of commonplace situations: conducting a conversation in a busy restaurant or over a noisy phone line and orienting visual attention to any event occurring out of sight. The ability to communicate with others is an essential part of social interaction: a patient's lack of understanding may be attributed to other cognitive impairments when they could be ameliorated by a change in environment. The present findings also highlight the need to look outside

memory to gain a holistic picture of how AD affects an individual's daily experiences. Modification of patients' environments and awareness of these symptoms may increase quality of life. Patients' enjoyment of musical stimuli has proven more difficult to unpick, as despite their difficulties in perceiving polyphonic music, global pitch patterns and tonality, listening to music improves mood and cognition in AD (El Haj et al., 2012; Irish et al., 2006; Moussard et al., 2014; Simmons-Stern et al., 2010; Thompson et al., 2006). Patients may be able to use their preserved metre and rhythm perception to access some of these beneficial effects.

7.7 Limitations

The conclusions of this thesis are accompanied by inevitable general limitations. Due to the recruitment sources used, some of the patients had relatively young onset. Whilst this minimises any potential confounds such as higher likelihood of peripheral hearing loss, or concomitant white matter disease, the younger typical AD cohort used here may represent a slightly different phenotype with greater involvement of parietal regions compared to later-onset AD (Ossenkoppele et al., 2012). Furthermore, most patients were receiving acetylcholinesterase inhibitors to minimise cognitive symptoms; the extent to which this alters BOLD signal is unclear (Bentley et al., 2008; Kircher et al., 2005). Testing patient volunteers before they commence their treatment may resolve this, however may be problematic with such a short time window for testing availability. The use of musical stimuli is accompanied by the caveat that musical ability is widely varied in the general population. Furthermore, in order to utilise some of the rules that we acquire over a lifetime's worth of musical listening, I used stimuli that were tightly intertwined with Western classical music. This reduced the potential cohort to those who were culturally Western.

7.8 Future directions

The studies in this thesis have shown how ASA may aid in our understanding of DMN function in the AD brain. To confirm some of these findings, larger cohorts that represent the entire phenotypic spectrum are needed, potentially via multi-centre studies. Stratifying patients based on disease stage (or even pre-clinically, such as asymptomatic mutation carriers) may facilitate our understanding of how central auditory function changes over the disease course. The overlap of DMN regions and the dorsal auditory stream may affect processes that prepare an individual for action when parsing the auditory scene (Hickok & Poeppel, 2007; Warren et al., 2005), therefore assessing the effect of task versus passive listening may reveal separable substrates. Further work assessing how visual and auditory processing interact may elucidate additional mechanisms for the analysis of complex auditory scenes in both AD and the healthy brain (Delbeuck et al., 2007; McGurk & Macdonald, 1976). Furthermore, the use of fMRI to indicate altered function in areas of DMN may be applicable to other stimuli classes. Using multimodal stimuli that focus on general functions of DMN such as moderating the spotlight of attention or internal reference may tell us more about the AD brain than a narrow focus on memory functions. Future work could test these ideas directly by comparing large-scale brain network interactions in AD and diseases (such as the frontotemporal lobar degenerations) with distinct network signatures (Zhou & Seeley, 2014); and by manipulating spatial and nonspatial attributes of more complex, naturalistic auditory 'scenes', such as music or commonplace auditory environments.

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APPENDICES

Appendix 1: Participation of individual typical AD patients by study

Patient	Chapter 3	Chapter 4	Chapter 5	Chapter 6
1	√		√	
2	√			
3	√		√	
4	√			√
5	√		√	
6	√			
7	√			
8	√		√	
9	√			
10	√			
11	√			
12	√	√	√	√
13	√	√	√	√
14	√			
15	√	√	√	√
16	√	√	√	
17	√	√	√	
18	√	√	√	√
19	√			
20	√			
21		√		
22		√		√
23		√		√
24		√		√
25		√		√
26		√		√
27		√		√
28		√		
29			√	
30			√	
31			√	
32				√
33				√
34				√
35				√
36				√

Ticks for each study indicate participation in a particular study; numbers are not sequential and serve no other purpose than to differentiate between participants and display the extent of overlap between studies.

Appendix 2: Items used in the musical experience questionnaire

The questionnaire items used in chapter 6 are taken from Hailstone et al. (2009)

1. Have you ever had any musical training (music lessons at school, lessons on an instrument, etc)?
*(**yes/no**)*

1a. If Yes, what kind and for how long?

2. Have you ever played a musical instrument?
*(**yes/no** – if no, skip to question 6)*

3. If Yes, which instrument(s)?

3a. How long did you play it (them) for?

3b. What standard did you reach (grade, etc)?

4. Do you still play an instrument regularly?
*(**yes/no** - if no, skip to question 6.)*

5. If Yes, which instrument?

5a. Approx. how many hours per week do you play?

5b. Where do you play (at home, band, orchestra, etc)?

6. Do you listen to music regularly?
*(**yes/no**)*

7. If Yes, approximately how many hours per week do you listen to music?

8. What kind of music do you mainly listen to (pop, easy listening, jazz, classical, etc)?

Appendix 3: Items used in the embedded tunes task

These ten famous tunes comprised the embedded tunes task (chapter 6):

1) Mary had a little lamb

2) London Bridge

3) Jingle Bells

4) Three blind mice

5) Frere Jacques

6) God save the Queen

7) Twinkle twinkle

8) Silent night

9) When the Saints go marching in

10) Auld Lang Syne

Appendix 4: Division of Labour

The work described in this thesis was conducted by HLG in collaboration with other researchers based at the Dementia Research Centre. Contributions made by others for each chapter is detailed below.

Chapter 3 – Auditory spatial processing in AD: a neuropsychological and structural neuroanatomical investigation
Experimental design: HLG, JDW, SJC
Construction of tests: HLG, JDW
Data collection: HLG, KXXY, TJS, LED
Data analysis: HLG in consultation with JMN
Writing: HLG, JDW

Chapter 4 – Auditory spatial processing in AD: an fMRI investigation
Experimental design: HLG, JDW
Construction of tests: HLG
Data collection: HLG
Data analysis: HLG
Writing: HLG, JDW

Chapter 5 – Auditory masking in AD: an fMRI investigation
Experimental design: HLG, JCG, JDW, SR
Construction of tests: HLG, JDW
Data collection: HLG, LED
Data analysis: HLG in consultation with JLA
Writing: HLG, JDW

Chapter 6 – Assessing pitch, temporal, streaming and key functions as 'musical scene' elements in AD: a neuropsychological investigation
Experimental design: HLG, JDW, SJC
Construction of tests: HLG
Data collection: HLG, CNC, MHC
Data analysis: HLG in consultation with JMN
Writing: HLG

Appendix 5: Publications

Publications as a direct result of the work conducted in this thesis:

Golden H.L., Nicholas J.M., Yong K.X.X., Downey L.E., Schott J.M., Mummery C.J., Crutch S.J., Warren J.D. 2015. Auditory spatial processing in Alzheimer's disease. Brain. 138, 189-202. [Reprint below]

Golden H.L., Agustus J.L., Goll J.C., Downey L.E., Mummery C.J., Schott J.M., Crutch S.J., Warren J.D. 2015. Functional neuroanatomy of auditory scene analysis in Alzheimer's disease. Neuroimage: clinical. 7, 699-708. [Reprint below]

Golden, H.L., Agustus, J.L., Nicholas, J.M., Schott, J.M., Crutch, S.J., Mancini, L., Warren, J.D. 2016. Functional neuroanatomy of spatial sound processing in Alzheimer's disease. Neurobiology of Aging. 39, 154-164.

Warren, J.D., Fletcher, P.D., Golden, H.L. 2012. The paradox of syndromic diversity in Alzheimer's disease. Nature reviews. Neurology. 8, 451-464. [Reprint below]

Other substantial contributions:

Clark, C.N., Golden, H.L., Warren, J.D. 2015. Acquired Amusia. In The handbook of clinical neurology: human auditory system: Fundamental organization and clinical disorders. Ed. Celesia, G., C., Hickok, G. 129, 607-631

Golden, H.L., Downey, L.E., Fletcher, P.D., Mahoney, C.J., Schott, J.M., Mummery, C.J., Crutch, S.J., Warren , J.D. 2015. Identification of sounds and melodies in syndromes of anterior temporal lobe degeneration. Journal of the Neurological Sciences. 352, 94-98.

Halpern. A.R., Golden, H.L., Magdalinou, N., Witoonpanich P., Warren, J.D. 2015. Musical tasks targeting preserved and impaired functions in two dementias. Annals of the New York Academy of Sciences. 1337, 241-248.