

**Central and peripheral auditory changes and cognitive decline in ageing**

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# Abstract

Hearing loss (HL) is a common disorder of the elderly, and is associated with communication difficulties and social isolation. Most recently, HL has been inconsistently linked to cognitive decline and it has been postulated that HL may be an independent risk factor for dementia. The aim of this thesis is to determine whether HL is associated with cognitive decline during normal and/or pathological ageing by specifically investigating contributions from peripheral HL, central auditory processing and the psychosocial pathway.

Results show that central auditory processing was linked with cognition during normal and pathological ageing, but there was no independent association with peripheral hearing levels or psychosocial factors. The prevalence of HL was not significantly higher in the patient sample compared with matched controls, nor did HL influence the cognitive profiles in normal ageing or neurodegeneration. There was, however, a statistically significant interaction between HL and decline in executive function only in participants with HL who were high performers at baseline, thereby suggesting that peripheral HL is not an independent risk factor for cognitive decline. Higher scores on central auditory processing were associated with better performance on a test of visual long term memory, after controlling for the effects of peripheral HL, and could predict decline in cognitive performance over time on the Short Cognitive Evaluation battery. In keeping with this, the severity of pathological cognitive impairment was closely related to central auditory processing performance, and patients with mild cognitive impairment recruited the right hemisphere for linguistic processing, which was corroborated with findings of increased grey matter in the right auditory association areas.

In summary, it was concluded that the inconsistent findings in the literature may be due to differing influence of HL on normal and pathological cognitive ageing. Peripheral and central hearing changes may be a marker of impending neuronal decline or vulnerability to dementia in people with pathological cognitive impairment, but during healthy ageing, HL does not influence cognitive performance or increase the risk of developing dementia.

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# List of Abbreviations

**AChEi**= acetylcholinesterase inhibitor; **AD**= Alzheimer’s disease; **APP**= amyloid beta precursor protein; **ARHL**= age related hearing loss; **Aβ**= amyloid beta; **BA=** Brodmann area; **BMI**= body mass index; **CN**= cochlear nucleus; **CV**= cardiovascular; **C-V**= consonant- vowel, **dB**= decibel; **dB HL**= decibel hearing level; **DNMT1**= DNA methyltransferase 1; **DSS**= digit symbol substitution test; **FL**= forced left; **fMRI**= functional magnetic resonance imaging; **FR**= forced right; **GDS**= geriatric depression scale; **GM**= grey matter; **HHIE**= hearing handicap inventory for the elderly; **HL**= hearing loss; **IC**= inferior colliculus; **ICF=** International Classification of Functioning, Disability and Health; **KEMAR=** Knowles Electronic Manikin for Acoustic Research; **LEA**= left ear advantage; **MCI**= mild cognitive impairment; **MGN**= medial geniculate nucleus; **MMSE**= mini mental state examination; **MRI**= magnetic resonance imaging; **NEA**= no ear advantage; **NF**= non forced; **NFT**= neurofibrillary tangles; **NLL**= lateral lemniscus; **OOC**= organ of corti; OR= odds ratio; **PET**= Position emission tomography; **PTA**= pure tone audiometry; **PTAv**= pure tone average; **REA**= right ear advantage; **ReyDelay**= Rey complex figure test, delay component; **RR**= relative risk; **SAC**= self-assessment of communication; **SCEB**= short cognitive evaluation battery; **SEAH**= social and emotional associations of hearing loss; **ShiftL**= shift to the left; **SiN**= speech in noise; **SOC**= superior olivary complex; **SPM**= statistical parametric mapping; **VaD**= vascular dementia; **VBM**= voxel based morphometry; **VPA**= verbal paired associates.

# Chapter 1: Non pathological and pathological cognitive ageing

# Introduction - The challenges of senescence

The process of ageing can be described as “progressive physiological changes in an organism that lead to senescence, or a decline of biological functions and of the organism’s ability to adapt to metabolic stress” (Rogers et al., 2016). These biological functions tend to peak in the third decade, followed by a natural yearly linear decline (Strehler, 1999). In western societies, typically around retirement age of 60 or 65 is when an individual is classified as an older person. Currently there are 14.9 million people over the age of 60 living in the United Kingdom (UK), and this number is expected to exceed 20 million people by the year 2030 (Age UK, 2016).

With advancing age comes more experience and knowledge and thus ageing populations have been found to be advantageous to their communities (Healy, 2004). Although studies of ageing are not necessarily concerned with increasing debility (Healy, 2004), it is well documented that it is naturally associated with declines in sensory, physical, social and cognitive aspects (Horn and Cattell, 1967, Burke and Mackay, 1997, Hebert, 1997, Courtin and Knapp, 2015, Rogers et al., 2016). Although only 25% of the UK population is made up of people over the age of 65, over 67% of health service clients are of this age (Age UK, 2016), highlighting the importance of deteriorating health and the burden that disorders of ageing have on society.

It is important to note, age itself does not always correlate with functional disability, and certain modifiable risk factors, diseases and degeneration play an important role in functional decline (Leclercq et al., 2014). Certain lifestyle and behavioural factors can protect against decline, such as physical exercise, which can improve mobility, cognition, mental health and reduce risk of cardiovascular disease (Tsai et al., 2016, Schroeder et al., 2017).

Dementia is one of the leading causes of disability in later life (WHO, 2016). It is estimated that at present 850,000 people in the UK are living with some form of dementia, with over 90% of them being over the age of 65. Along with the ageing population, it is estimated that the prevalence of dementia will increase; it has been predicted one in three people born in the UK in 2015 will develop dementia at some point in their lives (Lewis, 2015), thus increasing the financial burden on the health service (Rice et al., 2001). However, there is also evidence that due to risk reduction including successful prevention of heart disease and increasing levels of education, this estimated increase in prevalence of dementia may be overinflated, and in fact incidence may decrease (Norton et al., 2014). A recent study comparing two randomly sampled cohorts, two decades apart, reported the current prevalence of dementia to be 24% lower than the expected prevalence based on the ageing population (Matthews et al., 2013). Despite advances in technology and clinical practice, experts often have difficulty in distinguishing between pathological and non-pathological ageing, for example in Alzheimer’s disease (AD). AD is the most common form of degenerative dementia (Scheltens et al., 2016), and tends to be associated with a negative prognosis, owing to an often late diagnosis and lack of effective treatments, which are symptomatic at best. This is due to its insidious onset and early symptoms which overlap with normal ageing (Tuokko et al., 2003); a differential diagnosis is not easy in the earliest stages when treatments are the most effective.

The remainder of this chapter will outline the spectrum from normal cognitive ageing to cognitive decline and dementia, and explore factors that influence the decline and protect against it. It will explain in more detail the challenges with identification of pathological cognitive ageing and differential diagnosis of dementia.

# Normal ageing

Normal ageing is biologically characterised by structural and functional alterations of organs and systems, due to accumulation of molecular and cellular damage through various physiological processes (Carmona and Michan, 2016). The detail and extent to which is beyond the scope of this thesis but it is necessary to appreciate changes are happening at the most basic cell levels to understand the underlying mechanisms of the cognitive neuroscience of ageing.

The term ‘healthy ageing’, therefore, refers to permitting our cells to remain healthy and functioning for as long as possible. There are well known factors that promote health in these cells in terms of resistance to the effects of ageing, but also the contrary, there are certain factors that accumulate to make our cells more vulnerable to the effects of ageing (Carmona and Michan, 2016). These biological changes with ageing can and do affect all bodily systems, but their effects on the central nervous system are particularly dramatic, as even cognitively healthy elderly individuals lose significant amounts of neuronal volume as they age (Fox and Schott, 2004).

Cognition consists of the perception, attention and emotional appraisal of stimuli, representation of stimuli in memory, and the subsequent use of the information gained from the stimuli (Schumann, 1994). Generally speaking, cognitive abilities are the mental skills required to carry out all basic to complex tasks. Age related changes to the central nervous system manifest as changes in cognition. The advent of in-vivo imaging techniques has enabled researchers to study the connections between changes in cognitive processing in ageing, and relate them to structural and functional changes in the brain (Whalley et al., 2004).

## Cognitive ageing

Cognitive ageing refers to the process of cognitive decline that occurs during ageing (Bergman et al., 2016, McCarrey et al., 2016). Subjective accounts from older adults tend to report subtle forgetfulness, difficulty learning new tasks and lack of concentration (Reid and Maclullich, 2006, Vestergren and Nilsson, 2011). This is supported by cross sectional neuropsychological studies, which have shown that older persons tend to score lower on a range of cognitive tests than younger populations (Yam et al., 2014), and neuroimaging studies which demonstrate a reduction in whole brain volume (Fox and Schott, 2004) and changes in regional brain activation (Cabeza, 2001).

Cross sectional and longitudinal studies have defined domain specific cognitive decline, where some processes and areas of the brain are more vulnerable to the effects of ageing. These include, attention (Madden and Langley, 2003), language (Bergman et al., 2016), processing speed (Salthouse, 1996) and various aspects of memory (Reuter-Lorenz et al., 2000, Bergman et al., 2016). Working memory and episodic memory show the largest age related decline (Nyberg et al., 1996, Solesio-Jofre et al., 2016), but there is little evidence for age related changes in the procedural and semantic aspects of long- term memory (Nyberg et al., 1996, Budson and Price, 2005). General knowledge, semantic memory and emotional regulation tend to be maintained or, in fact, improve, with advancing age (Salthouse, 2004, Carstensen et al., 2011).

A feature not widely recognised is that declines may actually begin in early adulthood and do not necessarily run a linear course (Vercammen et al., 2016). Evidence from autopsy and in vivo MR imaging has shown that brain atrophy begins in early adulthood, and continues, with a marginal increase in rate into old age (Dekaban, 1978). Multiple studies have shown the overall percentage rate of atrophy to be about 0.2% in brains aged between 30 to 50, which increases to 0.3-0.5% when aged 70 to 80 years old (Scahill et al., 2003, Resnick et al., 2003). There is also evidence for fluctuations in levels of grey and white matter throughout the adult lifespan, again suggesting a nonlinear course of ageing (Fox and Schott, 2004).

To demonstrate this, Vercammen et al., (2016) compared performance on three measures of working memory between three different age groups of adults, young (20-30 years old), middle aged (50-60 years) and old (70-80 years). They reported that young adults performed consistently better on all three tests of working memory compared to the older two groups, who had a relatively similar performance. This suggested to the authors that decline in working memory ability start after early adulthood, and then remain stable through the middle ages into old age. Other aspects involving working memory, such as problem solving abilities, may actually have an inverted trajectory of age related decline. Middle aged adults outperform younger and older adults on tasks of positive problem orientation and rational problem solving (D' Zurilla et al., 1998), suggesting that problem solving abilities increase with age, then reduce into old age.

Long-term memory refers to items in the memory that can be recalled from the past. This can be subdivided into three components, procedural memory, episodic memory and semantic memory (Tulving, 1987). Procedural memory relates to the knowledge of how to perform tasks, such as walking or riding a bike. Episodic memory refers to memories that have a specific spatial and temporal context and includes a collection of personal experiences, usually involved with emotions, and semantic memory includes common knowledge, for example names of colours and meanings of words. Not all aspects of long-term memory are equally affected by age, whilst aspects of procedural memory and semantic memory remain relatively immune to the effects of ageing, episodic memory is greatly affected (Luo and Craik, 2008).

Older adults often remember the facts of a piece of information, but have difficulty remembering the source of information; for example. Evidence for age related decline in episodic memory has been extensively reported (Bernard et al., 2007, Tromp et al., 2015), and one study demonstrated that age is a significant predictor of poorer performance on a battery of tests assessing episodic memory, explaining 4.3% to 34.8% of the variance (Nyberg et al., 1996). Comparisons with the same group of adults undertaking tests of semantic memory, found that there was no association between age and semantic memory scores.

Another area commonly reported to show an age related decline is attention. Attention, often thought of as a basic process, simply defined as ‘taking notice of something’, is a complex entity, involving a momentary enhancing of some information for further processing, at the same time as inhibiting other information that is not important (Raz, 2004). Attentional processing is not a single process, but as with long-term memory, there are different categories of attention, which include selective, divided, and sustained attention (Quigley and Muller, 2014). Selective attention is the ability to focus on one entity or task, ignoring other factors. Divided attention is the focusing on and successful execution of more than one task at a time, and sustained attention is the ability to focus on one task over time, or in a changing environment. Not all of these subcategories are affected in the same way by age, and usually elderly individuals tend to perform worse on tasks of divided attention, rather than selective or sustained attention, which remain relatively preserved in healthy ageing (Cona et al., 2013, Lufi et al., 2015, Getzmann et al., 2016).

Older adults increasingly perform worse on tasks of divided attention, compared to younger adults, and require a greater amount of attentional resources to be allocated to perform these tasks (Wild-Wall and Falkenstein, 2010). Performance on a simple auditory reaction time task was compared between 8 younger (22 - 34 years old), and 8 older (66 - 79 years old) adults under two conditions, whilst in a static position, (seated or standing with support,) or whilst walking (Lajoie et al., 1996). All 16 participants had longer response times during the walking task, when attention was divided, with the older group taking significantly longer than the younger group. The older adults also adopted a slower walking speed and shorter stride length, suggesting greater amount of attentional resources were being allocated to posture control (Lajoie et al., 1996) at the detriment of speed.

Sustained or selective attentional processes are not affected by the normal ageing process (Tales et al., 2002). Visuospatial attention is relatively preserved in healthy ageing, where age only portrays a weak influence on task performance in the eighth decade (Greenwood et al., 1993). Certain tasks of selective attention, however, have shown a negative correlation with age (Quigley and Muller, 2014). This could be due to sensory decline with ageing and not purely to deficits in attentional processes (Baltes and Lindenberger, 1997). Interestingly adults over the age of 50 show declines in performance of auditory selective attention, during tests of dichotic listening compared with younger adults (Hugdahl et al., 2001).

Cohort and individual differences may complicate this relationship further, as in the case of gender. Age only provided a significant effect in males, relating to rational problem solving abilities, and females, on tasks of positive problem orientation (D' Zurilla et al., 1998). Similarly, trials of episodic memory have shown higher performance in females compared with males of the same age (Herlitz et al., 1997, Lundervold et al., 2014). Conversely, Cheke and Clayton, (2013) found no effects of gender on episodic memory performance when comparing three neuropsychological tests of episodic memory. They did report, however, a lack of internal consistency between tests. There was only a correlation between scores on two out of the three tests claiming to measure the same processes. This highlights that measurement of specific domains of cognition may be challenging due to the overlapping nature of cognitive functions (Peters, 2006), and therefore testing a unitary construct alone may not be possible.

Similarly, education has a role to play in cognitive ageing. A recent study showed that elderly people with at least nine years of formal education, had a higher cognitive level and a slower rate of cognitive decline over 18 years (Zahodne et al., 2015a). This introduces a protective effect of education, and the concept of cognitive reserve, which will be further explained in section 1.4.1.

To control for these differing characteristics, a prospective study aiming to define the neural correlates of age-related episodic memory decline, measured episodic memory performance longitudinally in a group of individuals with the same apparent background characteristics (Persson et al., 2006). Although the researchers found an age related decline in overall group performance, there was a great variability in individual performance, with some individuals’ remaining stable over time (Persson et al., 2006). This suggests that some individuals with poor performance, who are apparently healthy, may have latent neurodegeneration which is yet to manifest clinically, biasing the effects of cognitive ageing (Whalley et al., 2004).

Taken together this conflicting evidence indicates that results must be interpreted with caution and are influenced by cohort effects on group levels. It is therefore difficult to interpret the effects that age alone may have on cognition, as risk factors that accumulate with age may play more of a role in cognitive decline, for example, as a result of poor health (Bergman et al., 2016). Vascular risks and current levels of vascular damage to the brain are hard to control for and it is still unknown what effect age has on haemodynamic reactivity (Park et al., 2001, Tsvetanov et al., 2015). As the strength of signal of many imaging modalities, including position emission tomography (PET) and functional magnetic resonance imaging (fMRI), depend on vascular changes, age related vascular fluctuations could account for some of the differences in strength of the signal between young and older adults (Park et al., 2001, Hillary and Biswal, 2007), and therefore studies on group levels comparing ages may be misleading.

Despite an increase in whole brain atrophy, voxel based morphometry has revealed some areas of the neocortex are more sensitive to the effects of ageing. The most affected areas are the frontal cortex and cerebellum, intermediate levels of neuronal loss are found in the mediotemporal cortex, and there is relative sparing of the parietal and occipital cortex (Raz et al., 2005). This is consistent with the behavioural declines reported in executive function (frontal) and episodic memory (frontal and mediotemporal). However, a recent study showed that atrophy is not the best structural biomarker of physiological ageing (Cherubini et al., 2015). Due to limited changes in brain volume during normal ageing, which may not directly correlate with decreases in cognitive function (Hultsch and MacDonald, 2004), there has been increased interest in exploring the functionality and connectivity of brain regions. Evidence from studies of functional neuroimaging have suggested that there may be adaptive neural mechanisms in elderly brains to compensate for these atrophic changes, for example, by reorganisation of neuronal networks (Park et al., 2001).

There is some evidence that different brain areas are activated during the same tasks in younger and older brains. Participants aged between 20 and 87 scored the same on cognitive tasks of verbal memory, but analysis of activation demonstrated involvement of different brain areas (Hazlett et al., 1998). Younger adults showed activation in the dorsolateral prefrontal cortex, and older adults had more activation in the occipital cortex. This suggests that to perform to the same level on cognitive tasks, there may be a dynamic reallocation of resources within networks, compensating for the age related structural changes seen in frontal cortex (Grady, 2008).

Contralateral recruitment may occur in older adults to continue to perform at a similar cognitive level to younger adults (Davis et al., 2012), a term known as Hemispheric Asymmetry Reduction in OLDer adults, or HAROLD (Cabeza, 2002). PET imaging can be used to investigate the neural substrates of verbal and spatial working memory. During tasks of episodic memory and working memory, younger and older adults have different activation patterns, with differing levels of asymmetry (Ranganath et al., 2003). Younger adults had left lateralised prefrontal cortex activation during verbal working memory tasks, and right lateralised prefrontal activation during spatial working memory tasks. Older adults showed a more global pattern of anterior bilateral activation for both verbal and spatial working memory tasks (Reuter-Lorenz et al., 2000). Younger adults showed left frontal and mediotemporal activation during encoding of long-term memory, and right frontal activation at the retrieval stage. Older adults showed less activation in both left frontal and mediotemporal lobes during the encoding phase, with bilateral activation of frontal lobes during the retrieval stage, again demonstrating contralateral recruitment to help maintain performance on long-term memory tasks (Cabeza et al., 1997). These findings suggest that supplementary areas may have been recruited to augment task performance, or possibly, that the effects of ageing may lead to a decrease in functional specificity of working memory (Peters, 2006, Grady, 2008).

To conclude this section, a general age associated decline was seen in various cognitive domains, and no difference or continual improvement in other areas. The advent of MRI has allowed scientists to discover and follow structural and functional effects of ageing on the brain in vivo, and link these to behavioural functions. A wide array of heterogeneous brain changes has been documented. Despite this, cognitive ageing is a phenomenon that is not fully elucidated due to individual differences, compensation, variability amongst cognitive domains, and the overlaps with neurodegeneration. Studies of non-pathological ageing exclude disorders that are known to affect cognition, such as dementia or stroke (Whalley et al., 2004). Thus, a cognitively healthy sample will also include individuals with pathological ageing that has not yet manifested clinically. This variability makes it challenging to distinguish between the cognitive alterations found in normal and pathological ageing, and therefore, it is not known whether any true age –related differences in cognition are apparent when all disease is accounted for (Whalley et al., 2004). ‘Healthy’ cognitive ageing is difficult to study as problems arise from the methodology used to investigate it (Rabbitt, 2011), but nevertheless some understanding of the behavioural, structural and functional changes associated with ageing is emerging and the findings can be used to aid in the early identification of abnormal cognitive ageing.

# Abnormal ageing- cognitive decline and dementia

The challenges of classifying normal cognitive ageing make the classification of abnormal ageing even more problematic. Alongside the mild normal age-related impairments in cognitive functions, there is another trajectory of pathological cognitive impairment, which also increases with age, but is abnormal. This includes mild cognitive impairment (MCI) and dementia syndromes.

With the continually improving techniques of in vivo brain imaging, there is an increased level of understanding of the neurobiology of healthy ageing (Whalley et al., 2004). These techniques may help aid a clinical diagnosis of abnormal ageing at the earliest stages (Beltrachini et al., 2015). This is of great importance, as currently, there are no disease modifying treatments available for most dementia syndromes (O’Brien et al., 2016). Identification of factors which lead to the conversion from healthy ageing to the abnormal cognitive ageing trajectory remains of upmost importance.

## Mild cognitive impairment

MCI is the intermediate, or transitional state between normal ageing and dementia (Petersen et al., 2001). The decline of cognitive processes is more than what would be expected for the person’s age and level of education, but not severe enough to interfere with activities of daily living (Petersen, 2004). Approximately 20% of people over the age of 65 will develop MCI, and the relative risk of progression to dementia is almost 16 times higher for people with MCI compared to the healthy elderly (Mitchell and Shiri-Feshki, 2009).

There is extensive amount of literature regarding the structural and functional changes in specific regions and large scale networks in brains of people with MCI (Grady, 2012). fMRI studies have shown that patients with MCI have greater activation of the left hippocampus and surrounding areas of the medial temporal lobes during tasks of memory encoding, compared with healthy controls (Kircher et al., 2007). The authors suggested this greater activation could be a compensatory mechanism for underlying neuropathology.

There are two classifications of MCI, amnestic MCI, which is used to describe cases where cognitive decline is associated with memory loss, and non-amnestic MCI, where cognitive impairment is found in other domains, not related to memory (Petersen, 2004). In the cases of amnestic MCI, 90% of progressions to dementia are of AD phenotype (Petersen, 2011), suggesting amnestic MCI is a precursor to AD, or the earliest stage in which the patient experiences clinical symptoms of AD. Non-amnestic MCI may be more predictive of a different underlying aetiology, although there are insufficient numbers and studies investigating this to report on conversion rates to other types of dementia (Smith, 2013).

Not everybody with MCI will transition to develop dementia (Smith, 2013, Di Carlo et al., 2016). This estimated annual conversion rate is between 10-15% per person year (Tifratene et al., 2015). However, some researchers have proposed that these percentages are over exaggerated. During a naturalistic longitudinal study of conversion in MCI patients, over a three year period, it was found that only 20% developed dementia (Wolf et al., 1998). Almost 20% of patients had ‘recovered’, with the further 60% remaining stable. Therefore this might suggest that MCI should not be solely thought of as the intermediate phase leading to development of clinical dementia, but a result of many different underlying diseases, sharing the same symptoms of cognitive decline (Wolf et al., 1998, Mitchell and Shiri-Feshki, 2009, Smith, 2013).

However, there are some risk factors which accelerate conversion from MCI to dementia, such as diabetes (Degen et al., 2016), cardiovascular risk factors (Ettorre et al., 2012), smoking (Anstey et al., 2007), and weight loss (Cova et al., 2016). A recent study reported that the strongest predictor for progression to dementia were high levels of impairment on the Instrumental Activities of Daily Living scale (Di Carlo et al., 2016). This scale measures a range of tasks which are assumed necessary for an independent lifestyle, including items such as cooking and driving. Due to the trajectory of cognitive impairment, it could be that people with lower scores on Instrumental Activities of Daily Living Scale are already at a more clinically advanced level, explaining the increased conversion from MCI to dementia. Further discussion of risk and preventative factors will be included in section 1.4.

## Dementia syndromes

Dementia is the umbrella term used to describe a group of clinical syndromes that lead to a progressive decline in two or more cognitive domains, resulting in the inability to carry out activities of daily living and independent functioning (Mesulam, 1985). There are over a hundred known types of dementia, which are classified according to aetiology and pathology, but can be diagnosed clinically during life (Mesulam, 1985). Longitudinal studies have shown there are different cognitive trajectories amongst the different sources of dementia (Smits et al., 2015). Although there are other causes, the two main aetiologies of dementia syndromes are primary neurodegenerative, or secondary to other causes (Barker et al., 2002).

Neurodegenerative dementias are caused by various diseases or conditions, which lead to an abnormal accumulation of proteins and an irreversible degeneration of neurons (Caberlotto and Nguyen, 2014). They are defined and distinguishable by neuropathology, but there are often overlaps in clinical symptoms (Sancesario and Bernardini, 2015). AD is the most common form of neurodegenerative dementia, accounting for up to 50% of dementia cases, currently affecting 400,000 people in the UK and over 35 million people worldwide (Selkoe, 2012). Other, less common forms of neurodegenerative dementias include frontotemporal dementia and dementia with Lewy bodies (Alzheimer's Association,, 2016).

As well as dementia caused by neurodegeneration, there are also dementia syndromes which are secondary to other factors, such as vascular dementia (VaD).

Most forms of dementia can be diagnosed in vivo, but a definitive diagnosis can usually only be confirmed upon post mortem examination (Hyman et al., 2012, Beach et al., 2012). A clinical diagnosis is not always straight forward, as neurodegenerative forms of dementia pose a challenging early diagnostic problem, due to the insidious onset of symptoms in the preclinical stage. Currently there is no single indicator that helps clinicians to differentiate between normal ageing and preclinical dementia, and therefore a multidisciplinary approach must be used (Nicholl, 2009).

In 2015, the World Alzheimer Report predicted the global prevalence of dementia to be 46.8 million, and this number is expected to rise (Prince et al., 2015). AD and VaD are the most common forms of dementia (Barker et al., 2002). These will be discussed below, highlighting similarities and differences in aetiology, clinical symptoms, progression, management, treatment and prognosis.

### Alzheimer’s disease (AD)

AD is the most common cause of dementia. It is familial in only a small proportion of cases, but there are a number of genes and genetic factors that increase the risk of developing sporadic AD (Reitz and Mayeux, 2014). The vast majority of cases, are sporadic, and typically affect people over the age of 65 (Goedert and Spillantini, 2006). As the greatest risk factor for AD is age (Hebert et al., 2013), AD is classed as an age related disease, but it is not age dependant, cases have been documented in people as young as 30 years old (Kumar-Singh et al., 2006). When AD affects people under the age of 65 it is classified as an ‘early onset’ form. Early onset AD has more of a genetic component and a different progression (Panegyres and Chen, 2013), which will not be discussed in this thesis.

In 1906, Alois Alzheimer, a German psychiatrist and neuropathologist, described the disease which now bears his name using a single case study (Alzheimer, 1907). The patient was a 51 year old female who was suffering with severe memory loss, paranoia, delusions, aphasia and behavioural disturbances. She died within four and a half years from the onset of clinical symptoms (Möller and Graeber, 1998). Upon post mortem dissection, Alzheimer noticed protein deposits in and around the neurons, neuronal loss and brain atrophy. These substances are now known as the hallmarks of AD pathology, and are commonly termed senile plaques and neurofibrillary tangles (NFTs) (Perl, 2010).

#### Aetiology of AD

The definitive mechanism of AD is yet to be fully elucidated, but is associated with two pathological hallmarks, amyloid-β (Aβ) plaques and NFTs. Aβ plaques consist mainly of insoluble aggregations of Aβ peptides, which are cleaved from Aβ precursor protein (APP) (Schachter and Davis, 2000). APP is processed by various secretases, and dependant on the site of cleavage, the Aβ peptide can be short, Aβ40, or long, Aβ42. Long peptides of Aβ42 are insoluble and neurotoxic (Schachter and Davis, 2000). NFTs are formed from aggregates of cytoskeletal Tau protein which form insoluble polymers of hyperphosphorylated Tau (Kopke et al., 1993). Hyperphosphorylation leads to a breakdown of stabilisation in microtubules, causing self-aggregation and disruption in axonal transport (Zaidi et al., 2001).

Both aggregates are believed to interfere with cytoskeletal integrity, disrupting axonal transport, and synaptic and neuronal function. This ultimately leads to microgliosis and widespread white matter and neuronal degeneration. Originally believed to be separate entities, it is still not clear which is the primary abnormality, or the exact mechanism of interaction between the two protein aggregates (Ballard et al., 2011).

There is evidence that the pathological accumulations are apparent up to 50 years before the onset of clinical symptoms (Braak and Braak, 1991, Sperling et al., 2013a, Sperling et al., 2013b), suggesting a prodromal phase of AD. Various studies have shown a widespread presence of neuritic plaques and NFT throughout the cortex in the late stages of AD, but in the early stages, these accretions are found solely in the medial temporal lobes, and accumulation follows a uniform arrangement (Braak and Braak, 1991, Braak and Braak, 1995, Thal et al., 2000).

Braak & Braak (1991) proposed six stages for the development of NFT, eventually leading to widespread neuronal atrophy. There is a linear correlation between progression through the stages and the onset of clinical symptoms. Stages I-IV are preclinical, where NFT development begins in transentorhinal regions in stage I, extending to entorhinal regions in the later phase of stage II. During stage III NFT become more abundant in the entorhinal regions and begin to encroach upon the neocortex, where during stage IV there is a more extensive progression to neocortical association areas, eventually leading to widespread accumulation in stages V and VI (Braak and Braak, 1991, Braak and Braak, 1995, Braak et al., 2006, Mortimer, 2012).

More recently, a similar hierarchical pattern has been discovered for deposition of Aβ in regions of the medial temporal lobe (Thal et al., 2000), and expansion to the whole brain (Thal et al., 2002). Aβ staging correlates well with Braak staging, although the significance of the correlation to clinical disease severity is much reduced for Aβ depositions compared to NFT staging (Gold et al., 2001).

Over the years, various theories for the development of the pathophysiology of AD have been proposed. For example, the cholinergic hypothesis (Drachman and Leavitt, 1974, Bartus et al., 1982) and amyloid cascade hypothesis (Hardy and Allsop, 1991, Hardy and Higgins, 1992).

The cholinergic hypothesis suggested that cholinergic dysfunction may be the primary factor driving the pathogenesis of memory decline and AD (Bartus et al., 1982). This idea originated from the findings that brains of patients with AD had selective degeneration of neurons of the nucleus basalis of Meynert, leading to reductions in cholinergic connections to the cortex and hippocampus (Whitehouse et al., 1982).

As research into the pathogenesis of AD developed over the years, another theory, the amyloid cascade hypothesis, was developed. This hypothesis suggests that the abnormal accumulation of Aβ proteins acts as a pathological trigger for a cascade involving the hyperphosphorylation of tau, ultimately leading to neuronal dysfunction and cell death (Selkoe, 1999). Similarly, it was suggested that accumulation of Aβ leads to cholinergic dysfunction, driving the process of neurodegeneration leading to cognitive decline and dementia (Francis et al., 1999). For example, Aβ has been shown to inhibit cholinergic neurotransmission in rat hippocampal slices (Kar et al., 1998), thereby suggesting that cholinergic neurons are not the driving force behind the pathogenesis but rather one of many targets of AD pathology (Roberson and Harrell, 1997).

Evidence to support the role of Aβ in initiating AD development comes from genetic studies showing disruption in Aβ processing causing familial early onset AD (Hüll et al., 1998, Goate, 2006). Also, individuals with Down’s syndrome have an increased risk of early onset AD, with 66% developing AD by the age of 60 (Wiseman et al., 2015). This is due to an extra copy of chromosome 21, which leads to three copies of the gene encoding APP, leading to increased production of insoluble Aβ fragments and development of plaques and NFT (Lott and Head, 2001). Similarly, ApoE 4, a major risk factor for sporadic and familial forms of late onset AD, has been shown to promote development of insoluble plaques but not NFT (Olichney et al., 1996).

A study followed 28 older adults with yearly neuropsychological examinations, and compared scores to post mortem neuropathological burden (Crystal et al., 1988). At the time of death, 9 individuals (32%) were clinically dementia free, but post mortem examination showed six out of the 9 brains had heavy pathological load. Levels of Aβ plaques throughout the brains of these six did not differentiate between the individuals with clinical AD, but a higher load of NFT was reported in the demented subjects (Crystal et al., 1988). Controversially, Price and Morris (1999) suggested that high levels of NFT rather than amyloid-β were present in non-demented elderly brains, with tangle density increasing exponentially with increasing age. The oldest adults also had higher levels of Aβ plaques, suggesting, therefore, that the two hallmarks are separated in time and Aβ does not precede nor is it responsible for tau hyperphosphorylation and deposition. This finding questions the relevance of the amyloid cascade hypothesis due to the temporal and spatial properties of aggregations of Aβ throughout the disease (Mesulam, 1999, Price and Morris, 1999). Interestingly, Crystal et al., (1988) did find an interaction between the levels of plaques and NFT after the initial depositions and, therefore, the role amyloid may play in accelerating the tauopathy cannot be ignored. Consequently, there is still controversy surrounding the isolated functions of the lesions and how they interact and lead to the neuronal dysfunction found in AD. It is possible that another unidentified factor may actually be the driving force behind this process of neurodegeneration (Armstrong, 2014).

Regardless of the mechanism, the presence of Aβ plaques and NFT are necessary for the pathological diagnosis of AD. However, due to these conflicting lines of evidence, they are not sufficient for development of the clinical features of AD (Crystal et al., 1988, Dickson et al., 1992). Post mortem analysis has shown levels of protein aggregates do not necessarily correlate with clinical symptoms, as various studies of healthy ageing have documented high levels of neuropathology in cases with no clinical cognitive decline (Crystal et al., 1988), and vice versa. For example, the nun study (Mortimer, 2012), found that one third of a group of participants classified with AD pathology were actually dementia free at their last cognitive assessment, suggesting that neither Aβ plaques nor NFT contribute to the initiation of cognitive dysfunction (Mesulam, 1999). However, it could be that the nuns were in the preclinical or prodromal phase of AD, and if they had lived longer they may have developed the clinical symptoms of AD (Sperling et al., 2013b). Interestingly, the presence of an infarct in the brains of nuns with AD pathology significantly increased their chances of a clinical diagnosis of AD, but in individuals with pathology negative brains, infarcts had no influence on cognitive impairment (Mortimer, 2012). Mortimer (2012) suggested that the vascular insults were not responsible for cognitive impairment, but instead proposed a role for an interplay between vascular infarctions and neuropathology.

#### Diagnosis and Clinical symptoms of AD

The clinical course of AD reflects the underlying and expanding neuropathology, as outlined in the section above. It has been estimated that AD pathology starts to accumulate some 20 to 30 years before the onset of clinical symptoms (Sperling et al., 2013a). The manifestation of cognitive symptoms is relatively inconspicuous in the early stages, but progressively, declines leading to irreversible cognitive deficits become apparent in the later stages of the disease (Förstl and Kurz, 1999).

A clinical diagnosis of AD, or other types of dementia, involves lack of independent functioning. Due to the pathological burden of the medial temporal lobes, one of the earliest and most prominent features characterising AD is memory loss, namely deficits in episodic memory and semantic memory. Neuropsychological testing shows healthy age- matched controls significantly outperform AD patients on almost all tasks of cognitive function, where the biggest deficits are seen on a global measure of cognition and tests of episodic memory, attention, language comprehension and semantic association (Wakefield et al., 2014). Deficits in semantic memory may be one of the most reliable early indicators of underlying AD pathology, as semantic memory usually remains stable into old age, but it is affected early on in the disease course of AD (McGeown et al., 2009, Venneri et al., 2016). Category fluency tasks, which effectively assess semantic memory, show discrimination between healthy ageing and the AD trajectory. Cognitively healthy adults produce significantly more words per category than patients with AD and amnestic MCI (p<0.0001) (Wakefield et al., 2014), suggesting that tests of semantic memory may be the best discriminator for the earliest signs of AD.

The onset of behavioural features, such as apathy and depression, occur early in the clinical manifestation and are often the reason patients seek medical attention (Venneri et al., 2016). The memory and behavioural deficits, together with a significant impairment of new learning, can interfere with other cognitive domains and have a knock on effect on the activities of daily living, where patients have great difficulty in planning, judging and organising (Förstl and Kurz, 1999). As the disease progresses, language difficulties increase so there are challenges with word finding ability, also reading, comprehension and writing can be affected (Blair et al., 2007). In the later stages, when widespread neurodegeneration is seen, clinical symptoms also expand to affect other brain functions, and often insight into the condition is lost (Alzheimer’s Association, 2013) ("2013 Alzheimer's disease facts and figures,") ("2013 Alzheimer's disease facts and figures,") ("2013 Alzheimer's disease facts and figures,") ("2013 Alzheimer's disease facts and figures,") ("2013 Alzheimer's disease facts and figures,"). Ultimately, AD leads to personality changes, severe language impairment and in some cases deficiency of the most basic motor functions, including chewing and swallowing (Secil et al., 2016). Patients are often totally dependent in the later stages of the disease, when it is obvious that dementia has set in (Förstl and Kurz, 1999).

A wide range of behavioural and psychiatric symptoms are common in AD, although their manifestations are variable (Mega et al., 1996, Reisberg et al., 1996). It is these symptoms that are often reported as the most troublesome for the carer (Torrisi et al., 2016). As previously mentioned, depression and apathy are common early symptoms of AD. A recent study measuring depression, apathy, anxiety and agitation levels, in a cohort of AD patients, found the prevalence of these to be up to 90% (Torrisi et al., 2016). Subsequently, about one third of patients with AD develop delusions, (Forstl et al., 1993, Mega et al., 1996) and up to 20% of AD patients develop visual hallucinations, which may be due to the cholinergic deficit (Lauter, 1968, Perry et al., 1990).

As the progression of the disease is heterogeneous, symptoms and the degrees to which cognitive domains are affected will differ (Friedland et al., 1988). A definitive diagnosis of AD is only available upon post mortem, therefore only a probable diagnosis can be given during life (Ballard et al., 2011). After exclusion of all other factors which could lead to the symptoms, together with consideration of a detailed history, neuropsychological testing and neuroimaging, clinicians can usually make an accurate clinical diagnosis of AD (Ballard et al., 2011).

#### Treatment and prognosis of AD

At present, there are no disease modifying treatments available, current treatments only aim to reduce symptoms and slow disease progression (O’Brien et al., 2016). To date, three Acetylcholinesterase inhibitors (AChEi) have been licenced for treatment of mild to moderate AD (donepezil, galantamine and rivastigmine); an NMDAR antagonist (memantine) has been licenced for use in moderate to severe cases of AD (Schneider et al., 2014). It has been suggested that the AChEi may also be useful in combination with memantine in the severe stages of AD (Howard et al., 2012). Despite this, the AChEi provide only a modest effect of improving cognition and indirectly managing behavioural symptoms over 6 to 12 months, with great variance in effectiveness between patients (Ballard et al., 2011).

Antipsychotic drugs have historically been used to treat behavioural symptoms of AD (Lantz and Marin, 1996) although effects are only moderate, and due to adverse side effects are now seldom prescribed (Tolppanen et al., 2016). Instead, alternative therapies and non-pharmacological treatments, such as aromatherapy and musical therapy are recommended (Jimbo et al., 2009, Chang et al., 2015).

Life expectancy is reduced by a third after clinical diagnosis of AD (Förstl and Kurz, 1999); prognosis is between 3 and 10 years (Zanetti et al., 2009). There is much controversy in the literature over an exact prognosis, due to the lengthy prodromal phase of the disease, individual differences and overlaps with healthy cognitive ageing (Whalley et al., 2004). Studies have proposed that early onset AD has a more severe disease progression (Snider et al., 2009, Koric et al., 2010), but also there is evidence against this (Newens et al., 1993, Bracco et al., 1994). There are some symptomatic features, such as language problems (Cosentino et al., 2005), aphasia (Bracco et al., 1994) and psychosis (Vilalta-Franch et al., 2013) that are associated with a worse or more severe disease progression. Presence of microbleeds and stroke (Benedictus et al., 2015) as well as smoking status (Batty et al., 2014) can predict mortality in AD. However, the most common causes of death to patients with AD are pneumonia, heart disease and stroke (Kukull et al., 1994, Förstl and Kurz, 1999, Todd et al., 2013).

### Vascular dementia (VaD)

Vascular disease is very common in the ageing population (Nichols et al., 2013). Dementia caused by solely vascular disease, accounts for around 15% of all dementia cases (Barker et al., 2002, O'Brien and Thomas, 2015), although there is evidence to suggest that other forms of dementia may include vascular components and therefore may be of mixed pathologies (Fernando and Ince, 2004, Schneider et al., 2007).

#### Aetiology of VaD

Vascular disease is the second most common cause of dementia, second to AD, and is caused by changes in the vascular system. These changes lead to cerebrovascular disease, which includes large cortical infarcts, subcortical vascular disease, hypoperfusion, haemorrhagic damage, hereditary vascular disease (CADASIL), and post stroke dementia (O'Brien and Thomas, 2015). In VaD, there are no pathological hallmarks of the disease, but a heterogeneous pathology of large and small vessel atherosclerosis, cerebral amyloid angiopathy, cortical and sub-cortical infarcts and haemorrhages (Jellinger, 2005, O'Brien and Thomas, 2015).

Initially, most cases of VaD were believed to result from single or multiple-infarcts, but these are now known as a subtype of VaD (Wallin et al., 2003). The most common cause of VaD is subcortical ischemic vascular disease, which is visualised on MRI by presence of lacunar infarcts and deep white matter changes (Román et al., 2002). These subcortical infarcts usually interrupt fronto-striatial circuits, leading to the clinical symptoms such as reduced attention and executive function (O'Brien and Thomas, 2015).

Post stroke dementia is also common, usually defined as cognitive impairment three months post stroke (Brainin et al., 2015). The risk of post stroke dementia is the highest in the immediate months following a stroke; however, there is evidence that some survivors can develop cognitive symptoms some time post stroke (Ihara and Kalaria, 2014). A meta-analysis concluded that one in ten stroke patients develop dementia after their first stroke, one in three stroke patients develop dementia upon recurrent strokes, and one in ten stroke patients already have dementia before their stroke (Pendlebury and Rothwell, 2009). Thus, a stroke may trigger the further development of clinical symptoms and exacerbate the dementia, or activate clinical symptoms of already present underlying pathology (Kalaria et al., 2016). The prevalence of mixed dementia, which describes overlapping cases of AD and VaD, supports this theory.

Mixed dementia is estimated to account for 20% of all dementia diagnoses, as about 30% of AD cases have coexisting vascular pathology (Langa et al., 2004). The theory behind this is, for example, a build-up of neuropathology in the prodromal stages of AD, which is yet to breach a critical threshold for development of clinical symptoms, (see section 1.4.1. on brain and cognitive reserve) (Katzman, 1993, Stern, 2002). Following further pathological build up, or due to major neuronal damage such as stroke, the brain no longer has capacity to function with this level of pathology, therefore leading to the clinical features of mixed dementia. The presence of common vascular risk factors for both VaD and AD suggests a further link. Due to the high frequency of microbleeds and stroke in people with AD (Benedictus et al., 2015), it has been suggested that mixed dementia may actually be a sign of the later stages of AD (De Reuck et al., 2016).

#### Diagnosis and Clinical symptoms of VaD

Clinical features of VaD are more heterogeneous than any other dementia subtype, as they are dependent on the strategic location of the lesions (O'Brien and Thomas, 2015). VaD is hard to diagnose in the early stages as there is not always a clear cut trajectory from healthy ageing to MCI to dementia like it has been proposed for AD. Many cognitively healthy elderly individuals have a mild extent of cerebrovascular disease, with one study showing that brains of 30% of the healthy elderly have had silent infarcts, and up to 90% have white matter lesions (Longstreth et al., 1998, De Leeuw et al., 2001).

Typical clinical features of cortical subtypes of VaD include, abrupt onset of cognitive impairment and aphasia, with lateralised sensorimotor changes and mild memory impairment. Conversely, subcortical VaD produces deficits in attention, executive function, processing speed, bradyphrenia, motor manifestations and behavioural and psychological symptoms (Erkinjuntti and Rockwood, 2001, Wallin et al., 2003, O'Brien and Thomas, 2015).

#### Treatment and prognosis of VaD

Like for AD, there are currently no disease modifying treatments for VaD, with the most effective intervention being prevention by controlling cardiovascular (CV) risk factors (Douiri et al., 2013). This will be discussed in more detail in section 1.4.2.1. There is some evidence that drugs prescribed for the treatment of AD, such as AChEi and memantine, have shown modest benefits on cognition in VaD (Wilcock et al., 2002, Auchus et al., 2007). This could, however, be effective in cases of mixed dementia where there may have been a misdiagnosis of VaD (Erkinjuntti et al., 2002), therefore the effectiveness of AD treatment in pure cases of VaD remains unknown.

The different aetiologies of VaD present and progress at different rates. Although not as widely studied as amnestic MCI, believed to be the prodromal stage of AD (Petersen, 2011), there is also evidence for vascular MCI (Gorelick et al., 2011). This is usually non-amnestic MCI, where progression from MCI to dementia is of similar rate to that of amnestic MCI to AD (~50%) (Wentzel et al., 2001). However, non-amnestic MCI or vascular MCI does not always lead to VaD. Wentzel et al., (2001) found that 20% of cases of vascular cognitive impairment no dementia progressed to VaD, but a further 26% progressed to other forms of dementia, most commonly AD. This once again highlights the importance of investigating the pathophysiological mechanisms around vascular changes and the onset of cognitive impairment and dementia (De La Torre, 2002).

Due to an increase in primary care CV management, the incidence of stroke and deaths by stroke are declining in Europe (Zhang et al., 2012). However, the levels of cognitive impairment associated with stroke or vascular changes are not decreasing (Portegies et al., 2016). Due to the heterogeneous nature of VaD, many factors need to be considered to help predict the nature and progression of cognitive symptoms. For example, for post stroke dementia, prognosis will vary depending on the location and volume of the stroke. Strokes affecting the dominant hemisphere, or lesions affecting the prefrontal-subcortical circuits are particularly at risk of decline (Pendlebury and Rothwell, 2009). Prognosis is also worse if there is evidence of coexisting neuropathology or vascular changes (Yang et al., 2015). Mortality in VaD is particularly high, with estimated survival time being around 3 to 5 years (Erkinjuntti and Rockwood, 2001, Kua et al., 2014).

# Risk and preventative factors for cognitive decline

Many forms of dementia are currently incurable, with only a few rare cases, due to vitamin deficiencies, medications, infections or injury, which can be effectively cured by appropriate drug treatment or surgery (Klinge et al., 2005, Werder, 2010). For the most part, there is lack of effective disease modifying treatments for MCI and dementia (Buckley and Salpeter, 2015). Most research efforts, therefore, have shifted onto identifying elements which increase the risk of developing dementia and exploring factors which may be protective against cognitive impairment. Findings from epidemiologic, observational and clinical studies have suggested biological or lifestyle factors may exacerbate underlying neurodegeneration or changes in vascular architecture in the ageing brain (Plassman et al., 2010), leading to an increased risk of cognitive decline. It has been suggested that up to 50% of dementia cases can be attributable to modifiable lifestyle factors (Barnes and Yaffe, 2011). The effects of education, social stimulation, diet and other negative lifestyle factors will be discussed in more detail below. The concept of reserve will be introduced to try to explain these risks and preventative factors, along with overlaps between healthy ageing and dementia.

### Brain and cognitive reserve

As discussed in section 1.3.2.1.1., the level of neurodegenerative pathology does not necessarily correlate with manifestations of clinical symptoms. To try to explain the disjunction between degree of damage and severity of clinical symptoms, the concept of reserve emerged. There are two kinds of reserve, a passive brain reserve (Katzman, 1993) or an active cognitive reserve (Stern, 2002).

The theory of passive brain reserve suggests that larger brains can sustain clinical function in the face of increasing levels of pathology, as there are still adequate numbers of neurons to support normal cognitive function (Satz, 1993). This is based on a quantifiable threshold model, where pathology has to breach a certain level to lead to cognitive dysfunction. Evidence to support this comes from an early study investigating the cognitive and functional status of 137 elderly nursing home residents, 107 (78%) were diagnosed with dementia prior to death. Post mortem examination showed a small subsample of non-demented individuals’ brains contained neuropathological features consistent with mild AD. Interestingly, these participants also had greater numbers of neurons and total brain volume compared with the rest of the sample (both the demented and non-demented residents) (Katzman et al., 1988). The authors suggested that these individuals maintained their cognitive and functional ability due to their larger brains, which could better withstand the levels of neuropathology and neuronal loss. Similarly, a more recent study has found cognitive abilities in older age to be partially dependent on maximal brain size, as measured by intracranial volume (Royle et al., 2013).

However, this concept of a larger brain being able to mitigate the effects of ageing or pathology on cognition has been criticised for being too over simplistic (Tucker and Stern, 2011). Cases have been documented where larger brains are not associated with a better clinical outcome or cognitive performance (Jenkins et al., 2000, Raz et al., 2005). An MRI study comparing the premorbid brain size between a group of patients with AD and matched controls, found there was no difference in intracranial volume between patients and controls, suggesting that disease onset is not delayed in individuals with larger brains (Jenkins et al., 2000).

Cognitive reserve on the other hand, is a dynamic process, where the brain actively attempts to sustain optimum performance in the face of increasing levels of pathology, by utilising brain networks more efficiently, or compensating by the recruitment of alternate brain networks (Stern, 2002). Evidence for cognitive reserve stems from years of research which suggests that cognitively stimulating life experiences may mitigate the risk of dementia, in particular, formal education (Brayne et al., 2010), occupational attainment (Correa Ribeiro et al., 2013), socioeconomic status (Scazufca et al., 2010), leisure activities (Barnes et al., 2004) and physical exercise (Tolppanen et al., 2015). The link between these factors and the risk of dementia will be discussed in more detail below.

#### Education and occupational attainment

There is evidence to suggest that education and occupational attainment may impart cognitive reserve. This reserve leads to better cognitive function in the elderly, thus allowing the maintenance of cognitive performance during normal ageing or increasing levels of pathology (Katzman, 1993). Studies have shown that higher levels of education and occupational achievement may reduce the risk of dementia (Brayne et al., 2010, Meng and D'Arcy, 2012, Mirza et al., 2016). Even very low levels of formal education have been shown to contribute to cognitive reserve after adjustment for sociodemographic variables (Farfel et al., 2013).

Education can modify the relationship between degree of global atrophy and level of cognitive function. Higher levels of global AD pathology were significantly correlated with cognitive performance, but when the researchers covaried for education, this association between neuritic plaques and cognition declined (Bennett et al., 2003). This supports the cognitive reserve model as it suggests that for two patients with the same levels of plaque neuropathology, cognitive function is higher in patients with a higher education.

A prospective study investigated the relative risk (RR) of developing dementia in 600 non-demented individuals with varying levels of education and occupational achievement. Over the four year study period, 18% of the cohort developed incident dementia, where risk was greater for individuals with low education (RR 2.02) or low occupational attainment (RR 2.25), and the highest risk was seen in those with low levels of both (RR 2.87) (Stern et al., 1994). The authors concluded that higher levels of education and occupational achievement may reduce the risk of dementia through building up of cognitive reserve.

Continued education and mental stimulation occurs through occupational duties throughout life. Lack of cognitive engagement at work increases the risk of cognitive decline upon retirement (Sabbath et al., 2016). Similarly, more cognitively stimulating or complex work-related tasks have been linked to better cognitive performance in old age, independently of age and levels of early education (Correa Ribeiro et al., 2013).

A prospective population based study found that people with higher socioeconomic status had a reduced risk of developing dementia (Sattler et al., 2012). As low education is associated with low occupational achievement, individuals with low levels of education may be more likely to develop dementia due to other lifestyle factors which may increase susceptibility, rather than the effects of education alone (Scazufca et al., 2010).

However, a study which aimed to minimise the effects of lifestyle factors and individual differences showed that early education remains important in the development of dementia (Snowdon et al., 1996). Snowdon et al., (1996) studied a cohort of nuns who shared the same environment and lifestyle habits, and investigated how the linguistic ability of the nuns as young adults translated into the risk of cognitive decline and autopsy confirmed AD in old age. The researchers considered the linguistic properties of handwritten autobiographies, written by each nun in their early 20s. Snowdon et al., (1996) found low idea density and grammatical complexity in the autobiographies to be associated with lower cognitive test scores in old age, and interpreted the findings to suggest that linguistic proficiencies in early life are important for cognitive function in old age. This again suggests that early education may help govern cognitive reserve, and thus influences individuals’ chances to overcome cognitive decline in later life. On the contrary, this idea of early competency predicting cognitive performance in later life also suggests that these individuals already had a vulnerability to cognitive impairment. For example, some unknown factor which may be genetic or the underlying presence of pathology may have led to the poorer linguistic performance in their 20s and thus prevented them from acquiring the same levels of reserve. This is to suggest that there may be an underlying biological advantage or disadvantage for the ability to build up a robust brain or cognitive reserve.

To corroborate these findings, a recent study examined the age of onset of cognitive impairment in all patients visiting a memory clinic over a ten-year period, to determine whether people with a lower education developed cognitive impairment earlier than those with high levels of education. Paradoxically, the mean reported age of onset of cognitive impairment was lower in the more highly educated group compared to those with lower education, suggesting that education alone cannot account for the delay in cognitive symptoms (Treves et al., 2016). Therefore, it may be important to investigate the combined relationship of risk factors and their effects on cognition (Schreiber et al., 2016). There is also the possibility that highly educated individuals seek help sooner than those with lower levels of education (Richardson et al., 2012), which could explain the disparity in the findings.

#### Physical exercise

Higher levels of physical exercise throughout the life have been associated with a lower risk of development of cognitive impairment and dementia in later life. Physical activity has well known benefits for reducing the risk of many chronic disorders, such as hypertension (Borjesson et al., 2016), cardiovascular disease and diabetes (Papataxiarchis et al., 2016). These disorders may themselves increase the risk of dementia, but there is also evidence that physical exercise may directly contribute to cognitive reserve (Cheng, 2016).

The Canadian Study of Health and Ageing, which included almost 5000 participants over the age of 65, reported adults who exercised regularly to have a reduced risk of developing cognitive impairment and all cause dementia (OR 0.63 CI 0.40-0.98), compared to people who did not exercise at all (Laurin et al., 2001). There was, in fact, a dose response relationship, where the risk of cognitive impairment decreased with increasing levels of physical activity. The authors suggested that physical exercise could, consequently, be protective in the development of cognitive decline and dementia. Similarly, a recent study conducted by Tolppanen et al., (2015) found a reduced risk of dementia in people who were more active at midlife, compared with those who had low and moderate levels of physical activity, suggesting that early physical activity may contribute to cognitive reserve.

Dementia risk was also reduced in individuals who increased their exercise routines from moderate to high levels after midlife (Tolppanen et al., 2015), suggesting that the protective effect of physical activity may be effective at any stage. However, short-term improvement of aerobic capacity may not be sufficient for improvement of cognitive function. Three groups of healthy older adults underwent 16 weeks of, either, aerobic exercise training, yoga, or were held on a waiting list with no exercise. The aerobic exercise group had improved aerobic capacity, but there was no effect on cognitive task performance, suggesting that short-term exercise does not improve cognition (Madden et al., 1989). Therefore, it is important to maintain moderate to high levels of activity throughout the life, to influence cognitive reserve capacity and efficiency of cognitive functioning.

Similarly, recent meta-analysis’ have suggested that exercise has little or minimal effect on cognition in people with clinical symptoms of dementia (Forbes et al., 2015, Groot et al., 2016), but to have even a minor effect, it must be of aerobic capacity.

As with other factors such as isolation and depression, low physical activity may occur as a result of impending cognitive impairment and may be, therefore, present in the prodromal stages of the disease rather than being a risk for development of dementia (Scarmeas and Stern, 2003). In contrast, Laurin et al., (2001) found this not to be the case. When they reanalysed the data from the Canadian study of Health and Ageing, removing cases where cognitive impairment was apparent in the first two years of the study, there was no difference in the relationship between physical exercise and the development of cognitive impairment, suggesting that low levels of physical exercise were not a consequence of insidious cognitive decline.

Rather than looking at one aspect alone, a randomised control trial has demonstrated that multimodality intervention can improve or maintain cognitive function amongst elderly people at risk of cognitive impairment (people with mean or slightly lower than mean cognitive performance expected for their age according to normative data) (Ngandu et al., 2015). Participants were randomised to either intensive intervention including personalised diet plans, exercise plans and cognitive training, or the control group who received regular health advice. Over a 2-year period, the intervention group had improved between 25% and 150% more than the control group in terms of performance in various cognitive domains, and cognitive decline was significantly increased in the control group compared to the intervention group, suggesting that multi domain intervention may be more beneficial than risk reduction in one area alone.

#### Social Engagement and isolation

Social isolation, defined as a combination of not being married, living alone, small social networks, lack of social engagement and little participation in group activities (Holwerda et al., 2014), is a major risk factor for the development of cognitive impairment and dementia (Cacioppo and Hawkley, 2009). Alongside intellectual factors, leisure activities may too be associated with the protective effects of cognitive reserve (Scarmeas et al., 2001, Scarmeas and Stern, 2003).

By participating in social activities in early and late life, the brain is more stimulated which could contribute to the building up of cognitive reserve. In a cyclic process, these individuals could be further protected from cognitive impairment as they are more motivated to maintain better social and cognitive function (Scarmeas and Stern, 2003). Also, greater social networks may be a marker of social and emotional support (Heaney and Israel, 2008), thus leading to decreased levels of depression and anxiety (Lee et al., 2016), which may also contribute to the diminished risk of dementia (Gutzmann and Qazi, 2015, Chen et al., 2015).

To investigate this, a longitudinal study following an elderly community cohort for 12 years, found links between the levels of global social engagement and cognitive function (Bassuk et al., 1999). The authors reported that a low baseline level of social engagement was significantly associated with the probability of cognitive decline at subsequent follow ups. Compared to someone with six social ties, a person with no social ties had twice the odds of developing cognitive decline (Bassuk et al., 1999). It is important to note, cognitive status in this study was ascertained using a 10-item questionnaire, which may not be sensitive enough to detect the early stages of cognitive impairment. Thus, low social engagement scores at baseline may actually be reflective of underlying neuropathology, rather than a risk factor for the development of clinical features.

Another longitudinal population based study investigated the effects of social networks and social isolation on the risk of cognitive impairment in 4,000 participants, over an average of five years. Barnes et al., (2004) found a much reduced risk of incident dementia in individuals reporting an increased number of social networks and frequent social engagements at baseline, compared to those with fewer social networks and engagements. Similarly, the same study showed the annual rate of cognitive decline was greatly reduced in those who were more socially active (Barnes et al., 2004). Due to such a large population based cohort, the complete spectrum of socioeconomic status was included, so economic status as a possible mediating factor can, therefore, be excluded, to conclude that in the general population greater social resources and connections lead to a reduced risk of cognitive impairment.

Animal model studies support the role of social stimulation on cognitive reserve. Performance on complex maze tasks, as a marker for cognitive function, were compared between sets of rats that had either been brought up in an enriched environment (with greater levels of social interaction) or an impoverished environment. A series of experiments, moving rats into different environments showed that initial exposure to the enriched environment was protective to older rats in terms of cognitive function (Winocur, 1998).

However, more recently, the mechanism of cognitive reserve, linking social engagement and cognitive function has been questioned. Using years of education and the National Adult Reading Test (Nelson, 1982) as a proxy of cognitive reserve, Lavrencic et al., (2016) found that there was no correlation between social abilities and cognitive reserve. Therefore suggesting the increased risk for cognitive decline and dementia in people with fewer social networks may not be due to social stimulation imparting a cognitive reserve. However, Scarmeas and Stern, (2003), have suggested that the relationship between an engaged lifestyle and cognitive function is in fact mediated by cognitive reserve, brought about by increased levels of education. People with higher levels of education and thus cognitive reserve, will be more likely to adopt a healthier and socially stimulating lifestyle in later life, leading to the diminished risk of dementia. Other hypothesis linking social factors and cognition have also been generated, including the stress hypothesis and vascular hypothesis (Fratiglioni et al., 2004, McHugh Power et al., 2016).

### Other lifestyle risk and preventative factors

Epidemiological studies have shown that there is a varied prevalence of dementia worldwide (Fratiglioni et al., 1999, Ballard et al., 2011), which could be in part down to different cultural and lifestyle factors. Some potentially modifiable lifestyle factors are presented below with evidence to suggest an increased risk or protective factor. It has been suggested that almost half of dementia cases worldwide could be attributable to potentially modifiable factors (Barnes and Yaffe, 2011).

#### Diet, Obesity & cardiovascular risks

There is recent evidence to suggest that diet and lifestyle has an effect on the risk of dementia, although there is much contention in the research. There are more overweight or obese people living in the USA compared to people of a normal weight (Ogden et al., 2014). Studies have shown that both Japanese American and African American individuals have an increased risk of incident dementia, compared to individuals still living in their countries of origin (Hendrie et al., 1995, Graves et al., 1996), suggesting the western diet may have an influence. Mediterranean diet has been suggested to have beneficial effects in preventing dementia in various cohorts (Safouris et al., 2015), due to high levels of nutrients, antioxidants and dietary fibre (Mennini, 2014). However, a prospective cohort study in France found no evidence for a link between adherence to the Mediterranean diet and incident dementia (Féart et al., 2009). Similarly, prevalence of dementia is lower on the African continent (Hendrie et al., 1995) where the Mediterranean diet is not adopted.

Many studies have shown that obesity in midlife greatly increases the risk of developing dementia (Loef and Walach, 2013, Wotton and Goldacre, 2014). However, an inverse relationship is seen for older ages, where low body mass index (BMI) and weight loss is associated with greater levels of cognitive impairment and risk of incident dementia (Wotton and Goldacre, 2014). It has been suggested that the link between obesity and risk of cognitive impairment in midlife are due to vascular mechanisms, and a low or declining BMI is reflexive of underlying neurodegeneration (Kiliaan et al., 2014).

The opposite was found, however, in a large UK based retrospective study of almost 2 million individuals. Qizilbash et al., (2015) compared BMI data and rates of incident dementia between healthy individuals over the age of 40 for an average of 9 years. They found, people who were obese at midlife to have a 29% lower risk of dementia compared to people of a healthy weight. In fact, underweight people had a 34% higher chance of dementia compared to people with midlife healthy weight. The authors concluded low BMI in middle and old age to be associated with a greater risk of dementia (Qizilbash et al., 2015).

The lack of consistent evidence could be due to other covariates associated with obesity, such as hypertension, dyslipidemia and diabetes (Lopez-Jimenez and Cortes-Bergoderi, 2011). Obesity is linked to higher rates of cardiovascular disease through interactions with these covariates (Lopez-Jimenez et al., 2004), which in turn increases the risk for cognitive decline and dementia (Eggermont et al., 2012, Abete et al., 2014).

Obesity leads to reductions in the size of low density lipoprotein particles and a lower concentration of high density lipoproteins (Lopez-Jimenez and Cortes-Bergoderi, 2011), both known to increase the risk of coronary artery disease. A 25-year longitudinal study found total cholesterol levels were associated with a higher prevalence of dementia and increased risk of MCI in nearly 3000 participants (Beydoun et al., 2011). Research has also shown that low levels of high density lipoprotein cholesterol particles are associated with poorer performance on tests of short-term memory compared to matched controls with high levels of high density lipoproteins in midlife {Singh-Manoux, 2008, Low HDL cholesterol is a risk factor for deficit and decline in memory in midlife: the Whitehall II study}(Singh-Manoux et al., 2008). Therefore, obesity could lead to increased rates of cognitive impairment through increasing cardiovascular risks.

Similarly, there is evidence to suggest that high intake of whole-fat dairy products may have a detrimental impact on cognitive health (Eskelinen et al., 2008), due to containing high levels of saturated and other fatty acids (Laitinen et al., 2006, Markey et al., 2014). However, much of this research has focused on the negative impact of saturated fatty acids, which are found in high concentrations in products such as cheese and butter (Aro et al., 1998), and have ignored other beneficial nutrients found in milk. Thus, more recently, researchers are changing their views on the role of dairy products in influencing cognitive health and wellbeing (Camfield et al., 2011, Kliem and Givens, 2011). Low fat milk and dairy contain many constituents which might protect against neurodegeneration (Ano et al., 2015), and high levels of milk and dairy intake have been associated with a decreased risk of dementia in a Japanese population (Ozawa et al., 2014). This could account for some of the discrepancies associated with obesity, cardiovascular risk and highlights the complexity of the diet.

#### Smoking

The literature regarding smoking and risk for cognitive impairment and dementia is controversial (Beydoun et al., 2014). A recent pooled analysis of 10 prospective cohort studies, suggested smoking was the only CV risk factor associated with dementia death, and mortality in dementia was higher in smokers than non-smokers (Batty et al., 2014). However, numerous studies have also reported no association with smoking and cognitive decline or incident dementia (Chen et al., 2003, Peters et al., 2009); and one longitudinal study has even reported the neuroprotective benefits of smoking (Wang et al., 2010). This discrepancy could possibly be due to other serious adverse health outcomes and high mortality rate found for elderly smokers (Chen et al., 2003), which would also explain the higher mortality rates in smokers with dementia (Batty et al., 2014).

To address whether smoking may be an independent risk factor for dementia, Zhong et al., (2015) carried out a meta-analysis and reported that smoking increases the risk of dementia, but by stopping smoking the risk is reduced to the same level of those who have never smoked. It is, therefore, likely that smoking may increase the risk of cognitive impairment and dementia due to the CV risks associated with smoking, or the build-up of oxidants and free radicals leading to increased levels of oxidative stress. Oxidative stress has been shown to contribute to formation of AD pathology (Durazzo et al., 2010).

Smoking increases the risk of stroke, and subsequently, VaD (Gorelick et al., 1999). Teipel and Grothe (2016) recently hypothesised that smoking can also increase the risk of AD, by exhausting cholinergic system reserve capacity. Although structural neuroimaging showed no association with smoking status and regional brain volumes in late MCI and AD, a significant level of atrophy was reported in the basal forebrain of cognitively healthy smokers compared with non-smokers (Teipel and Grothe, 2016). The authors concluded that the nicotine in cigarettes leads to atrophy of the cholinergic input areas of the basal forebrain in cognitively healthy and early MCI, leaving people at greater risk of AD.

#### Depression

Depression and cognitive impairment are both common conditions that affect the elderly. It is still not well understood whether depression may act as an independent risk factor for dementia or whether it is part of the prodromal phase (Bennett and Thomas, 2014).

There is a plethora of evidence to support depression as a major risk factor for dementia (Da Silva et al., 2013, Diniz et al., 2013). As shown by a nationwide longitudinal study in Taiwan, people with a history of depression and bipolar disorder have a significantly increased risk for developing dementia in later life (depression HR 3.02 and bipolar disorder HR 5.58) (Chen et al., 2015).

A German longitudinal study aiming to investigate the effects of depression on incident dementia, however, found no significant associations between these two conditions (Luppa et al., 2013). These results were mirrored by Becker et al., (2009) who found that people who reported themselves as depressed were no more likely to develop dementia than those who were not depressed. However, it could be that depressed people have an erroneous perception of cognitive impairment which is not related to neuropathology (Mesulam, 1985).

Conflicting lines of evidence and lack of consistent risk reduction in those treated for depression (Bennett and Thomas, 2014); together with the suggestion that it is only late life depression that is associated with dementia (Li et al., 2011), may propose that depression is a symptom of underlying neuropathology, and therefore a consequence rather than a risk factor. Underlying pathological changes may lead to hormonal fluctuations, which in turn could be responsible for the depressive symptoms that appear before the clinical features of dementia (Brown et al., 1999). Evidence to support this theory includes the high prevalence of depression in patients with dementia (Gutzmann and Qazi, 2015), which{Gutzmann, 2015, Depression associated with dementia;Chen, 2015, Risk of subsequent dementia among patients with bipolar disorder or major depression: a nationwide longitudinal study in Taiwan} significantly contributes to the functional impairment and exacerbates cognitive decline (Rapp et al., 2011).

#### Sensory loss

Sensory declines with ageing are common (McCallum et al., 1992, Correia et al., 2016) and it is becoming increasingly recognised that sensory loss is a comorbidity with cognitive decline and dementia (Baltes and Lindenberger, 1997).

Olfactory impairment has been suggested to be a marker for cognitive decline and transition from MCI to AD (Roberts et al., 2016). A longitudinal study found that taste impairment was common in people with cognitive decline compared with healthy elderly people (Steinbach et al., 2010). Individuals with visual impairment have an increased risk of developing AD, which is in line with symptom severity (Uhlmann et al., 1991), and wearing glasses correlates with better cognitive function in those with poor visual acuity (Spierer et al., 2016). Cross sectional studies have shown that there is a correlation in regional prevalence of hearing loss (HL) and incident dementia (Teipel and Grothe, 2016) and it is the only sense for which a dose-response relationship between sensory loss and risk of dementia has been reported (Uhlmann et al., 1989a, Lin et al., 2011b, Deal et al., 2016). Longitudinal evidence linking HL to dementia has led to the inclusion of midlife HL as a potentially modifiable risk factor for dementia (Livingston et al., 2017). Again, it is not completely understood whether this may be a risk for dementia, a sign of impending dementia or a consequence of underlying neurodegeneration.

# The challenges of identifying and treating pathological cognitive ageing- looking at modifiable risk factors

Due to overlaps with normal ageing, cognitive reserve and identification of a plethora of risk factors proposed to predispose elderly people to cognitive impairment and dementia, identifying pathological ageing remains a challenge in the earliest stages (Tucker and Stern, 2011).

The conflicting evidence surrounding modifiable risk factors and the role of cognitive reserve means it is still not clear which factors directly increase the risk of a person developing dementia, or which may be reflexive of the prodromal stages of cognitive impairment. It is also unknown how these factors may interact together to mediate healthy or pathological ageing. Research suggests that a healthy lifestyle (balanced diet, regular physical exercise, control of cardiovascular risk factors) and lifelong social and cognitive stimulation may prevent the onset of cognitive impairment (Baumgart et al., 2015). However, it is hard to contribute the effort of a sole factor to a reduced risk of dementia. For example, someone with low education may be more likely to take up a low grade employment, leading to lower income and consequently poorer diet and lifestyle choices (Le Carret et al., 2003). There is also some evidence to suggest that this healthy lifestyle should be adopted in early life to maintain the protective effects of cognitive reserve (Fratiglioni et al., 2004, Schreiber et al., 2016), and therefore individual differences complicate the picture further.

Pathological studies have demonstrated that there are no given threshold levels of neuropathology that delineate clinical symptoms or the presence of a certain type of dementia (Neuropathology group., 2001). For this reason, the differences between primary neurodegenerative and secondary classifications of pathological ageing are also not clearly defined. In many cases, a large overlap between neurodegenerative and vascular changes in aged brains challenges the conventional diagnosis, making a differential diagnosis even harder (Langa et al., 2004, De Reuck et al., 2016).

Without this accurate diagnosis, treatments cannot be administered and, even then, currently available treatments have no impact on disease modification, and only a moderate symptomatic effect (O’Brien et al., 2016). Further research into risk factors that have the potential to be modified is, therefore, needed to prevent or delay the onset of cognitive impairment and dementia. One of the challenges is that the earliest signs of dementia could be masked by another primary factor associated with ageing, such as sensory loss. Section 1.4.2.4 outlined links between all aspects of sensory loss and their associations with incident dementia. A dose-response curve, where severity of sensory loss predicts the onset and severity of incident dementia, has only been documented for HL (Uhlmann et al., 1989a, Lin et al., 2011b, Deal et al., 2016). The next chapter will focus on existing evidence linking HL to cognitive decline and dementia, and inform on the possible mechanisms by which HL could be either an independent risk factor, or an early manifestation of underlying pathological changes.

# Chapter 2: Hearing loss and cognitive decline

# 2.1. Introduction

Without effective treatments or cures for pathological cognitive decline and dementia, risk reduction is a major public health concern. Well documented risk factors such as age, genetics and cardiovascular factors do not account for all of the risks (Selkoe, 2012), so other factors must be explored. It is still not clear who is at the greatest risk of developing dementia, nor can we predict the onset and progression. HL is often seen as an inconsequential part of ageing (Peracino, 2014). The prevalence is underestimated and remains, therefore, undetected and untreated in the population (Wallhagen and Pettengill, 2008). This occurs even though hearing disability has been linked to numerous health issues, including depression, poor balance and risk of falls, social isolation, and early mortality (Davis et al., 2016). Emerging evidence has suggested that the presence of an age related HL, or presbycusis, could lead to an accelerated rate of cognitive decline in the elderly (Lin et al., 2013), and an increased risk of dementia (Lin et al., 2011b). Despite the formation of many hypotheses suggesting the underlying nature of this association, the links between HL and general cognitive decline are still not well understood. Other factors complicate this relationship further, such as shared risk factors and symptoms, social isolation and the use of hearing aids, which will be all discussed in this chapter.

# 2.2. A brief introduction to age related hearing loss

The presence of sensory loss is well established in the ageing population and can lead to declines in physical and mental health and wellbeing, ultimately leading to poorer quality of life (Crews and Campbell, 2004). Prevalence estimates are varied, but consistently high in the ageing population. A recent cross sectional study investigating the prevalence of impairment of the five classical senses (vision, smell, hearing, touch and taste) found 94% of people aged between 57 and 85 to have at least one sensory deficit, with 67% having two or more (Correia et al., 2016).

HL is the most common sensory decline, with a varied incidence throughout the ages. Estimates suggest that the occurrence approximately doubles for every decade (Lin et al., 2011c, Goman and Lin, 2016). Presbycusis or age related hearing loss (ARHL) is the label given to HL related to ageing, regardless of the aetiology (Parham et al., 2011, Lee 2013). Again, estimates for the prevalence of ARHL vary depending on which populations have been studied and according to which definition has been used to define it. A widely used classification, which has been adopted by the World Health Organisation (2017), is ‘Speech-frequency pure tone average of thresholds at 0.5, 1, 2 and 4 kHz tones in the better-hearing ear of >25 dB’. Using this definition, HL is expected to affect between one to two thirds of people over the age of 65, and up to 80% of people over the age of 80 (Helzner et al., 2005, Lin et al., 2011d, Goman and Lin, 2016, Homans et al., 2016). With the ageing population, this ratio is on the increase, as shown by a doubling of prevalence over a 30 year period between the 1960s to the 1990’s (Wallhagen et al., 1997).

ARHL is characterised by a bilateral, symmetrical, high frequency threshold shift due to degeneration of the inner hair cells at the basal end of the cochlea, and loss of cochlear neurons and stria vascularis (Lee, 2013). For a detailed description of the mechanism of hearing and HL, see Chapter 5.

Over time there is a gradual decline in hearing acuity across lower frequencies, including those relating to human speech, leading to a loss of speech detection and understanding (Gates and Mills, 2005). Secondary to this peripheral degeneration, a functional decline of the central auditory processing system leads to difficulties following group conversations, or understanding speech against background noise (Lee, 2013). Central auditory processes are how the brain perceives the peripheral sounds, and allows word understanding. Speech comprehension is a complex phenomenon that involves an assortment of brain functions including short-term memory, attention, inhibition and decision making (Gates, 2012b, Parham et al., 2013). Thus, ARHL involves degeneration of both peripheral and central auditory processes.

It is difficult to separate out the effects of ageing alone from the intrinsic and extrinsic influences on cochlear degeneration (Liu and Yan, 2007, Parham et al., 2011). Exposure to general environmental noise, as well as excessive noise, can make a person more susceptible to ARHL, and may even accelerate the rate of ageing of the cochlea (Gates et al., 2000). Other negative lifestyle factors, such as cardiovascular risks, smoking and diabetes can also increase the risk for ARHL (Helzner et al., 2005, Agrawal et al., 2008, Morrison et al., 2014).

## 2.2.1. Treatment for ARHL- Hearing aids

There is currently no cure for ARHL (Lee, 2013), as damaged auditory hair cells cannot spontaneously regenerate (Lee, 2013, Fujioka et al., 2015), but ongoing research shows promise for future stem cell therapy (McLean et al., 2017). Presently the best and most widely used symptomatic treatment is amplification by hearing aids (Yueh et al., 2003). Pure tone audiometry (PTA) is the gold standard measurement of HL and changes in hearing thresholds (Bagai et al., 2006) which are used for personalisation and administration of hearing aids. Hearing aids are small electronic devices which can be worn in or behind the ear. The basic features consist of three separate parts, the microphone, amplifier and speaker. The primary aim of hearing aids is to detect (speaker) and amplify sounds according to the PTA hearing thresholds (Mueller, 2005), to send the signal along the auditory canal. (See Chapter 5 for a more in depth description of the mechanisms of hearing and HL.)

Hearing aids have been shown to not only improve hearing thresholds, but to also improve social and emotional wellbeing, having a knock on effect to overall quality of life. A recent review of five randomised controlled trials suggested that hearing aids had a beneficial effect on both hearing- specific and general- health related quality of life (Ferguson et al., 2017). The number of hearing aid users varies across the globe, partially due to issues surrounding funding, but also due to central auditory issues which aids cannot correct (Parham et al., 2011). An epidemiological survey published in 2012 claims that hearing aid use is consistently low in younger people with a mild HL (<4%), and this number only increases to 22% in individuals 80 years and older, suggesting that 80% of people who would benefit from hearing aids do not regularly use them (Chien and Lin, 2012). Many factors, including education and social stigma may play a part in the decision to be identified as a hearing aid user (Kochkin, 2009, Fischer et al., 2011).

It is important to recognise that PTA only measures the ‘structural’ aspects of HL, and therefore may not give an accurate representation of the impact on quality of life and aspects of daily living. According to the International Classification of Functioning, Disability and Health framework, the impact of HL may be different for different individuals (WHO, 2001), and therefore functioning depends on more than just the audiogram. This will be introduced in terms of the psychosocial features of HL in section 2.3.3.3, further discussed in Chapter 4 and subsequently throughout this thesis.

# 2.3. Uncovering the relationship between HL and cognitive impairment/dementia

For many years the associations between HL and the effects on cognition have been of interest to researchers, but ultimately research into these two fields together has been limited. During the last 25 years, gathering much more attention recently, there has been an increased interest in HL as an independent risk factor for dementia. Although shared risk factors exist (including age) which act to increase the prevalence of both HL and cognitive impairment independently of one another, the association between them remains after statistically controlling for age and other covariates such as hypertension, diabetes and gender (Lin et al., 2011b).

Epidemiological studies have shown a correlation between the regional prevalence of HL and incident dementia rates (Teipel et al., 2015). Many studies have demonstrated that HL is associated with poor cognitive performance (Uhlmann et al., 1989a) or accelerated rates of cognitive decline (Gurgel, 2014). One animal model study, which induced a moderate HL in rats, suggested that HL directly causes the subsequent cognitive decline as litter mates with an induced HL performed worse on tasks of spatial and recognition memory (Park et al., 2016). Similarly, using a Bayesian method to explore HL as a risk factor for dementia in a Chinese population, it was found there was 1.57 times increased risk of dementia in people with a hearing loss (Wen et al., 2016). It appears, therefore, that there is a relationship between HL and cognitive decline and dementia, but the nature of this association is yet to be defined. Research has led to the proposal of many mechanisms underlying this relationship (Fulton et al., 2015, Wayne and Johnsrude, 2015).

Firstly, people with ARHL may be at risk of being over-diagnosed with cognitive impairment, due to shared risk factors and overlapping early symptoms. Candidates with HL could be disadvantaged by testing procedures in both clinics and during research studies, due to the verbal nature of many of the cognitive tests (De Silva et al., 2008, Acar et al., 2011). Another theory is that long-term sensory deprivation leads to or causes cognitive impairment, either directly or indirectly. This theory suggests that over time HL causes either reversible (information degradation hypothesis) (Schneider et al., 2002, Li and Lindenberger, 2002) or permanent neuronal degradation and cognitive impairment (Oster, 1976, Lin et al., 2014) via different pathways. An inverse of this, the cognitive load on perception hypothesis has also been proposed, which suggests the presence of cognitive decline or dementia reduces the cognitive resources available for auditory perception, manifesting as a HL (CHABA, 1988, Li and Lindenberger, 2002). Lastly, the common cause hypothesis (Lindenberger and Baltes, 1994), which suggests the links are due to a third and common factor, causing widespread neural degeneration affecting both sensory and cognitive processes.

## 2.3.1. Shared and overlapping risk factors for ARHL and dementia

Like many other disorders, there are factors which act to increase the risk for developing ARHL and factors which are suggested to have a preventative effect. ARHL is believed to result from a combination of multiple intrinsic and extrinsic factors, some of which have the potential to be modified (Liu and Yan, 2007). Epidemiological studies have suggested there are four main categories that increase the risk of people developing ARHL: ageing, environment, genetics and health co-morbidities (Yamasoba et al., 2013).

As with cognitive decline and dementia, the most prominent risk factor for ARHL is ageing (Lee, 2013). Recent estimated rates of HL from the USA show an increased prevalence and average severity with increasing decades, reporting ARHL to affect 27% of people aged between 60 and 69, 55% of people between 70 and 79, and over 80% of people over the age of 80 (Goman and Lin, 2016). Similar prevalence has been reported in other populations (Akeroyd et al., 2014).

Aside from ageing, gender and race are two other non-modifiable factors which show a strong association with the risk of ARHL. Firstly, many studies have reported an increased prevalence of ARHL amongst males compared to females, with Agrawal et al., (2008) describing a 5.5 fold increased risk of ARHL in males. However, genetic studies looking into familial inheritance have suggested that a genetic predisposition to ARHL is more profound in females rather than males (Gates et al., 1999), suggesting that some of this increased risk of ARHL in males could be due to environmental factors, such as occupational noise exposure. Evidence to support this comes from a more recent study of over 5,000 elderly Dutch participants, which found that current prevalence estimates between elderly men (33%) and women (29%) are not as different as once reported (Homans et al., 2016). This could be due to changing lifestyle and environmental circumstances with increased knowledge of noise protection in the workforce.

Reports of the associations between gender and dementia are also inconsistent, initially, many incidence studies suggested that females are more likely to develop dementia, in particular AD (Andersen et al., 1999, Brayne et al., 1995), but this has been challenged by larger scale studies, which find no such association. For example, the Rotterdam Study with evidence from over 40, 000 person years, suggested that there are no gender differences in the onset of dementia, although males are more likely to develop VaD at any age, and females over the age of 90 are more likely to develop AD (Ruitenberg et al., 2001). It is not clear, therefore, what role gender plays on risk development for either ARHL or dementia.

A decreased risk of ARHL is consistently seen in people of African American descent (Helzner et al., 2005), with one study showing that black participants had a 70% lower risk of ARHL compared to white participants (Agrawal et al., 2008). However, once again dementia prevalence according to race is varied, and varies between different dementia subtypes (Froehlich et al., 2001). A recent systematic review suggested that the annual incidence of dementia in the USA is highest in African Americans when compared with other races (Mehta and Yeo, 2016), the contrary to the decreased risk seen for ARHL.

To summarise, gender and race interactions with cognitive decline and dementia are varied and inconsistent throughout populations, it could be that these effects may be due to interactions with other risk factors such as hypertension, obesity and diabetes (Azad et al., 2007), or due to cognitive testing inaccuracies or cultural differences (Froehlich et al., 2001).

Many of the modifiable risk factors for dementia outlined in Chapter 1 have a similar risk for development of ARHL. Risk factors for ARHL which have the potential to be modified include environmental factors and health comorbidities such as cerebrovascular disease, diabetes, hypertension, poorer cognitive status and smoking (Helzner et al., 2005). These factors have been suggested to lead to an earlier onset (Agrawal et al., 2008) or increased risk (Lohi et al., 2015) amongst men and women of all races. A recent longitudinal study following over 31,000 people over 11 years has suggested that, after controlling for age, sex and education, these health problems or comorbidities alone have little impact on risk of ARHL (Engdahl et al., 2015). An interaction between many factors is more likely, therefore, to increase both the risk of ARHL and dementia in the elderly population.

As introduced in sections 1.4.1.3. and 1.4.2.3., both social isolation and depression are commonly reported alongside cognitive impairment and dementia, although it is not clear whether these factors pose an increased risk for the development of cognitive decline, or whether they are a by-product of underlying neuropathology (Bennett and Thomas, 2014). The links between ARHL, social isolation and depression will be discussed in further detail in section 2.3.3.3.

## 2.3.2. Misdiagnosis or over diagnosis

An early study which suggested the auditory status of a patient could predict cognitive functional decline was presented by Uhlmann et al., (1986), who found that a decline in cognition, measured using the Mini Mental State Examination (MMSE), in patients with AD was almost twice as severe if the patient had HL compared to normal hearing at a one year follow up. HL was measured using the nonspecific finger friction test, where the clinician rubs or clicks his fingers together close to the patients ears. Given the rather crude nature of this type of test, levels of HL reported in this study may not be accurate. Nevertheless, Uhlmann and colleagues concluded that HL may be exacerbating or accelerating cognitive decline.

Following up from this work, in 1989, Uhlmann et al., investigated the hypothesis that HL contributes to the prevalence of cognitive decline, by comparing levels of HL and MMSE scores between 100 patients with AD and 100 age, sex and education matched controls. HL was more commonly seen in patients with AD compared with the controls (OR=2.0, 95% CI=1.2 to 3.4), but level of HL also significantly correlated with MMSE scores irrespective of patient or control group, suggesting that HL may have an impact on cognitive performance regardless of cognitive status, and, therefore, confirming their previous findings (Uhlman et al., 1989a). However, due to cognition simply being assessed using a verbally administered test, the correlation of HL to MMSE scores in cognitively healthy participants could be as a consequence of test administration, rather than an actual difference in cognitive performance. People with HL are, therefore, immediately at a disadvantage which could lead to an incorrect or over diagnosis of cognitive impairment in this cohort of people.

To investigate whether using an alternative written version of the test may help to overcome any verbal bias with cognitive screens or testing, Uhlmann et al., (1989b) commenced a randomised control trial, randomly assigning a group of AD patients with varying levels of HL to undertake either the standard verbally administered MMSE or a modified written version of the test. They found that people with HL scored significantly lower on the MMSE compared to people with normal hearing, but on the contrary to what they hypothesised, the HL group scored better on standard verbal MMSE compared to the modified written MMSE, and patients with normal hearing scored better on the written version, although results were not statistically significant. These findings suggest the lower cognitive scores reported for people with HL are not just an artefact of the testing procedure. It is important to note that all patients had AD, and, as the patients with HL were significantly more cognitively impaired at baseline compared with the normal hearing group, this could also suggest that other domains which would be assessed using the written version would be more impaired. Levels of cognition and severity vary between patients with AD, and there was no control for disease severity, duration or individual differences in this study. The differences reported could, therefore, reflect variation in AD severity, rather than due to HL. Nevertheless, the fact that patients with AD scored statistically the same on the written and standard versions of the MMSE, does suggest that the written test could be beneficial to potentially remove bias in people with HL, but it would be necessary to validate this in a cognitively healthy sample of hearing impaired and non-hearing impaired participants.

This finding was echoed by another more recent study (De Silva et al., 2008), which, again contrary to the groups expectations, found no overall significant difference between performance on the written and standard MMSE scores, for 82 participants with a range of cognitive functions and levels of hearing acuity. Although 75% of participants with HL reported that they preferred the written version of the test, it was concluded that, although comparable, the written version is by no means superior to the standard version in this sample of patients. Similarly, another global measure of cognitive function, the Montreal Cognitive Assessment, modified to control for sensory loss, found people with HL still performed worse on average, again suggesting that people with HL have poorer cognitive function or are at a greater risk for cognitive decline (Dupuis et al., 2015).

Lindenberger et al., (2001) hypothesised that sensory acuity reductions offer a likely explanation for the connection between HL and performance on cognitive tests. This group ‘induced’ an ARHL onto middle-aged participants by the use of noise protection headphones and asked them to undertake an extensive battery of cognitive tests, measuring different cognitive domains. Ultimately they found that compared to controls and placebos (who were wearing non-functioning headphones), there was no difference in scores on cognitive tests, again suggesting that it is not the physicality of low hearing levels that induce the decline in cognitive performance. Thus concluding, lower cognitive scores are not an artefact of the testing procedure, but are reflective of an underlying difference in cognition.

Evidence to support an over or misdiagnosis, however, comes from trials of short-term hearing aid use. For example the cognitive and psychological benefits of hearing aid administration were investigated in a group of 34 participants over the age of 65, with moderate to severe HL. They all completed the MMSE and geriatric depression scale (GDS) at baseline, and then were fitted with appropriate hearing aids (Acar et al., 2011). At baseline, mean MMSE scores were 20.3 (+/- 7.7), but upon repeating the questionnaires three months later, a significant improvement in cognition was seen (p <.005), mean MMSE scores were now reported as 23.0 (+/- 7.5). There was a similar improvement on GDS scores. This apparent improvement in cognition over such a short period of time, could suggest that prior to hearing aid administration, participants did not actually hear parts of the test, so the improvement reflects a more complete understanding of the questions. This short time period could also indicate a practice effect, or due to the significant psychological improvement, could give evidence for interplay between depression and cognitive performance.

To conclude, the evidence for over diagnosis of cognitive impairment in people with HL is varied and inconsistent. It may be unlikely that people with HL would score lower as an artefact of the testing procedure, as the performance on non-verbally administered tests did not differ. Also, in general, experienced clinicians testing cognitive performance do take sensory deficits into account when undertaking their examinations (Lindenberger et al., 2001), and ensure that the participant has heard and understood the instructions for the tests. However, retesting the same groups of individuals has shown an increased performance when wearing hearing aids, which could suggest that they didn’t hear the questions the first time round, accounting for an apparent drop in scores on cognitive tests. This also provides evidence for the sensory degradation hypothesis, described below, as the brains of individuals with HL may be working harder to process the degraded auditory signals, therefore decreasing the capacity of resources available to complete the cognitive tasks. However, the performance on cognitive testing does not change when ARHL is simulated in younger groups of people, but this could reflect differences in cognition between younger and older individuals.

## 2.3.3. Sensory degradation and deprivation

The sensory deprivation hypothesis suggests that long-term HL could lead to cognitive impairment via many different mechanisms, either temporarily or permanently, directly or indirectly (Li and Lindenberger, 2002, Schneider et al., 2002). The main features of these hypotheses will be discussed in more detail in subsequent paragraphs.

### 2.3.3.1. Information degradation

The evidence reported in section 2.3.2 could also lend some support for the information degradation hypothesis, which assumes impoverished perceptual input results in a temporarily reduced cognitive performance. This theory suggests that listening requires more effortful processing in people with HL, compared to those with normal hearing (Pichora-Fuller and Singh, 2006), increasing cognitive demand for auditory processing, at the detriment of other cognitive processes (Peelle et al., 2011). For example, an fMRI study demonstrated that people with poorer hearing had decreased activation in core auditory processing areas during more complex grammatical tasks compared to those with normal hearing, or during simple sentence tasks (Peelle et al., 2011). The authors concluded that sensory loss may therefore impact on the cognitive resources required to perform higher-level cognitive tasks rather than simply the ability to process sounds.

The fact that individuals with HL perform to a lower level on various tests of cognition compared to those with normal hearing (Uhlmann et al., 1986, Dupuis et al., 2015) could be explained by this hypothesis. For example, HL was associated with a greater decline in MMSE scores over a 25-year period, with a mean group difference of 0.06 points per year, leading to approximately a 1.5 point difference over the whole study period (Amieva et al., 2015). Although the authors reported a statistically worse cognitive performance and greater rate of cognitive decline, the difference in scores in clinical terms are marginal and do not reflect a clinical cognitive impairment. This is more likely to reflect variation in the population, and poorer performance by certain members in the HL group could be due to more effortful processing, rather than actual cognitive impairment. Similarly, an improvement in cognitive performance three months post hearing aid administration (Acar et al., 2011) could show more resources are available to undertake the cognitive tasks, rather than effortful processing of degraded sounds. This does highlight the overlapping nature of the hypotheses and could suggest that some people with HL may be over diagnosed with a cognitive impairment when poorer performance may not necessarily reflect this. This theory alone, however, may be too simplistic to fully explain the increased risk of incident dementia in people with HL (Lin et al., 2011b)

### 2.3.3.2. Sensory deprivation

A recent imaging study showed that people with HL had higher rates of whole brain atrophy as well as specific volumetric declines in the medial temporal lobes compared to those with normal hearing thresholds (Lin et al., 2014). The authors suggested that long-term sensory deprivation has directly influenced functional and structural changes in the brain, leading to neuronal degeneration. These findings are interesting, as the temporal regions are not only important for language processing, but selective degeneration in these areas is also seen in MCI and the early stage of AD (Kantarci and Jack, 2004).

Longitudinal studies have provided evidence for the independent association of HL and risk of cognitive decline and all cause dementia. Many have shown that people with ARHL perform worse on tests of cognition over time compared to those with normal hearing. For example, over a 12- year period, participants with self-reported HL were more likely to develop incident dementia compared to those with normal hearing (16.3% vs 12.1%, p<0.001) (Gurgel, 2014). The authors also found the mean time to onset of dementia was significantly shorter for those with HL, reporting a 54% faster rate of annual decline from baseline. Similarly, a French epidemiological study, which followed 3,670 participants over 25 years, regularly assessing cognition using the MMSE, found that HL was associated with lower baseline MMSE scores, and a greater yearly decline, independent of age, sex and education (Amieva et al., 2015). Both of these studies, however, relied on self-report for identifying the presence of HL, which was only recorded at baseline, and not followed up at subsequent visits. As the samples included elderly participants over the age of 65, one would expect more of the participants to have developed an ARHL over the 12 and 25-year period. This also highlights the problem of self-report and social stigma, as there are likely to be many individuals who report no hearing problems, but would be diagnosed with HL on an objective test.

A study which formally and objectively tested hearing levels using PTA also found a 24% increased risk of cognitive impairment in participants with HL compared to those without (Lin et al., 2013). Lin et al., (2013) followed up 1,984 elderly participants with no evidence of cognitive impairment at baseline, using a modified MMSE (3MS) (Teng and Chui, 1987) to measure global cognition, and digit symbol substitution test (DSS) (Wechsler, 1981) to evaluate speed of processing and executive function. It was shown that, over the 6-year period of observation, over 30% of the participants developed cognitive impairment. Annual rates of cognitive decline according to the 3MS were 41% greater in those with a HL, and similarly 32% greater on the DSS. This evidence suggests that HL is associated with greater levels of cognitive impairment and greater rates of yearly cognitive decline. However, and as also reported in the epidemiological study by Amieva et al., (2015), in this study, participants with HL had poorer cognitive scores at baseline, which could suggest that there may be other factors already influencing cognition, providing evidence for the common cause hypothesis, which will be presented in the subsequent section.

It is important to note, that these studies are correlational studies with large numbers of participants, and statistical differences on cognitive tests may not necessarily represent a clinical cognitive profile. There is a natural variance of cognitive performance in the ageing population, which could be used to explain differences on test scores.

In another study with a more robust methodology, the severity of HL was associated with an increased risk of clinically diagnosed incident dementia. Six hundred and thirty nine participants were followed up for an average of 12 years with in depth neuropsychological testing and PTA. Findings reported a linear correlation between the severity of HL and all cause incident dementia, with an increased risk of 1.89 for people with a mild HL, 3.00 for moderate loss and 4.94 for a severe loss (Lin et al., 2011b). The authors did note that these results could be slightly biased due to the fact that participants with HL at baseline were significantly older than the people without HL, which could account for some of the increased risk of dementia over time.

The idea that the severity of HL could predict dementia risk and onset was corroborated by a recent study which followed up elderly participants aged between 70 and 79 years, over a nine year period. Deal et al., (2016) found that moderate and severe HL was associated with an increased risk of developing dementia (HR= 1.55, 95% CI= 1.10, 2.19). There were again limitations to this study, dementia was defined using an algorithm, rather than a clinical diagnosis, and baseline levels for cognition were lower for people with a HL, which could again suggest that there is impending cognitive impairment at the time of baseline assessment in these people.

Various studies have investigated the role of hearing aid administration on risk for cognitive decline and dementia. Earlier, it was reported that people with HL performed better on the same cognitive tasks, three months after hearing aid administration (Acar et al., 2011). Another recent study, investigating the relationship between HL, hearing aids and cognitive impairment over time, found that the risk of cognitive decline in people with HL wearing hearing aids was the same as for those with no HL, and it was only people with untreated HL who were at a greater risk of cognitive impairment over the 25-year period (Amieva et al., 2015.) The authors also reported that, when controlling for psychosocial variables, the association between HL and cognitive decline was no longer significant, suggesting that the link between the two could be mediated by social factors and depression, rather than a physical change in the brain.

Altogether, this evidence suggests that the presence of HL can predict the development of dementia in a cohort of people over time, and that people with a more severe HL may be even more likely to develop cognitive impairment than people with a mild or no reported HL. Similarly, the presence of hearing aids may help to mitigate this potential decline. If this is the case, then sensory deprivation may be indirectly influencing the risk of cognitive impairment and dementia via socio-emotional factors (Dawes et al., 2015b). People who have a more severe HL or those who do not wear hearing aids, may be more likely to experience greater difficulty in these situations (Mick et al., 2014).

### 2.3.3.3. The psychosocial pathway

One of the main debilitating features of ARHL is that it interferes with communication and, as a consequence, people often withdraw from social situations, which can affect personal relationships (Strawbridge et al., 2000). Multiple studies have shown that, regardless of hearing thresholds there is a strong correlation between ARHL and depression (Gopinath et al., 2009), functional decline, lowered self-esteem and social isolation (Yueh et al., 2003, Gates and Mills, 2005, Mick et al., 2014), contributing to reduced quality of life (Cacciatore et al., 1999, Kramer et al., 2002). It is possible that it is these factors, associated with ARHL, which indirectly predispose an elderly individual to cognitive impairment or dementia.

A cross sectional study designed to evaluate the relationship between HL and depressive symptoms, using the medical outcomes study 36- item short form survey, reported that females under the age of 70 with bilateral HL were five times more likely to suffer depressive symptoms than those without HL, or older females with HL (Gopinath et al., 2009). The authors also reported subjects who wore their hearing aids for a minimum of one hour every day were significantly less likely to suffer from depressive symptoms than those who never wore hearing aids. This suggests that untreated HL is more associated with depression, and therefore correct diagnosis and treatment with hearing aids may help keep the individual socially active, reducing the risk of depression. There is also the possibility that by wearing hearing aids, the individual may be more accepting of their HL, and as a consequence, friends and family members may become more sympathetic towards the challenges of HL; all helping to reduce levels of depression, loneliness and isolation (Heaney and Israel, 2008). As described in Chapter 1, people with depression are more likely to develop cognitive impairment and dementia (Li et al., 2011, Chen et al., 2015).

A community based longitudinal study found that social isolation is an independent risk factor for dementia, with the degree of isolation relating to the relative risk of dementia (Fratiglioni et al., 2000). One thousand, two hundred and three participants were enrolled in the study for an overage of three years. During this time, 176 (15%) of people developed dementia; analysis showed people with a poor social network were 60% more likely to develop dementia compared to those with good social networks. Similarly, people who reported themselves as lonely were almost twice as likely to develop AD over a four year period (Wilson et al., 2007). These findings were reiterated in another study which reported lonely people to have an accelerated level of cognitive impairment (Tilvis et al., 2004). Hearing status was not described in these studies, but it has been previously reported that people with HL are more likely to be socially isolated and have feelings of loneliness, than those without (Strawbridge et al., 2000). Therefore, the links between HL and cognitive decline could be mediated via this pathway.

There is little research to explain the interaction between HL, psychosocial factors and cognitive decline (Fulton et al., 2015). Although the underlying mechanisms are not well understood, there is evidence that psychological disturbances lead to physiologic changes which could increase the risk of cognitive impairment (Cacioppo et al., 2002). It has been suggested that long-term loneliness in older adults may lead to an elevated systolic blood pressure (Cacioppo et al., 2002) independent of all other cardiovascular risks (Hawkley and Cacioppo, 2010). HL may lead to increased levels of loneliness, which in turn increases the risk of hypertension and cardiovascular disease, all together leading to an increased rate of cognitive decline. Alternatively, HL may accelerate the cognitive trajectory in a population who may already be at risk of developing dementia, due to the interactions with cardiovascular risks. Similar hypothesis have been formed for negative social interactions, such as feeling rejected, which have been shown to increase the risk of mild cognitive impairment (Wilson et al., 2015).

Of course, when evaluating this evidence, the role of reverse causality cannot be ruled out. Impending cognitive impairment could lead to depression, feelings of loneliness and isolation due to underlying physiological changes (Bennett and Thomas, 2014). Similarly, isolated people may be less likely to participate in cognitively stimulating activities, exacerbating cognitive decline. However, the temporal relationship between the factors in longitudinal studies has suggested that these associations are not just an early manifestation of cognitive decline. For example, although levels of loneliness at baseline predicted subsequent cognitive decline, cognitive status at baseline did not predict loneliness, suggesting that this relationship may be unidirectional (Wilson et al., 2007).

Evidence from hearing aid studies may again help to clarify the association between HL, psychosocial factors and dementia. Using this hypothesis, one would expect that people who wear hearing aids would be less likely to be isolated (Mick et al., 2014), and therefore less likely to develop dementia. Reports are inconsistent and often inconclusive, with some studies showing that hearing aid rehabilitation has no effect on cognitive function (van Hooren et al., 2005), whilst others have shown a beneficial effect (Acar et al., 2011).

For example, a longitudinal study has documented that over a 25-year period, participants with hearing aids do not decline to the same extent as hearing level matched participants without hearing aids (Amieva et al., 2015). However, these groups were not matched for confounding factors, and HL and hearing aid use were only assessed using a single question at baseline. Therefore, it is not known whether the people who reported to have HL and not use a hearing aid, did in fact get hearing aids at a later date, nor are the hearing aid compliance levels known or controlled for, meaning these results are not necessarily generalisable.

Structural equational modelling using a large sample of data from the UK biobank was used to investigate whether HL is indirectly associated with cognitive decline via the social isolation pathway, and whether the use of hearing aids mitigates this decline (Dawes et al., 2015b). HL was defined using the digit triplet test, and cognition was evaluated using a battery of visually presented tests. After controlling for age, sex, gender, socioeconomic status and general health, it was found that poorer hearing was associated with poorer cognition. When evaluating the role of hearing aids, by comparing people with equivalent levels of HL, hearing aid use was associated with better cognitive performance, but hearing aid users still performed lower than individuals with no HL, suggesting that the use of hearing aids does not fully lessen this decline. This suggests that using hearing aids does help with cognition to some extent, but as it takes on average 11 years for people with HL to come forward for rehabilitation (Wong et al., 2014), irreversible neuronal damage may have already taken place. Interestingly, Dawes et al., (2015b) found that although social isolation was associated with worse hearing and worse cognition, hearing aid use was actually associated with marginally higher levels of social isolation compared to those with HL not using hearing aids. This suggests that firstly, hearing aids do not necessarily improve social functioning, but also the improvement in cognition in people with hearing aids is not due to the psychosocial pathway.

Therefore, results are conflicting and longitudinal data is essential to confirm the role of hearing aids on cognition, whether they can in part lessen this decline, and if it is not via the social isolation pathway, there must be another fundamental mechanism by which HL can accelerate cognitive decline. As with all help-seeking behaviours, there may be a difference between those with HL who seek hearing aid rehabilitation and those who do not (Fischer et al., 2011), which might also be used to explain some of the differences in cognition.

## 2.3.4. Cognitive load on perception

The theory of cognitive load on perception suggests that cognitive impairment could lead to HL, or this relationship may be bidirectional, where cognitive decline exacerbates the symptoms of HL (CHABA, 1988). There is little evidence in the literature to support this theory, although, a longitudinal study investigating the risk factors for ARHL found that, apart from age, the only significant risk factor was probable cognitive impairment, defined by MMSE of less than 23 (Kiely et al., 2012). However, there are confounding factors and other health comorbidities which may have influenced the relationship and few other studies have suggested that cognitive impairment precedes HL.

The links between social isolation, HL and cognitive impairment could lend, albeit weakly, some support for this hypothesis, suggesting a possible bidirectional relationship. For example, as described earlier, ARHL is a gradual process, and individuals may have to allocate greater neural activity to hearing and language comprehension at the detriment of other brain processes (Martini et al., 2014). Therefore in noisy social situations, people with HL will use more cognitive resources to overcome the bias of HL (Pichora-Fuller and Singh, 2006), to stay socially connected. Someone with cognitive decline, however, may not be able to allocate the extra resources needed to engage socially, and thus they may be more likely to withdraw, exacerbating the cognitive impairment.

## 2.3.5. Common cause- widespread neuronal degeneration

Longitudinal studies have shown that people with HL at baseline are more likely to develop cognitive impairment and dementia compared to those without HL (Lin et al., 2011b, Lin et al., 2013), suggesting HL comes first and may be an independent risk factor for dementia. However, the common cause hypothesis proposes a central degenerative process, which simultaneously affects sensory and cognitive processing in ageing (Lindenberger and Baltes, 1994). HL and cognitive decline could be part of the same ageing spectrum, but HL may appear to manifest earlier due to obvious symptoms and readily available assessments, whereas neuropsychological testing and brain imaging only detect cognitive decline in comparably advanced stages. There is evidence that prenatal and childhood development can influence hearing and cognitive function in midlife. An observational study reported within the normal birth weight range, babies with a higher birth weight had significantly better sensory and cognitive function when assessed at middle age, and those with the smallest and largest birth weights had significantly poorer function (Dawes et al., 2015a). The authors suggested that a common influence of early life factors may help to explain the link between hearing acuity and cognitive function regardless of age. Also, genetic mutations in DNA methyltransferase 1 (DNMT1) lead to both HL and dementia, where a progressive HL develops at a much earlier stage and followed by cognitive decline in later life (Klein et al., 2013). As DNMT1 is involved with neural cell development, maintenance and connectivity, it is plausible that a widespread neurodegeneration may also lead to HL many years prior to the onset of dementia (Fulton et al., 2015).

The common cause hypothesis would predict that the use of hearing aids would have no positive effect on cognitive performance, as there is another factor driving the cognitive decline or neurodegeneration, which hearing aids cannot correct for.

For example, three aged matched groups were investigated over six months to evaluate performance on a variety of functions, including cognition. Two groups included individuals with mild to moderate HL, one of them rehabilitated with hearing aids, one group no hearing aids, and the final group was a control with no HL (Tesch-Romer, 1997). The authors found that over six months of rehabilitation with aids there was no significant improvement in cognitive functioning or any difference between any of the three groups. However, the follow up period was very short, and the fact that people may have improved over time cannot be discounted. Also, most of the individuals in the hearing aid rehabilitation group (74%) were only fitted with one aid, rather than the desired two aids, which could suggest that the rehabilitation was insufficient in this study.

The inconclusive benefit of hearing aids on cognitive functioning may be due to the fact that there are other components involved with auditory degeneration. It has become increasingly recognised that ageing and presbycusis concern both peripheral and central auditory structures (Parham et al., 2013), making the diagnosis of ARHL much more complex as PTA does not assess central auditory function.

Gates et al., (1995) investigated the types of auditory dysfunction in ageing and AD by observing 82 subjects, half of whom were cognitively healthy and half with a diagnosis of mild probable AD. Findings reported no significant difference between average pure tone thresholds when controlling for age, but there was a significant reduction on scores testing central auditory processing. Although limited by the small sample size, this suggests that central processing may be an important factor linking HL and AD, regardless of peripheral HL.

Gates et al., (2002) also proposed that central auditory processing dysfunction may be able to predict people at risk of dementia. They followed up 747 cognitively healthy volunteers for an average of 8.5 years. Over this time 40 participants (5.4%) were diagnosed with AD, and of these people, 18% had an auditory processing deficit as identified by synthetic sentence identification and ipsilateral competing message test scores of <50%. This resulted in a positive predictive value of AD in people with central auditory dysfunction of 47%. These results have been mirrored by Pai et al., (2014) whose results showed a significant relationship between AD and central auditory dysfunction. Age was a significant factor for poorer performance on tests of auditory processing, but cognitively healthy controls always outperformed matched participants with AD (Pai et al., 2014).

Similarly, Gates et al., (2008a) tested central auditory function in three groups: people with AD, people with memory problems not sufficient to be diagnosed as AD, and people with no memory loss. They found the lowest performance in patients with AD, the group with memory problems scored worse than those reporting no memory problems, even after controlling for age and peripheral hearing levels. This suggests a way in which people with memory problems may be monitored for the risk of AD, although further investigation is needed into the neuropsychological profiles of these people.

To further complicate this relationship, social isolation and loneliness can have an impact on auditory processing tasks (Cacioppo et al., 2000). Young adults undertook a dichotic listening task and although there was no difference in performance when attending to the dominant ear between lonely and socially connected groups, the lonely group performed significantly worse when directed to shift attention to the non-dominant ear, suggesting that effortful attentional processes are compromised in lonely individuals (Cacioppo et al., 2000). Therefore, loneliness and social isolation could be indirectly influencing or exacerbating auditory processing difficulties.

The fact that HL has been consistently associated with incident dementia (Lin et al., 2011b) rather than one cause for dementia also supports this common cause hypothesis. Lin and colleagues found a conversion to dementia in 58 participants over the twelve year follow up. They reported that almost 65% of cases were of AD diagnosis, but this leaves a further 35% with other forms of dementia. As the different types of dementia have different underlying aetiologies, risk factors and time to conversion, it is not easy to comprehend how HL would lead to an increased risk for development of all of them, and therefore is more likely that another common factor is linking them.

The shared risk factors as outlined in section 2.3.1 also lend some support to this theory, as well as a decline in central auditory processes. The pathology of different types of dementia may start to accumulate many years before the onset of clinical symptoms (Sperling et al., 2013a, Sperling et al., 2013b), and this increased cognitive pathological burden could manifest earlier as symptoms of reduced perception. This is an important hypothesis to investigate, as it could suggest that HL could be a reliable marker of underlying or impending brain changes. More evidence to support this link comes from studies which show the relationship between sensory and cognitive decline increases with advancing age (Baltes and Lindenberger, 1997), and log linear increased risk of cognitive decline with severity of HL (Lin et al., 2011b, Deal et al., 2016). Many of the studies did not repeat hearing testing objectively or longitudinally and so the possibility of a relationship between the rapidity of declining HL is yet to be explored. It would be interesting to investigate this, and it would lend evidence towards a common cause.

# 2.4. Quality assessment

There is conflicting evidence for and against the roles of peripheral and central HL, and to which extent each may influence cognitive decline. There are problems with methodology in many of the studies, some are retrospective or cross sectional in nature and therefore it is hard to infer causality. Many of the studies do not have a unanimous outcome measure for cognitive outcome, some use any decline on a test over time, even if this is not to a clinical level (Lin et al., 2004) an algorithm or software to compute possible dementia (Deal et al., 2016), self-report or clinical dementia diagnosis. The same is seen for measures of HL regardless of aiming to measure peripheral or central function, many of the reported methods for classifying HL are either using self-reported measures (Gurgel, 2014), questionnaires, or simple clinical tests that are not accurate audiometric tests (Uhlmann et al., 1986, De Silva et al., 2008). Using these methods, various small scale studies have not found a correlation between peripheral hearing levels and cognitive decline or dementia (Lin et al., 2004), and effect sizes tend to be marginal in larger scale studies (Lin et al., 2013, Deal et al., 2016). However, even with small numbers of participants, an increased risk for cognitive decline and impending dementia has been documented in people with central auditory dysfunction (Gates et al., 1995, Gates et al., 2002). We cannot exclude the fact that cohort differences could act to make the associations appear bigger or smaller in each case. Although all offering slightly different contributions to various research questions, the methodologic quality of each article has been assessed against a set of criteria based on those described in (Kmett et al., 2004) to assess quality of diverse study designs. Questions and criteria adapted to meet the needs of this review (Welton et al., 2015). As the criterion is relating specifically to this research question, studies were scored as either criterion is not met =0 or criterion is met =1. Criteria were unweighted to allow equality across all items; total scores are to a maximum of 12. As discussed by Kmett et al., (2004), 55% is an acceptable quality to include studies in the review, with 75% being a conservative threshold for high quality. The quality assessment criteria used for assessment is described in Appendix 1.

Table 2.1 shows that quality is moderate to high in all of the studies included in this review chapter, but scores may be confounded by differing aims, meaning some of the quality assessment criteria may not have been relevant. The studies reported to have the highest methodological quality are longitudinal studies which have directly measured dementia according to clinical criteria, and a full audiometric assessment including auditory processing.

**Table 2.1.** *Quality assessment of the studies included*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Total | |
| Uhlmann et al., (1986) | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | | 10 |
| Uhlmann et al., (1989a) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | | 10 |
| Tesch-Romer, (1997) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | | 10 |
| Gates et al., (1995) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | | 11 |
| Gates et al., (2002) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | | 12 |
| Lindenberger et al., (2001) | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | | 6 |
| Lin et al., (2004) | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | | 9 |
| Tay et al., (2006) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | | 9 |
| De Silva et al., (2008) | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | | 7 |
| Gates et al., (2008a) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | | 11 |
| Acar et al., (2011) | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | | 6 |
| Lin, (2011) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | | 9 |
| Lin et al., (2011b) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | | 11 |
| Kiely et al., (2012) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | | 10 |
| Lin et al., (2013) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | | 10 |
| Gurgel, (2014) | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | | 10 |
| Teipel et al., (2015) | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | | 8 |
| Dupuis et al., (2015) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | | 7 |
| Dawes et al., (2015a) | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | | 9 |
| Dawes et al., (2015b) | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | | 8 |
| Amieva et al., (2015) | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | | 7 |
| Wen et al., (2016) | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | | 8 |
| Deal et al., (2016) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | | 10 |

# 2.5. Summary

There is a link between ARHL and cognitive impairment and dementia, although current research is no further in establishing the mechanistic pathways of this relationship. Epidemiological studies have shown an overlapping prevalence (Teipel et al., 2015), although causality cannot be assumed. Case control trials have suggested that people with HL are more likely to develop all cause dementia and cognitive decline in various domains, which may be suggestive of a common underlying aetiology, rather than the specific factor of HL leading to cognitive decline or a certain type of dementia. It is clear that social isolation and depression may play a role as a ‘mediator’ between HL and dementia; ARHL leads to depression, which increases an individual’s chance of dementia. The extent to which the psychosocial features associated with HL link to cognition are not well defined and are always presented with confounding variables. Hearing aid studies, which might help to clarify the mechanism of this relationship, are inconclusive, and large scale tightly controlled studies have shown that people with HL who use hearing aids are still at greater risk of developing dementia compared to those with normal hearing. It has been documented that auditory deprivation may not be fully compensated for by hearing aids (Wong et al., 2014) which could help to explain some of the discrepancy. These inconsistent results could also suggest that perhaps people with higher cognitive function are more likely to be aware of a decline in their hearing, and be more likely to seek help (Lunner et al., 2009).

Although the independent theories have been proposed to try to further understand the mechanism of the relationship, they are not mutually exclusive, and many of the key features of each overlap. It may be too simplistic to suggest the links between HL and dementia could be explained by one of these mechanisms in isolation. For example, both over diagnosis and information degradation hypothesis can be used to explain various results relating to improvement in performance after hearing aid administration, however, due to time constraints and confounding factors, the common cause cannot be ruled out. Similarly, the results from imaging studies suggest that peripheral HL leads to an accelerated rate of atrophy, specifically in temporal areas and the whole brain (Lin et al., 2014), which in itself is strong evidence to suggest that ARHL does contribute to an accelerated rate of cognitive decline. These findings, however, could also be explained by the common cause hypothesis, as the atrophy could simply be a by-product or a comorbidity of impending dementia.

To conclude, findings from the current literature show a consistent association between different measures of HL and cognitive decline. However, it is still not clear whether HL is an independent risk factor, what is the role of social isolation and depression in this relationship, and which type of cognitive decline or dementia is selectively affected in people with HL. Answers to these questions may help us to understand a possible causality or more robust hypothesis for mechanisms of this relationship. The remainder of this thesis will try and answer these questions.

# Chapter 3: Aims and Objectives

Past research has indicated links between HL and cognition in normal ageing, cognitive decline and dementia. However, how the two factors are definitively linked is yet to be elucidated. Many confounding factors complicate this relationship further, and despite the generation of various plausible hypotheses, it is still unknown whether the association is overestimated, causal or consequential.

Understanding the association between hearing and cognition in the elderly is further exacerbated by increased comorbidities and risk factors, namely age, which brings both declines in sensory and cognitive processes. Similarly, hearing is not as simple as testing peripheral hearing levels, as speech comprehension is a complex entity involving peripheral and central auditory processes, together with cognitive processing to translate sounds into meaningful data. Therefore, the nature of testing cognition often relies on intact auditory processing, and vice versa.

Major methodological issues are represented in the literature, where many studies have failed to tightly control the measurements of HL, cognition or both. Therefore conclusions may be over or under representing associations dependent on the tools used to measure both factors.

The overarching aim of this thesis is to understand further the links between HL and cognitive impairment in normal ageing and pathological cognitive decline, with specific reference to peripheral hearing levels, subjective hearing disability and central auditory processing, to establish which measure of HL best detects risk of cognitive impairment.

This thesis will aim to answer the following questions:

1. *Can subjective hearing disability in relation to current hearing problems be identified?*

People often report that HL reduces quality of life, as it can have an impact on communication, socialisation, feelings of self-esteem and fatigue. Currently available assessment tools used to measure hearing disability were ultimately designed to estimate hearing difficulties in the absence of audiometric testing, thus are not entirely relevant to answer the questions regarding current functioning levels. Therefore, an aim was to develop and validate a tool to quantify current hearing disability, regardless of hearing diagnosis or rehabilitation. The results are presented in Experiments 4.1 and 4.2.

1. *Are people with hearing loss being disadvantaged by the testing procedure?*

The association between HL and cognition in healthy adults may be overestimated by the confounding influence of HL on verbally administered cognitive tests. The aim is to identify whether using a battery of tests designed to remove over reliance on auditory perceptual processing will still yield an association between HL and cognitive performance in a sample of cognitively healthy individuals. It is hypothesised that during healthy aging, HL would not be associated with poorer cognitive performance when controlling for the effects of hearing acuity. The results are presented in Experiment 5.1.

1. *Are behavioural hearing thresholds or subjective hearing disability more important in terms of cognitive performance and cognitive decline?*

Hearing disability is a common factor associated with HL in the elderly population, which may be associated with decreased quality of life, social isolation and low feelings of self-esteem; all of which may increase the risk of cognitive impairment. The aim is to identify if there were an association between HL and cognitive performance, whether this were related to their measured hearing thresholds or due to the influence of disability associated with HL, and what role do hearing aids play. It is hypothesised that people with HL who have higher levels of disability may have poorer cognitive performance compared to those without subjective disability. The results are presented in Experiment 5.2.

1. *Is hearing loss independently associated with a change in performance over time? If so, is this linked to decline in hearing acuity or hearing disability?*

Past research has suggested people with HL have accelerated rates of cognitive decline both in normal ageing and in dementia. It is not known whether this is linked to a decline in their hearing acuity, subjective hearing disability or another factor. The aim was to investigate whether there is any decline in a cognitively healthy sample over a one-year period, and if so, whether it was related to baseline HL, decline in hearing thresholds or hearing disability. It is hypothesised that participants who were low performers might be more likely to decline, and those with HL might be at a further risk of decline than those with normal hearing. Results are presented in Experiment 5.3.

1. *What is the role of central auditory processing on cognitive performance in cognitively healthy individuals?*

As presbycusis also involves central auditory processes, and central auditory processing is closely affiliated with cognition, it is likely that central auditory integrity may give some insight into the relationship between hearing and cognitive acuities. The aim is to identify whether auditory processing scores, measured using the iDichotic, a computerised measure of central auditory processing developed by the Bergen fMRI group (Bless et al., 2013, Bless et al., 2015), were independently associated with Overall Cognition or linked to any cognitive correlates, regardless of age and peripheral hearing thresholds. The secondary aim was exploratory, to evaluate the relationship between iDichotic performance and hearing disability scores, to help elucidate the possible mechanisms linking these factors. The hypothesis is that performance on different aspects of the iDichotic which use different cognitive processes would correlate with cognitive performance. Results are presented in Experiment 6.1.

1. *Can central auditory processing performance predict decline in cognition in a cognitively healthy sample?*

As the mechanisms of testing auditory processing involve cognitive functions, it is possible that auditory processing tests may be a more sensitive measure to detect subtle changes in cognitive and underlying neuronal function, thus subclinical deficits may manifest earlier than in neuropsychological testing. As there are no ceiling effects, it is possible to investigate changes in cognitive control over time, and the aim is to investigate whether the iDichotic could be used as a marker for impending cognitive changes. It is hypothesised that poor performance on the iDichotic at baseline might predict a decline in cognitive performance. The results are presented in Experiment 6.2.

1. *Is there an increased prevalence of hearing loss in people with cognitive impairment? If so, does this reflect peripheral or central auditory changes?*

Previous research has inconsistently reported a higher prevalence of peripheral and central auditory disruptions in people with cognitive impairment and dementia, as results are often confounded by the older age of persons with HL. Therefore, the aim is to investigate whether prevalence of HL is higher in individuals with varying degrees of cognitive impairment, which might help elucidate a possible mechanism. If HL were a risk factor, or a sign of impending cognitive decline, the hypothesis is that there would be an increased prevalence of HL in the patient sample compared to controls. Results are presented in Experiments 7.1 and 7.3 and discussed together in section 7.6.

1. *Does hearing loss lead to a different neuropsychological and socioemotional profile in individuals with cognitive decline?*

There is evidence that people with HL have accelerated rates of cognitive impairment, and the severity of HL is closely linked to the risk and onset of dementia. Therefore it will be investigated whether the thresholds of HL would be more severe in persons with dementia compared to MCI, what role subjective hearing disability would play and whether the neuropsychological profiles would be more severe in people with HL. As both conditions are progressive, the hypothesis was that severity of HL would be related to severity of cognitive decline, and patients might feel more restricted by their HL due to limited cognitive resources to help overcome the challenges. The results are presented in Experiments 7.1 and 7.3 and discussed together in section 7.6.

1. *Can hearing loss masquerade as subjective memory problems and the early stages of AD?*

There are common overlapping symptoms between untreated HL and the early stages of AD, where HL may lead to confusion, memory loss and low mood; all relevant symptoms for impending AD. Experiment 7.2 presents a case study of a gentleman with a diagnosis of early AD and severe HL.

1. *Does hearing loss lead to structural grey matter changes, and are these exacerbated in people with cognitive impairment?*

The literature on the effects of HL on grey matter in the auditory and auditory areas are limited and inconsistent, where some studies have presented that HL drives grey matter atrophy in the auditory and extra-auditory areas, others have found no association over the effects of ageing, and others have found increased levels of grey matter associated with HL. However, none have investigated the role of cognition or neurodegeneration, and it could be that premorbid cognitive impairment may be driving the cortical changes. The aim is to investigate, in a pilot study, whether HL would be associated with grey matter changes in clinically validated cognitively healthy controls, and how these changes would differ in a sample of patients with cognitive impairment. It is hypothesised that HL might lead to grey matter atrophy in auditory regions during healthy ageing, which might be exacerbated during pathological ageing. The results are presented in Experiment 7.4.

# Chapter 4: Hearing loss, social isolation and cognitive decline

# 4.1. Introduction

The links between hearing status, cognitive impairment and dementia have been introduced in chapter 2, but factors mediating this relationship remain unknown. One of the main theories linking ARHL and cognitive decline is the sensory deprivation hypothesis (Li and Lindenberger, 2002, Schneider et al., 2002) which proposes that sensory deprivation may have an impact on cognition, either directly, via impoverished signals coming into the brain, or through its effects on the social and emotional pathway.

Major consequences of HL are social and emotional dysfunction (Strawbridge et al., 2000), where social isolation (Mick and Pichora-Fuller, 2016) and depression (Gates and Mills, 2005, Parham et al., 2011) are commonly reported. HL is the most common sensory disorder affecting communication (Mathers et al., 2000), which is believed to be particularly disadvantageous for elderly people (Lubinski and Welland, 1997), who have not developed the skills necessary to cope with communication difficulties. Adapting to a disability in later life may be more challenging than for those who were born with, or developed one in their early years (Livneh and Wilson, 2003), thus ARHL often leads to the breakdown of personal and social relationships.

Social and emotional dysfunction are independently associated with the risk of cognitive decline (Barnes et al., 2004, Wilson et al., 2007), and as the risk for dementia increases linearly with the severity of HL (Uhlmann et al., 1989a, Lin et al., 2011b, Deal et al., 2016), it is plausible that these difficulties may play a role in this association. Evidence to support this comes from numerous studies which have found that treatment of ARHL with hearing aids improves quality of life (Mondelli and Souza, 2012, Niemensivu et al., 2015, Contrera et al., 2016). Also, albeit inconsistently, the use of hearing aids have been shown to improve short-term cognitive performance (Kalluri and Humes, 2012), with some studies reporting hearing aid use attenuates the risk of cognitive decline associated with HL (Amieva et al., 2015, Dawes et al., 2015b).

# **Experiment 4.1 – Development of the ‘Social and Emotional Associations of Hearing loss’ (SEAH)**

# 4.2.1. Introduction

It has long been recognised that people with the same or similar audiometric profiles may cope with their HL in very different ways, and as expressed by Ewertsen and Birk-Nielsen, “*A heavy hearing impairment can be, but does not have to be, a condition causing heavy social handicap, and a slight hearing loss may (rarely) be experienced as a heavy social handicap”* (Ewertsen and Birk-Nielsen, 1973, p185).

Historically, the term ‘handicap’ was used to describe the subjective social and emotional consequence of HL, focusing on the disease and disabilities associated with it. However, the revision of the International Classification of Functioning, Disability and Health (ICF), an international standard set by the World Health Organisation, states diagnosis alone is not enough to describe the day to day problems in functioning that an individual with a health condition experiences (WHO, 2001). The ICF biopsychosocial model of functioning and disability (WHO, 2001) emphasises health rather than the disease, and introduces a single spectrum to describe this, moving away from disability being purely a consequence of disease severity (Kostanjsek, 2011). Therefore, the terms ‘activity limitation’ and ‘participation restriction’ have replaced the term ‘handicap’. It is now recognised that many factors are responsible for functioning, including an interaction between the disease or disability, activity limitations and participation restrictions, as well as environmental and personal factors. In the case of HL, activity limitations may be struggling to hold a conversation and participation restrictions could include withdrawing from noisy social situations; environmental factors may relate to the use of hearing aids, support and relationships and personal factors such as the age and background of the individual with HL.

It is therefore an important research question to investigate whether the effects of the ‘functioning and/or disability’ which may accompany HL contribute more significantly to the increased risk of cognitive decline, compared to hearing thresholds alone, and whether the use and perceived satisfaction with hearing aids help people to feel less isolated. This may have a major impact on future public health as a case for more aggressive treatment of ARHL and social isolation, to reduce the burden and onset of cognitive impairment.

Multiple questionnaires have been created to measure hearing disability in adults and the elderly (Ewertsen and Birk-Nielsen, 1973, Ventry and Weinstein, 1982, Schow and Nerbonne, 1982). Many of these instruments, however, were ultimately designed to estimate the prevalence of ARHL, and as such have been used as an alternative or preliminary screen for hearing impairment in the absence of formal audiometric testing, or to monitor the benefits of audiological rehabilitation (Barbosa et al., 2015, Oberg, 2016). Thus as a consequence, they are not entirely relevant for assessing the current levels of disability associated with HL.

One such questionnaire that is widely used as a screen for hearing disability is the Hearing Handicap Inventory for the Elderly (HHIE) (Ventry and Weinstein, 1982). This questionnaire was developed as a tool to identify hearing disability specifically in elderly people. It comprises of 25 scenarios where the patient is asked to score ‘yes’, ‘sometimes’ or ‘no’ for presence of hearing difficulty in each situation. Overall scores are then graded to a maximum score of 100 and handicap is distributed as follows, scores between 0-16 indicate no hearing handicap, 17-42 indicate a mild to moderate handicap and over 43 indicate a severe handicap. There are many benefits to using the HHIE, including self-assessment, it is relatively short and easy to administer, and has high sensitivity (between 69 and 100%) when compared with pure tone audiometry (PTA) (Sogebi and Mabifah, 2015, Brennan-Jones et al., 2015). It has been translated into many different languages, therefore is useful as a cross cultural screen for HL (Deepthi and Kasthuri, 2012) and is of great benefit in locations where PTA is not always accessible or available (Sogebi and Mabifah, 2015).

Various studies have demonstrated that the HHIE may not be sensitive enough to pick up a mild to moderate handicap (disability) in people with a mild HL, and is only useful in identifying significant handicap in people with a significant loss (Sogebi and Mabifah, 2015). As for any given degree of HL, there is a large variability in self-perception of disability associated with HL (Ewertsen and Birk-Nielsen, 1973), development of an accurate and culturally relevant tool is of upmost importance.

Similar results were seen when using this tool for the pilot study to generate the new questionnaire (data reported in 4.2.3.1.2.), where many participants expressed that the questions were not entirely relevant, or often not applicable. For example, question S-11, ‘Does a hearing problem cause you to attend religious services less often than you would like?’ This question would assume that everyone attends religious services and therefore excludes non-believers. Alternatively, religious buildings may be now well equipped for people with HL, as technology has moved on to supply amplification devices or loop systems to enable people with HL to continue to attend services. Similarly, questions regarding problems using the telephone may be outdated, as loud speaker functions are often employed, as well as a plethora of available amplified telephones which are recommended to people with HL. Finally, the HHIE instructs people to answer how they would hear or cope in these situations *without* a hearing aid, which in itself is not appropriate for addressing current activity limitations or participation restrictions, and thus disability may be overestimated in many cases where people regularly wear hearing aids.

Similarly, other tools such as the Self-Assessment of Communication (Schow and Nerbonne, 1982), Social Hearing Handicap Index (Ewertsen and Birk-Nielsen, 1973) and the Denver Scale of Communication function (Alpiner et al., 1974) have the same advantages and disadvantages and therefore are not satisfactory measures of social and emotional problems as a result of current levels of ARHL in this modern day. Accurate analysis of the social and emotional implications of hearing impairment is important as this could mediate the link between ARHL and declines in cognitive performance, as discussed in detail in Chapter 2.

The aim of Experiment 4.1 was to create a new, easy to administer, culturally relevant questionnaire to measure current levels of subjective hearing disability in the UK population.

# 4.2.2. Methods

## 4.2.2.1. Procedure

Three steps were involved in creating the SEAH, (1) a pilot study assessing the usefulness of the HHIE and consultation with people with HL, (2) selection of items and construction of the SEAH, (3) defining outcome levels. As such, these will be described separately as content (steps 1 and 2) and scoring and outcomes (step 3).

## 4.2.2.2. Content

### 4.2.2.2.1. Participants

The content of the questionnaire was generated from data from a pilot study of 80 cognitively healthy participants with varying hearing abilities and free feedback during HHIE administration. Participants were community dwelling volunteers, who identified themselves through posters in local GP surgeries, libraries, charity offices and through word of mouth. Testing took place in the most convenient location for the volunteers, either in the Royal Hallamshire Hospital, Sheffield; or Deafness Support Network office, Northwich. Inclusion criteria were broad to include individuals over of the age of 40 with or without HL (caused by any aetiology). Exclusion criteria included any history of head injury, stroke or cognitive impairment which may compromise the adequacy of research responses.

Participants were aged between 42 and 93 with a mean age of 63.55 (SD=11.85). There were 28 males and 52 females, who had between 7 and 25 years of education, with mean years of education being 14.38 (SD=3.52). Demographic data was collected from all participants by self-report who were then asked to undertake a hearing screening test and subjective hearing disability questionnaire, the HHIE. Participants were asked to complete the HHIE as best as they could, and to verbally expand on their responses to any of the questions if they felt it was necessary, which were noted by the experimenter.

Ethical approval was obtained from the University of Sheffield Medical School (ref: 002853) and NRES Committee North East- Newcastle and North Tyneside (ref: 170445, 15/NE/0152). All participants gave their informed written consent.

### 4.2.2.2.2. Hearing assessment

All participants undertook hearing screening using a CE70 Handheld Pure Tone Warbler in a quiet, adequately sized (over 3m x 3m) clinical room. The CE70 Warbler measured frequencies of 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz and 6 kHz at 20-70 dB HL and the modulation level was +/- 10%.

Ambient noise levels were retrospectively analysed at both sites of data collection using Casella CEL-24X Type-2 digital Sound level meter. These were collected at various points of the day, reported to be on average 29.4at The Royal Hallamshire Hospital, and 30.3 dB A at Deafness Support Network office, both under the permitted ambient noise level of 35 dB according to BS EN ISO8253-1:1998 standards. It should be noted that this standard is for measuring down to 0 dB HL and the CE70 equipment is limited to 20 dB, so the maximum permissible ambient sound level may by 20 dB higher.

Periodic calibration of the CE70 Warbler was performed annually by the manufacturer, PureTone, to dB HL. In addition to this, checks of frequency and linearity were undertaken using a B&K Type 2250 sound level meter/frequency analyser. The sound level meter had been calibrated with B&K Type 4231 sound calibrator at 94 dB at 1 kHz. Frequency checks were undertaken at 60d BHL across the six frequencies (Table 4.1) and linearity checks involved recording differences between 10 dB steps from 40 dB to 70 dB at 1 kHz (Table 4.2). Audiometers are calibrated to +/- 3 dB across frequencies 125 Hz to 4 kHz, and +/- 5 dB at 6 kHz (IEC 60645-1 standard tolerance specific), and the specification for the CE70 reports calibration +/- 5 dB across all frequencies at 50cm. Table 4.1 shows the CE70 tones were within this range for the majority of frequencies, demonstrating it is relatively accurate when taking into account the nature of the equipment- it is non clinical standard. Table 4.2 shows there was approximately 1 dB difference reported across the output levels, except for 40 dB which was higher at a 3 dB difference, which may be partially explained by background noise.

The screening procedure involved identifying a threshold according to the BSA recommended procedure (2011) to find the quietist tone at each frequency the person could hear. A Pure tone average (PTAv) of thresholds in the better hearing ear was determined for frequencies at 500, 1000, 2000, and 4000 Hz. The subject was seated, with room for the investigator to stand behind them to present the tones. The tones were presented (free field) to each ear separately, and a Bilsom® 303L ear bud was used to occlude the non-test ear (Kramer, 2014). These were presented at approximately 30cm behind the ear at approximately a 45 degree angle. The tones were presented starting at 1 kHz at 40 dB, and following a positive response the output was reduced in 10 dB steps until no response or 20 dB. If there was no response to a tone (above the 20 dB level), the output was increased in 5 dB steps until a response occurred, which was repeated until the subject responded at the same level on 50% (or more) of trials. Each tone was presented for duration of between 1 and 2 seconds, with variable pauses of between 1 and 4 seconds to ensure the participant could not predict the next tone. PTAv was classified as a categorical variable, according to the World Health Organisation severity of hearing loss criteria. Normal hearing was classified as PTAv <25 dB, hearing thresholds between 26 and 40 were classified as mild HL, between 41 and 60 as a moderate HL and over 61 dB as a severe HL (WHO, 2017).

Although care was taken to follow this recommended procedure, this was for using an audiometer and the CE70 Warbler equipment is a non-standard and non-clinical piece of equipment. This recommendation also involves instructions for the participant to respond using a button, and to press the button for as long as they hear the tone. The recommendation states that in some cases a more engaging response method may be required and this was employed during this procedure for two reasons; (1) there was no response button available as part of the CE70 Warbler, (2) part of this testing involves people with dementia who may require more encouragement. Therefore, all participants were asked to respond to the tone by the most comfortable method for them, for example by saying ‘yes’, or visually by raising a finger or tapping the table. It is understood that this

As the tester holding the device may introduce a significant or unpredictable variability, the audiometric testing was undertaken by the same researcher, who aimed to minimise the errors by standardising the distance and position of device as much as possible. To investigate how the angle and distance would impact on the response rate (and thus lead to inconsistencies between participants), sound levels were measured on a Knowles Electronic Manikin for Acoustic Research (KEMAR) head and torso simulator. The KEMAR was chosen as it is the most objective measure of this. All measurements were collected in a sound proof booth. The microphone connection in the KEMAR was connected to GRAS ear simulator and the output was recorded on a Hewlett Packard 3569A real-time frequency analyser. The CE70 warbler was attached to a microphone stand to ensure it remained at a consistent height, position and angle, where the distance could be changed. With the CE70 set at 1 kHz, 60 dB; three sets of recordings were taken for each position, which were at 0° (straight into ear canal), 90° behind the ear canal and at a 45° angle. Distances measured were 25cm, 30cm and 35cm away. The results are presented in Table 4.3, which, when taking into account the inverse square law (in a free field the intensity of sound drops by 6 dB for each doubling of distance from the source) shows that small changes in angle and distance which may have occurred as part of the testing procedure, did not affect the sound level reaching the participants ear. This is especially apparent when taking into account the testing 45° angle (<1 dB across a 10cm difference).

**Table 4.1.** *Calibration of the CE70 handheld warbler at 60 dB across the six different frequencies*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Frequency (kHz) | RETSPL\* | Dial (dB HL) | RETSPL + Dial | Measured | Difference |
| 0.5 | 4.0 | 60 | 64.0 | 60.0 | -4.0 |
| 1 | 2.0 | 60 | 62.0 | 63.0 | +1.0 |
| 2 | -1.5 | 60 | 58.5 | 58.4 | -0.01 |
| 3 | -6.0 | 60 | 54.0 | 56.2 | +2.2 |
| 4 | -6.5 | 60 | 53.5 | 57.2 | +3.7 |
| 6 | 2.5 | 60 | 62.5 | 68.0 | +5.5 |

NB. \*RETSPL= reference thresholds for equipment calibration (from ISO 389-7 2005). Dial responds to the setting on the CE70 equipment.

**Table 4.2.** *Calibration of the CE70 handheld warbler- measurement of linearity at 1 kHz*

|  |  |  |  |
| --- | --- | --- | --- |
| Dial (dB HL) | RETSPL\* + Dial | Measured | Difference |
| 70 | 72 | 73.2 | +1.2 |
| 60 | 62 | 63.5 | +1.5 |
| 50 | 52 | 53.0 | +1.0 |
| 40 | 42 | 45.0 | +3.0 |

NB. \*RETSPL= reference thresholds for equipment calibration (from ISO 389-7 2005). Dial responds to the setting on the CE70 equipment.

**Table 4.3.** *The effects of distance and angle of presentation to CE70 tones measuring using KEMAR*

|  |  |  |
| --- | --- | --- |
| Angle (°) | Distance (cm) | Measured |
| 0 | 25 | 69.50 |
| 0 | 30 | 67.71 |
| 0 | 35 | 66.96 |
| 45 | 25 | 68.15 |
| 45 | 30 | 67.43 |
| 45 | 35 | 67.28 |
| 90 | 25 | 67.34 |
| 90 | 30 | 67.75 |
| 90 | 35 | 66.03 |

NB. Angle is the angle of presentation where 0° is straight into the ear and distance is the cm away at that angle.

### 4.2.2.2.3. Subjective hearing disability

All participants undertook the 25-item HHIE. Frequency analysis was then performed on these 25 questions to rank which scenarios were the most relevant for the target population. During and following completion of the HHIE, any comments regarding the wording of the questions or personal views on different scenarios were recorded and labelled as free feedback.

For each participant, items with positive responses, i.e. a response of ‘yes’ or ‘sometimes’ were given a score of 1, which was tallied and the and the 10 highest scoring items were identified. These were selected together with information from the feedback to create the Social and Emotional Associations of Hearing loss (SEAH) questionnaire (Appendix 2). The consultation during the administration of the HHIE allowed us to adapt these questions to suit the influence of HL on our sample specifically and more generally to devise an assessment procedure suitable for a variety of individuals, with clinical and non-clinical samples.

Once the 14-item questionnaire was designed, a pilot test was conducted on 10 participants selected from as a convenience sample (mean age 57.2, SD= 9.74). Five participants had HL ranging from mild to severe, and five had normal hearing, although were chosen as they all had experience working with or supporting people with HL. Participants were asked (1) whether they felt the instructions on the questionnaire were clear and easy to understand; (2) if all of the questions were clear and easy to understand; and (3) whether the questions were relevant to the HL population. Participants were all in agreement that this questionnaire was easy to undertake and in their opinion, questions were relevant.

### 4.2.2.2.4. Hearing aid use

As the use of hearing aids may impact on the psychosocial associations of HL (Ferguson et al., 2017), a section has been added to the SEAH regarding hearing aid use and overall satisfaction from the hearing aids. This data may help to understand the relationship between all aspects of HL, hearing aid use and the links with cognitive impairment and dementia.

Participants are asked if they wear hearing aids, and if so, (a) on an average day how long do they wear the hearing aids for and (b) what is their overall satisfaction with their hearing aids. This is given on a scale from between 1 to 10, where 1 is not satisfied and 10 is completely satisfied with their hearing aids. As many intrinsic and extrinsic factors may affect satisfaction, a single question was chosen to encompass overall satisfaction, aiming to identify a personal evaluation of hearing aids against their personal expectations.

## 4.2.2.3. Scoring and outcomes

The 14 questions were formatted using a five-point Likert scale, to collect the frequency, ranging from 0 (never or almost never) to 5 (always or practically always). The five-point Likert scale was chosen as it would offer enough choice and be manageable for the participants at the same time. A criticism of the HHIE from free feedback was that the respondents needed an ‘in between’ measure as sometimes their response in each situation was not as clear cut as ‘yes’ or ‘sometimes’: “It is not never, but not as much as sometimes” or “It’s more than sometimes but I wouldn’t say that it was ‘yes’ a definite issue for me”. According to Millers law, there is a limit on the amount of information that can be held in our working memory at any one time. For humans, this capacity is 7 items, plus or minus 2 (Miller, 1956). Therefore, although a longer scale of 7 or 9 items may have been more sensitive, as this tool will be used ultimately with people with cognitive impairment and dementia, 7- or 9- point scales may be too difficult to fill in.

Only one of the five responses can be given for each question: 1=never, 2=occasionally, 3=half the time, 4=frequently, 5=always. The highest score from the participants was taken as the clinical cut off point, to ensure minimisation of false positive and false negative scores. Using Spearman’s Rho nonparametric correlation coefficient, the relationship between age of the participant and score on SEAH was evaluated. A coefficient of 0.3 is deemed to be a weak positive correlation, and over 0.7 indicates a strong positive correlation.

### 4.2.2.3.1. Participants

In order to establish appropriate outcome levels, 120 new participants over the age of 40 with no known HL, volunteered to complete the SEAH. Participants were again a volunteer sample, who were recruited as described in 4.2.2.2.1.

Participants were aged between 40 and 93 years old, with a mean age of 57.82 (SD=12.19). There were 36 males and 84 females in the sample. Participants had been educated for between 10 and 23 years, with a mean duration of education of 15.63 years (SD=3.04). Each participant was asked to complete the SEAH according to written instructions, following PTA screening according to the same parameters described in detail in 4.2.2.2.2. Normal hearing was classified as PTAv <25 dB (WHO, 2017).

# 4.2.3. Results

## 4.2.3.1. Content

### 4.2.3.1.1. Participants hearing loss

Forty five (56%) participants had normal hearing and 35 (44%) participants reported a HL. Severity of HL was further compartmentalised to mild HL (n=13), moderate HL (n=12) and severe HL (n=10).

### 4.2.3.1.2. Subjective hearing disability and adaption of questions

HHIE scores ranged between 0 and 84, with a mean score of 39.49 (SD=23.41) for participants with HL and 6.67 (SD=11.68) for participants with normal hearing.

Items on the HHIE were given a rank from 1 to 24 depending on scoring frequency, with question S.15 ‘Does a hearing problem cause you difficulty when listening on the television’ being most commonly reported. Results from this pilot data are shown in Table 4.4 and highlighted in blue are the top 10 ranking scenarios and themes which were subsequently included in the new questionnaire.

Free feedback and expansions on questions helped to identify these common themes, and modify them for inclusion into the new questionnaire. For example, many participants with HL stated they had difficulty listening to the TV or radio. This difficulty is yet not to the point that it stops them watching it, as with the use of subtitles, hearing aids or other equipment (loop system or headphones), they can continue to enjoy programmes and stay in touch with news items. They may have had to adapt new habits, but do not necessarily feel disadvantaged or restricted by this. Similarly, Question E4 ‘Does a hearing problem make you irritable’, although this was commonly reported, participants stated that it is not their hearing problem that makes them irritable but rather the situations that they find themselves in, therefore this was slightly modified before inclusion into the questionnaire.

Another common scenario which was amended for the new questionnaire was Question S6 ‘Does a hearing problem cause you difficulty when attending a party’. Here participants commonly stated that it is not the fact that it is a party, it is any social situation in which there are groups of people or excessive noise. It was noted that there was a big distinction between hearing difficulty during a one to one situation compared with being in a small or large group of people, which was notably harder, and even more difficult in a noisy environment. It was interesting to find that as ARHL progressed, even conversing in a one on one environment was becoming more difficult and led to the complete avoidance of group or party situations where there would be both groups and noise.

Many reported that ‘party’ situations they would avoid completely and so the question of avoidance at parties was included into the SEAH (question 7), along with a separation between the different restrictive elements. As a consequence, the first three questions on the SEAH ask specifically about difficulty with (1) one other person, (2) small groups of people and (3) noisy situations.

Expansions on the questions also helped to include other aspects which were not picked up directly from the HHIE rankings. For example, ‘E2: Does a hearing problem cause you to feel embarrassed when meeting new people?’ When answering this question, it was commonly reported that participants didn’t feel embarrassed when *meeting new people*, but embarrassment when losing track of conversations or not being able to answer questions in a social or work scenario as they have misheard what has been said. Therefore this has been included into the new questionnaire (SEAH Question 4.)

It was also noted that for other scenarios, the phrasing of the question makes it not entirely relevant to real life situations. For instance, ‘S10: Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbours?’ The comments were ‘yes, if I wasn’t wearing my hearing aids’ (as the questionnaire asks them to answer), ‘although I would always wear my aids in this situation, and therefore I don’t have any difficulty.’ Some people therefore answered this according to the questionnaire instructions, and some people answered ‘no’ as it did not seem to be a problem for them. For this reason it was imperative to ensure that the instructions on the questionnaire were clear in asking people to answer how they are currently feeling regarding their hearing situation. This also prompted the inclusion of the questions regarding hearing aids at the end of the questionnaire, where participants are asked whether they wear hearing aids, if so, how long for and how satisfied they are on a scale of 1-10. This would be useful when identifying what role hearing aids have on the social and emotional associations of HL, and whether people who wear hearing aids or are satisfied with their hearing aids are less likely to feel currently restricted by their HL and thus may be at a reduced risk for cognitive impairment or dementia.

Using this information and guidance, a 14-item questionnaire that assesses current activity limitations, participation restrictions and the influence of environmental and personal factors (ref ICF) associated with ARHL was created (Appendix 2).

## 4.2.3.2. Scoring and outcomes

Participants are asked how often their hearing causes them difficulty in the various situations (from 1- never or almost never, to 5- always or practically always) and responses from all 14 questions are summed to develop a raw overall score between 14 and 70, which is then converted into an overall percentage disability by simple calculation:

The higher the percentage, the more restricted a person subjectively feels. All 120 participants were included in the analysis, as PTAv confirmed hearing thresholds of <25 dB. PTAv scores varied between 20 and 24 dB.

As expected in a test assessing hearing functioning in people with normal hearing, the distribution of scores showed a positive skew towards the negative end (Figure 4.1). The modal overall score was 0, the median score was 5.5, IQR=9. As the distribution of scores from controls with normal hearing was positively skewed and did not follow a normal distribution, another standardised measure for selecting cut offs was followed (Capitani, 1997). Therefore, in this case, the standardised measure for selecting cut offs was followed where the worst or ‘highest’ score from the healthy population was chosen to minimise false positives.

From this, it was chosen that a score <25% would portray no disability, and therefore 25% is the cut off point for social and emotional hearing disability. The larger the percentage, the higher along the functioning-disability continuum the individual feels.

**Table 4.4.** *Ranked items of the HHIE (pilot study data)*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Questions on the HHIE | Yes | Sometimes | Total | Rank |
| S1. Does a hearing problem cause you to use the phone less often than you would like? | 18 | 1 | 19 | 11 |
| E2. Does a hearing problem cause you to feel embarrassed when meeting new people? | 10 | 8 | 18 | 13 |
| S3. Does a hearing problem cause you to avoid groups of people? | 14 | 4 | 18 | 12 |
| E4. Does a hearing problem make your irritable? | 11 | 9 | 20 | 10 |
| E5. Does a hearing problem cause you to feel frustrated when talking to members of your family? | 14 | 10 | 24 | 7 |
| S6. Does a hearing problem cause you difficulty when attending a party? | 27 | 10 | 37 | 3 |
| E7. Does a hearing problem cause you to feel stupid or dumb? | 10 | 11 | 21 | 9 |
| S8. Do you have difficulty hearing when someone speaks in a whisper? | 26 | 13 | 39 | 2 |
| E9. Do you feel handicapped by a hearing problem? | 17 | 4 | 21 | 8 |
| S10. Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbours? | 10 | 7 | 17 | 15 |
| S11. Does a hearing problem cause you to attend religious services less often than you would like? | 2 | 1 | 3 | 24 |
| E12. Does a hearing problem cause you to be nervous? | 7 | 4 | 11 | 19 |
| S13. Does a hearing problem cause you to visit friends, relatives, or neighbours less often than you would like? | 4 | 0 | 4 | 22 |
| E14. Does a hearing problem cause you to have arguments with family members? | 6 | 8 | 14 | 18 |
| S15. Does a hearing problem cause you difficulty when listening to the TV or radio? | 26 | 15 | 41 | 1 |
| S16. Does a hearing problem cause you to go shopping less often than you would like? | 2 | 2 | 4 | 23 |
| E17. Does any problem or difficulty with your hearing upset you at all? | 9 | 9 | 18 | 14 |
| E18. Does a hearing problem cause you to want to be by yourself? | 7 | 7 | 14 | 17 |
| S19. Does a hearing problem cause you to talk to family members less often than you would like? | 5 | 3 | 8 | 20 |
| E20. Do you feel that any difficulty with your hearing limits or hampers your personal or social life? | 19 | 6 | 25 | 6 |
| S21. Does a hearing problem cause you difficulty when in a restaurant with relatives or friends? | 21 | 10 | 31 | 4 |
| E22. Does a hearing problem cause you to feel depressed? | 3 | 4 | 7 | 21 |
| S23. Does a hearing problem cause you to listen to the TV or radio less often than you would like? | 14 | 1 | 15 | 16 |
| E24. Does a hearing problem cause you to feel uncomfortable when talking to friends? | 7 | 6 | 13 | 19 |
| E25. Does a hearing problem cause you to feel left when you are with a group of people? | 20 | 10 | 30 | 5 |



**Figure 4.1.** *Distribution of SEAH scores for the whole sample of participants*

There was no correlation between age of participant and score on the SEAH, *r*S = .056, *p*=.545. Table 4.5 shows the average SEAH scores according to each decade, where the highest scores were reported for the 50-59 decade ages.

**Table 4.5.** *SEAH scores according to age by decade*

|  |  |  |  |
| --- | --- | --- | --- |
| Decade (n) | Range | Mean (SD) | Median (IQR) |
| 40-49 (29) | 0 to 14 | 5.03 (4.91) | 4.0 (11) |
| 50-59 (46) | 0 to 25 | 8.80 (6.90) | 9.0 (12) |
| 60-69 (24) | 0 to 23 | 8.63 (5.65) | 7.0 (6) |
| 70-79 (14) | 0 to 16 | 5.57 (5.14) | 4.5 (10) |
| 80+ (7) | 0 to 20 | 4.57 (7.16) | 2.0 (5) |

# 4.2.4. Discussion

This experiment reported the development of a new questionnaire, the SEAH to measure subjective hearing disability in the general population, regardless of hearing levels. In a sample of participants with normal hearing, low scores <25% were found, which suggest that even within people with objectively normal hearing, some people do not feel their hearing is always good in every situation. This was not related to age, however, as reported in Table 4.5 that the mean SEAH scores were highest between the ages of 50 and 69, suggesting that age does not influence perceived hearing disability in a normal hearing population, but perhaps reflects that people of these ages may be worried their hearing is not as good as it once was.

The simplicity and ease of application of the SEAH increase usability in both clinical practice as a more effective measure, and also future research, to quantify the effects of social and emotional dysfunction as a result of HL. The SEAH remains to be validated in a population of participants with varying levels of HL.

# **Experiment 4.2 - Validation of the ‘Social and Emotional Associations of Hearing loss’ (SEAH)**

# 4.3.1 Introduction

Experiment 4.1 presents the development of a new questionnaire to measure subjective hearing disability in the general population. However, before it can be used in practice it must be validated to ensure it measures what it claims to measure (Boynton and Greenhalgh, 2004).

Thus, the aim of the Experiment 4.2 was to validate and measure the reliability of the new questionnaire, to be able to implement it with confidence as a tool in future tests. This would address and help to understand better the current levels of social and emotional disability as a result of ARHL, and ultimately, interactions with cognitive decline and dementia.

# 4.3.2. Methods

## 4.3.2.1 Participants

Participants were community dwelling volunteers, who identified themselves through posters in local GP surgeries, libraries, charity offices and through word of mouth. An email advertising the study, with the participant information sheet, was also sent to the University of Sheffield ‘volunteers’ mailing list. Inclusion criteria were broad to try to include a representative sample, and included males and females over the age of 40, with normal hearing or any form of HL. Again, exclusion criteria were any history of head injury, stroke or cognitive impairment which may compromise the adequacy of research responses.

Testing took place in the most convenient location for the volunteers, either in the Royal Hallamshire Hospital, Sheffield; or Deafness Support Network office, Northwich

Ninety five participants of mixed hearing abilities, over the age of 40, were recruited to this study as volunteers. Participants age ranged between 40 and 92 years with a mean age of 59.13 years (SD=12.67). There were 36 males and 59 females. Participants had been educated for between 9 and 22 years, with a mean duration of education of 15.47 years (SD=3.28).

Ethical approval was obtained as described in 4.2.2.2.1, and all participants gave their written informed consent. All participants were fluent in English language.

## 4.3.2.2. Study materials and procedure

Demographic data including cause of HL (if known) were collected. All participants completed 3 questionnaires regarding hearing limitations and restrictions; two previously validated questionnaires, the HHIE and Self-Assessment of Communication (SAC), and the newly designed SEAH.

Again, as defined in detail in 4.2.2.2.2, PTAv of thresholds in the better hearing ear was determined for speech frequencies at 500, 1000, 2000 and 4000 Hz with dB HL ranging from 20-70. PTAv <25 dB were classified as normal hearing, 26-45 mild, 46-65 moderate, >65 severe (WHO, 2017).

A convenience subsample of 35 participants (15M, 20F) with mean age of 57.06 (SD=13.01) were selected for retesting over a 4-8 week period. The participants were all asked whether they would be available for repeat testing, and the first 35 were recruited for a second time.

## 4.3.2.3. Data analysis

All analyses were performed using IMB SPSS v22. Internal consistency, validity, reliability and the role of experimenter bias of the SEAH were explored. All data were visually inspected and Kolmogorov-Smirnov tests of normality were undertaken. Where assumptions were violated, non- parametric analysis was utilised.

Internal consistency and reliability of the scale was measured using Cronbach’s alpha coefficient. A coefficient of .7 or .8 is generally regarded as having high internal consistency.

A Spearman’s Rho correlation coefficient (for non-parametric correlations) was employed to compare speech frequency PTAv thresholds with percentage scores on the SEAH, to identify whether this instrument could discriminate levels of disability. Although this is screening for subjective social and emotional associations of HL rather than a behavioural measure of HL, it would be expected that people with normal hearing have low (or no) perceived hearing disability, and people with severe HL to perceive themselves as more limited by their hearing. A coefficient of 0.3 is deemed to be a weak positive correlation, and over 0.7 indicates a strong positive correlation. After normality and homogeneity of variance checks were carried out and assumptions met, the difference between causes of HL and scores on SEAH were examined using a one way ANCOVA to control for PTAv thresholds.

Concurrent validity was examined using Spearman’s Rho correlation coefficient to observe similarities between outcomes on the SEAH and previously validated HHIE and SAC questionnaires.

To distinguish whether the new questionnaire was reproducible, in terms of test-retest reliability, an intra-class correlation coefficient was used to examine the degree of correlation and agreement between the scores at the different time points (T1 and T2). Intra-class correlation coefficient estimates and their 95% confidence intervals were calculated based on a single-rating, absolute-agreement, 2-way mixed-effects model. Subsequently a related-samples Wilcoxon Signed Rank Test was undertaken to compare differences between the two time points. Fifteen (43%) of the retest participants were followed up by a different examiner to control for experimenter bias and 95% confidence intervals were inspected.

# 4.3.3. Results

## 4.3.3.1. Participants

Forty percent (n=38) of the sample met criteria for HL (Table 4.6), which could be further compartmentalised into mild (n=25), moderate (n=8) and severe (n=5). The majority of participants reported HL due to ageing, but there were some who reported other known causes, or were not aware of HL, as shown in Table 4.7. As expected, people in the HL group were older than people with normal hearing, with a mean difference of 13.91 years. This difference was significant *t* (93) = -6.198, *p* = <.001.

**Table 4.6.** *Demographic characteristics of the sample according to hearing groups*

|  |  |  |
| --- | --- | --- |
|  | Normal Hearing | Hearing loss |
| Sample (n=95) | 57 | 38 |
| Male/Female | 20/37 | 16/22 |
| Mean Age (SD) | 53.56 (9.41) | 67.47 (12.44) |

**Table 4.7.** *Reported causes of hearing loss*

|  |  |  |
| --- | --- | --- |
| Cause | Number | Percentage (%) |
| Ageing | 15 | 40 |
| Congenital | 7 | 18 |
| Trauma/medical condition | 7 | 18 |
| Noise damage | 4 | 11 |
| Unknown (undiagnosed) | 5 | 13 |

## 4.3.3.2. Reliability of the scale

There is a high degree of internal consistency of the scale as illustrated by an overall α= .957, which is at the desirable level for clinical use (Bland and Altman, 1997). Individual items positively correlated with each other, ranging from *r* = .31 to .81. The mean inter-item correlation was *r* = .59. The reliability of the scale would not be improved by removing any of the items in the questionnaire.

## 4.3.3.3. Hearing thresholds and SEAH scores

Scores on the SEAH ranged from 0 to 71%. Participants with no HL scored much lower on the SEAH than participants with varying degrees of HL. Table 4.8 shows the mean, standard deviation and range of scores for the SEAH for each hearing group. There is a correlation between PTAv and SEAH scores (Figure 4.2), as level of HL increases so does the extent of self-reported disability, *rS*= .771, *p*< .001, 95%CI [.679, .837].

There was no significant difference in SEAH scores (F (4, 32) = 2.017, *p =* .116) between different causes of HL whilst adjusting for PTAv thresholds.

**Table 4.8.** *Scores on SEAH depending on hearing loss group*

|  |  |  |  |
| --- | --- | --- | --- |
| Classification of hearing loss | Mean score (%) | SD | Range (min-max) |
| Normal | 09.16 | 08.27 | 00-36 |
| Hearing Loss | 35.79 | 17.54 | 11-71 |
| Mild | 28.72 | 13.74 | 11-59 |
| Moderate | 47.25 | 18.13 | 20-71 |
| Severe | 52.80 | 14.18 | 32-68 |



**Figure 4.2.** *Scatter plot showing association between PTAv thresholds and social and emotional hearing disability per hearing loss group.*

NB. Dotted horizontal lines correspond to the outcome of no subjective disability (<25%)

## 4.3.3.4. Concurrent validity

Scores on the SEAH were significantly correlated to scores on the previously validated questionnaires, HHIE and SAC, representative of high concurrent validity, as shown in Table 4.9.

**Table 4.9.** *Spearman’s Rho correlation coefficient showing the association between participants scores on the SEAH, compared with both SAC and HHIE.*

|  |  |  |
| --- | --- | --- |
|  | SAC | HHIE |
| SEAH | 0.900\*  [0.790, 0.971] | 0.910\*  [0.862, 0.943] |

NB. \**p* < 0.01. [95% CIs reported in brackets]

## 4.3.3.5. Test-retest reliability and experimenter bias

There was a strong positive correlation between participants scores on the SEAH at time 1 and time 2 (4 to 8 weeks later), ICC = .905, *p*< .001, 95% CI [.812, .952] indicating a good test- retest reliability, shown in Figure 4.3. There was not a statistically significant change in SEAH scores between time 1 and time 2 (Z = -.216, p =.829).

Table 4.10 compares correlational coefficient to measure the relationship between the two time points, showing that SEAH had a higher *r* value and narrower confidence intervals when compared with the two previously validated questionnaires. In all cases results were statistically significant.

The presence of examiner bias was excluded, as the difference between test-retest correlations for Examiner 1, *r*S = .890, *p* < .001, 95% CI [0.677, 0.986], and Examiner 2, *r*S = .737, *p* =.002, 95% CI [0.235, 0.931] was not significantly different.



**Figure** **4.3.** *Scatterplot showing the correlation between scores on the SEAH at time 1 (T1) and time 2 (T2) demonstrating strong retest reliability*.

**Table 4.10.** *Comparing the relationship between the two time points for all study questionnaires*

|  |  |  |  |
| --- | --- | --- | --- |
|  | *r* | 95% CI | SE |
| SEAH | .823 | .679 , .921 | .063 |
| HHIE | .753 | .458 , .894 | .115 |
| SAC | .800 | .568, .943 | .096 |

NB, All values are significant at *p*<0.01.

# 4.3.4. Discussion

The SEAH has a high level of internal validity, as shown by α=.957 and further demonstrated by the strong Cronbach α scores for each item on the scale. This high Cronbach α score could suggest that some items are redundant as they may be tapping into the same question (Tavakol and Dennick, 2011). However, the mean inter-item correlation should fall within the range of .3 to .7, and here it is reported as .59, suggesting that all items are related to each other within normal limits (Ferketich, 1991). The choice to keep all questions was mainly due to the fact that social and emotional responses to HL are personal and varied, but also to ensure the breadth of relevant questions to maximise clinical potential. In the same way, these questions are all relevant as they were devised from a commonly used scale, the HHIE, and updated with information regarding current issues in our target population. The reliability of the scale is comparable to that of the HHIE of α=.95 (Ventry and Weinstein, 1982). The authors of the HHIE also highlighted potential problems which may arise if the questionnaire was shortened, including removal of the specificity of individual problems, and also, social and emotional responses to HL is heterogeneous and dependent on many different factors therefore different reasons may be behind scoring highly on two different questions. This could include environmental or personal influences and may not be static responses (Kostanjsek, 2011). A recent paper has highlighted that modern techniques including Rasch analysis may be more powerful than traditional techniques (Heffernan et al., 2018), which will be considered for future experiments.

Due to individual differences in lifestyle, attitudes and personalities, comorbid health conditions, and available support networks, it is logical to assent that not any two people with the same levels of HL will respond to, or manage their condition, in the same manner (Ewertsen and Birk-Nielsen, 1973, Guyatt et al., 1993). Because of this, there is no gold standard test for objectifying subjective responses to HL, and therefore in this study it was not possible to test for criterion validity. However, in cases where this is not suitable, measuring construct validity is adequate (Landy, 1986, Guyatt et al., 1993).

Although one shouldn’t necessarily assume that the severity of HL implies the severity of hearing related disability, due to the reasons stated above, it is reasonable to suggest that people with severe HL will be more restricted than people with mild HL, or normal hearing. In this study a positive correlation was found between PTAv and SEAH scores (*r*S= .77). This number is comparable with other previously established scales and questionnaires (Ventry and Weinstein, 1982, Sogebi and Mabifah, 2015). The correlation was lower compared with (*r=* .90) the social hearing handicap index (Ewertsen and Birk-Nielsen, 1973), but is reflective of the fact that other instruments were ultimately devised as a screen for presence of HL. The high variability of SEAH scores for people with HL (0 to 71) reflects these individual differences and attitudes towards HL. It is interesting to look at some of the individual scores from Figure 4.2, for example, one individual with a moderate HL (PTAv of 60) reported very minimal socio-emotional disability (below the <25% threshold), and compared with an individual with normal hearing and a PTAv of <25% who reported a higher hearing disability. This report of hearing disability when no objective measure of HL was calculated could be due to the conservative measure of PTAv of the speech thresholds, and perhaps a more comprehensive hearing assessment across a wider range of frequencies would indicate some aspects of HL. This all alludes to the fact that PTA ‘peripheral’ hearing testing may not be the best way to assess someone’s hearing, but central auditory processing abilities may be a more accurate measure of hearing capabilities in everyday life (Gates, 2012a), see Chapter 6.

If the variability in outcome scores are greater than the variability within patients, then a questionnaire is deemed to be reliable (Guyatt et al., 1993); and this has been shown in our study. The test-retest reliability of the SEAH is very satisfactory at ICC= 0.905, which has shown to be more reliable than our retest measures of the HHIE or SAC. However, results obtained for test-retest reliability of the HHIE in our sample of *r* = 0.75 were slightly lower than the value of *r* = 0.84 previously reported (Weinstein et al., 1986), and this could be due to the small sample of participants (37% of original sample) who took part in the study until T2.

Figure 4.3 represents individual scores on the SEAH at time 1 and time 2, and although a strong correlation, it can be assumed with reasonable certainty that the coefficient has not been inflated as a result of the retesting procedure, for example by participants remembering previous scores, as a six week timescale is deemed long enough to disregard this (Demorest and Walden, 1984). However, there are still some changes in SEAH scores over the six week period, and although ARHL is progressive, it tends to be gradual (Liu and Yan, 2007) and therefore one would not expect a dramatic change over this short period. These changes could be reflective of irrelevant temporal factors, such as mood, which may cause a fluctuation in scores over time (Demorest and Walden, 1984), or they could result from changes in participants attitudes towards their disability. Interestingly, one participant with a PTAv of 26.25, indicating a mild HL, showed a drastic reduction of nearly 30 points between T1 and T2. This participant advised us that although she felt no change in hearing threshold levels between T1 and T2, her attitudes towards her HL had changed, and her taking part in the research had made her realise that her hearing wasn’t as debilitating as she had previously believed it to be. This again supports the concept that perceived hearing disability is not necessarily related to hearing levels, there are many other factors that can influence it, and therefore should be investigated as a separate feature.

There is no evidence of experimenter bias using the SEAH, although some slight differences in scores were noted, these were not statistically different and again could be explained due to the influence of the irrelevant temporal factors described above. Altogether, this lends support for the use of the SEAH, not only as a cross sectional instrument to measure current subjective disability levels, but to be also used for longitudinal purposes. Due to the strong correlation, small standard error and no evidence of experimenter bias, it can be assumed that changes over time are as a result of intervention rather than experimental error (Nunnally, 1994).

Although the SEAH is based upon the HHIE and measuring slightly different aspects than both previously validated questionnaires, it is promising to see the significant correlation between scores on the SEAH and previously validated tests, supporting once more the specificity of the SEAH. Continuing research remains to evaluate the sensitivity to change of the SEAH, for a more valuable longitudinal measure, which could then monitor the effects of audiological rehabilitation.

# 4.4. General Discussion

Accurate screening tools to assess current levels of socio-emotional disability are of upmost importance for investigating the effects that ARHL has on quality of life. One of current health priorities in UK is to investigate possible risk factors for the onset of cognitive decline and dementia (Prime Minister's challenge 2015). Due to an increased prevalence of dementia in people with an ARHL (Uhlmann et al., 1989a, Lin et al., 2011b, Deal et al., 2016), it has been hypothesised that ARHL precedes and increases the risk for future development of dementia (Deal et al., 2016). The mechanism of this relationship is yet to be explored, however, it has been conjectured that the psychosocial difficulties interrelated with ARHL may in part mediate this relationship (Dawes et al., 2015b). Given the clinical importance of investigating this association, it is essential to have a specific, valid and reliable questionnaire to compute current levels of hearing functioning. Therefore a new tool was developed and validated for this purpose and Experiments 4.1 and 4.2 demonstrate that the SEAH is able to recognise and quantify levels of subjective socio-emotional difficulties as a result of ARHL. To the best of our knowledge, this is the first validated questionnaire to measure current levels of subjective hearing disability in recent years.

The SEAH has shown to have high internal validity and reliability in our sample, as expected, as it was ultimately designed based on the common problems reported from people in the same population. Therefore, it may have limited uses in other cultures and may not be generalisable to the wider non-English speaking countries. However, using the principles upon which the scale was designed and validated, would allow for translation into other languages and other cultures, which could then be validated. The high specificity of the SEAH means that it does not allow for cross-condition comparisons. For example, the socio-emotional difficulties measured are due to common problems in relation to HL, and not suitable for measuring quality of life affected by other conditions or disabilities. In the same vein, SEAH scores have not been compared to other measures of health related quality of life, to assess discriminant validity, in conditions such as depression or anxiety, which could lead to the same socio-emotional difficulties faced by someone with HL. Therefore although it cannot be said with certainty that the social and emotional associations are all directly related to HL and no other factors, due to the high levels of internal validity, it is plausible to assume that they are as a result of HL. Lastly, a limitation with all self-report questionnaires and the increased emphasis given to the subjective nature of the questions is the effects of desirability (van de Mortel, 2008). Perhaps some people with ARHL may not want to ‘admit’ that their HL is causing a problem, as they would prefer to be perceived as a confident person, and vice versa.

To conclude, this study has shown that the SEAH is the favourable and more relevant instrument to assess current levels of subjective hearing disability in our study population. It can be used with confidence to control for subjective levels of disability in people with varying levels of ARHL, to assess further the risk of cognitive decline. The use of the SEAH would help to determine whether the social and emotional associations of HL have more of an influence on the risk for dementia, compared with hearing thresholds alone.

# Chapter 5: Age related hearing loss, subjective hearing disability & cognitive performance

# 5.1. Introduction

Hearing is a complex entity, which involves both the perception (peripheral auditory system) and transmission (central auditory system) of sound, together with cognitive processing to transform simple sounds into meaningful data (Moore and Moore, 1995). The ear processes sound frequencies ranging from 20 Hz to 20 kHz, but is particularly sensitive to frequencies between 500 and 4000 Hz, which include the range of human speech (Yueh et al., 2003). Normal speech conversation level is considered to be approximately 20 to 70 dB (Kramer, 2014), but the healthy ear can process sounds through the range of 0 to 140 dB. Each region of the cochlea transduces a particular frequency of sound (Howarth and Shone, 2006), and age related changes in the cochlea affect the transduction of these frequencies into neural impulses (Lee, 2015). Presbycusis is characterised by a bilateral high frequency loss and difficulty hearing against background noise (Gates and Mills, 2005). In order to understand fully the processes driving presbycusis, the mechanism of hearing will be briefly introduced.

## 5.1.1. The structure of the human ear and mechanism of hearing

The ear is made up of three distinct structures; the outer ear, middle ear and inner ear. The outer ear consists of the pinna and external auditory canal. The main function is thought to be protective, although its physical arrangement allows for the channelling of sound waves into the middle ear (Yueh et al., 2003). The middle ear runs from the tympanic membrane to the oval window, and contains the three ear ossicles, which vibrate to bring about the transduction and amplification of sound waves from the tympanic membrane through to the oval window of the cochlea (Barrett et al., 2016). The main hearing organ of the ear, the cochlea, is found in the inner ear, along with the semi-circular canals (vestibular system), and the vestibulocochlear nerve. The cochlea is a coiled structure, which is divided into three fluid filled ducts, known as the scala vestibule, scala media and scala tympani (Liu and Yan, 2007), by the basilar membrane and Reissner membrane (Barrett et al., 2016). The scala media is distinct from the other two scalae for a variety of reasons, namely the fluid is of a different constitution due to the presence of the stria vascularis. The stria vascularis is a heavily vascularised structure with a high metabolic rate, and contains Na+ K+ ATPase pumps which supply a direct current resting potential in the scala media (Gates and Mills, 2005). For this reason it is filled with a potassium rich endolymph, rather than the perilymph found in the other two scalae. Along the basilar membrane of the scala media, the organ of corti (OOC) is found. The OOC contains the basic sensory units of the cochlea, the hair cells, (Russell, 1981) along with other structural support cells. There are two types of hair cells, inner and outer hair cells, which both contain stereocillia; the hair like projections responsible for transducing acoustic stimuli into a neural code on the auditory division of the vestibulocochlear nerve (Yates, 1995, Barrett et al., 2016). The hair cells are sensitive to different frequencies of sound waves, and are arranged tonotopically along the basilar membrane, with high frequency sensitive cells at the base of the cochlea, mid-frequency hearing at the middle turn of the cochlea and low frequency sensitive cells at the apex (Kramer, 2014). There is a positive feedback loop, known as the cochlear amplifier which acts to amplify travelling waves of different frequencies, by increasing the vibrations of the outer hair cells (Oghalai, 2004).

Sound waves are channelled through the external auditory canal into the middle ear, where they are amplified before reaching the cochlea of the inner ear. The vibration of the stapes, the third ear ossicle, onto the oval window produces a pressure force creating a wave in the fluid of the inner ear (Kramer, 2014). This wave then deflects the stereocillia of the inner hair cells to produce a mechanical opening of ion channels, depolarising the hair cells. This modulates a transmembrane potential current, which in turn stimulates neurotransmitter release from the afferent synapse (Yates, 1995, Liu and Yan, 2007). Through a series of synapses with multiple brainstem nuclei, the signal is transduced to the primary auditory cortex where the sounds are processed. This auditory processing pathway is described in more detail in Chapter 6.

## 5.1.2. Age related changes to the peripheral auditory system

Ageing affects the structure and function of all three aspects of the ear but specifically the cochlea, having a dramatic impact on the stria vascularis and hair cell function (Kramer, 2014). Schuknecht defined four distinct pathologies of presbycusis in humans: sensory (outer hair cell loss), neural (ganglion cell loss), metabolic (atrophy of the stria vascularis) and mechanical (stiffness of BM) (Schuknecht, 1974). Metabolic presbycusis is predicted to be the leading cause of presbycusis in the elderly (Gates and Mills, 2005) although it has been documented that many individuals have a combination of pathological changes rather than fitting into one of these aetiologies alone (Mazelova et al., 2003).

Degeneration of the stria vascularis, including loss of strial capillaries and the Na+ K+ ATPase pumps, has a knock on effect to cochlear physiology as the endocochlear potential is substantially reduced, reducing the transmembrane potential current, leading to a dampening of the cochlear amplifier and subsequently neurotransmitter release (Gates and Mills, 2005). This is further exacerbated by the loss of spiral ganglion and outer hair cells, again contributing to the impairment of the cochlear amplifier, and an increase in hearing thresholds (Oghalai, 2004). Along the basilar membrane of the cochlea there are only a small number of hair cells which correspond to each frequency, therefore, loss of the hair cells can have a dramatic effect on hearing as regeneration does not occur (Howarth and Shone, 2006, Lee, 2015).

As mentioned in Chapter 2.2, it is hard to separate out the effects of ageing and physiological degeneration alone, from the accumulated effects of genetics, environment, noise exposure and medical disorders (and their treatment) on the hearing system (Mazelova et al., 2003) which all act to increase the risk of presbycusis (Brant et al., 1996).

## 5.1.3. Peripheral presbycusis and cognition

As introduced in Chapter 2, many research studies have reported that people with a peripheral HL have a poorer cognitive performance at baseline and over time, their cognitive abilities decline at a greater rate and to a greater extent than people with normal hearing thresholds (Uhlmann et al., 1986, Lin et al., 2013, Gurgel, 2014, Amieva et al., 2015). Similarly, people with HL are at a greater risk of developing clinical dementia (Lin et al., 2011b, Deal et al., 2016, Livingston et al., 2017). There have been some studies which have reported the opposite, no association between hearing impairment and cognition or cognitive decline (Gennis et al., 1991, Lin et al., 2004, Hong et al., 2016).

During the early stages of presbycusis, mild high frequency loss does not usually pose a challenge for speech understanding in quiet (Gates and Mills, 2005) but can lead to conversational difficulties as these sounds include some consonants and word endings which are required for the decoding of speech (Howarth and Shone, 2006). Over time, there is a gradual degeneration of the outer hair cells which transduce the middle and lower frequencies (Gates and Mills, 2005) necessary for speech perception, which can have a dramatic impact on communication and the socialisation of the elderly (Mazelova et al., 2003). Many of the studies outlined in the paragraph above assess cognition using verbally administered tests which may influence baseline and follow up performance. Similarly people with HL had poorer baseline performance which could suggest impending cognitive impairment.

This chapter aimed to investigate the influence of HL on cognitive performance to identify whether poorer cognitive performance in a cognitively healthy sample was a true finding or an artefact of the testing procedure.

# **Experiment 5.1 - Hearing status and cognitive performance in cogntively healthy adults**

# 5.2.1. Introduction

As introduced in 5.1, speech perception requires more than just effective transduction of the sound, but includes cognitive processes such as attention, perception, memory and executive function (Lee, 2015). As discussed in Chapter 1 (1.2.1) there is a general age related decline in many of these processes (Nyberg et al., 1996, Reuter-Lorenz et al., 2000, Madden and Langley, 2003), and thus peripheral HL may pose an additional cognitive challenge in speech understanding. For example, extra cognitive resources may be required to process and understand degraded peripheral inputs, at the detriment of other brain processes- the information degradation hypothesis (2.3.3.1).

A recent study compared the effects of hearing acuity on a language comprehension task whilst increasing both processing and perceptual demands (DeCaro et al., 2016). The successful language comprehension of a group of older adults with mild to moderate HL and those of a group of age matched normal hearing older adults was compared. The trial consisted of 144 test sentences, of 6 sentence types, where participants were asked to recall the agent (male or female) that was performing the action during each sentence. The complexity of sentence varied throughout these six types, where they were either simple sentences (subject-relative) or more complex sentences (object-relative) of 6 words long, representing the base sentences. The processing challenge was further increased by adding a prepositional phrase to each base sentence, increasing sentence length to 10 words, where there was either a short or long (requires the most processing) distance between the agent and action for each case. The sentences were presented at two sound levels, either 65 dB or 20 dB above each individuals PTAv threshold. This 20 dB above hearing level was always well below 65 dB and therefore represented a case of increased perceptual demands for the individuals with HL. The results showed that comprehension was similar for both groups for the shorter sentences (simple and complex) at both sound presentation levels, but there was a significant difference in comprehension performance between the groups for the longer sentences (both simple and complex) at the 20 dB above hearing level presentation, i.e. the situation with increased processing and perceptual demands. This suggested that the successful comprehension of the simpler sentences did not require increased cognitive processing, even in situations with increased perceptual effort, but when the sentences imposed additional processing demands and/or a greater listening effort was required, there was reduced comprehension (DeCaro et al., 2016). The authors suggested that HL had a greater effect on comprehension of complex rather than simple structured sentences due to an ‘upper limit’ on working memory or attentional resources (DeCaro et al., 2016). Therefore any differences reported in cognitive testing may be due to increased brain effort to interpret the words, thus a reduction in available resources for successful completion of the neuropsychological task, rather than an (impending) pathological cognitive decline.

Many studies have reported that cognitive performance is poorer in individuals with HL compared to participants with normal hearing, although this may be confounded by the heavy reliance on verbally administered tests. For example, a cross sectional study assessing the influence of hearing impairment and cognitive impairment using the MMSE in a sample of over 3,500 older adults found that, after adjusting for age and confounding variables, adults with HL had a mean MMSE score of 28.10 (SD= 0.12) while adults with normal hearing had a mean MMSE score of 28.70 (SD= 0.04) (Tay et al., 2006). This mean difference of 0.6 points was statistically significant (*p* <.001), however it does raise the question of whether this result is clinically relevant, or rather that the conclusion of poorer cognitive performance may be overinflated. In the same way, the MMSE has shown to overestimate cognitive decline in a sample of individuals with ‘induced’ HL, suggesting that the poorer scores in other studies may be an artefact of the heavy verbal reliance on the MMSE (Jorgensen et al., 2016). Similar results have been reported for other language comprehension tasks (Lodeiro-Fernandez et al., 2015) which may immediately disadvantage older adults with HL. An early study reported people with HL perform worse on verbal cognitive tests but not on nonverbal cognitive tests when controlling for age (Thomas et al., 1983). Therefore performance could be confounded by increased listening effort or poor audibility, and might reflect the need to tightly control these aspects.

The first aim of Experiment 5.1 was to verify if HL influences cognitive performance in a sample of cognitively healthy volunteers, with a secondary aim to clarify, if there were a difference, which areas of cognition may be selectively influenced. To investigate whether there is a true difference in cognitive performance the battery of cognitive tests was specifically chosen to include tests which have minimal reliance on auditory perception, and thus would exclude the possibility that people with HL are disadvantaged by the testing procedure. The hypothesised was, after accounting for age, there would be no difference in cognitive performance between people with normal hearing and those with HL.

# 5.2.2. Methods

## 5.2.2.1. Participants and procedure

One hundred and twelve participants over the age of forty were recruited to this study as volunteers. The participants ranged between the ages of 41 and 93, with a mean age of 64.93 (SD= 12.09). There were 44 males (39%) and 68 (61%) females in this sample. The sample was highly educated with the mean number of years of education at 15.07 (SD= 3.20), ranging between 8 and 23 years.

This was a volunteer sample, where no specific inclusion criteria were used. The exclusion criteria were as follows: aged below 40 years, HL before the age of 40, or HL caused by trauma or disease. Participants could not have a cochlear implant, any previous history of head injury, stroke, seizures, cognitive impairment or substance abuse and had to be proficient in English language.

There were a number of reasons why 40 was chosen as the minimum age for participation, including evidence to suggest that hearing starts to decline before the age of 55 and subjective reports of HL often start around the age of 40 (Goman and Lin, 2016, Dawes et al., 2014).

The volunteers were identified through various streams including posters in local GP surgeries, libraries and charity offices, U3A groups and through word of mouth. Participants who completed the validation of the SEAH (Experiment 4.2, described in 4.3.2.1), who were eligible according to exclusion criteria and consented to be contacted again for future testing, were also emailed with details of the new study. Forty-one participants were recruited by this method.

All participants undertook detailed neuropsychological assessment and hearing assessment. The protocol also involved participants to complete the SEAH questionnaire (described Experiment 5.2) and tests of central auditory processing (described in Experiment 6.1). To control for other factors that could influence cognitive performance, demographic information was collected including years of formal education (self-report and kept as a continuous variable in number of years (Tognoni et al., 2005)) and presence of cardiovascular (CV) disease or risk factors, assessed by participants directly reporting a diagnosis, or taking any medication for CV purposes. Similarly, assessment of depression using the PHQ-9 (Spitzer et al., 1999) and anxiety using the GAD-7 (Spitzer et al., 2006) was undertaken to control for differences in performance on neuropsychological testing.

Ethical approval was obtained from the University of Sheffield Medical School (ref: 002853) and NRES Committee North East- Newcastle and North Tyneside (ref: 170445, 15/NE/0152). All participants gave their written informed consent.

## 5.2.2.2. Hearing assessment

All participants were asked if they had subjective hearing problems upon entering the study and (if present) duration of HL and rehabilitation were recorded. Pure tone audiometry screening was conducted using a CE70 Handheld Pure Tone Warbler in a quiet clinical room as outlined in detail in section 4.2.2.2.2.

## 5.2.2.3. Neuropsychological assessment

All participants undertook a battery of cognitive tests that was chosen to have minimal inclusion of verbal administration (with the exception of the MMSE), to ensure that hearing performance did not influence the outcome. Both raw scores from each test and an overall cognitive composite score (Overall Cognition) was included in the analysis. Overall Cognition was based on the results from the 6 tests (calculated as Z scores) with higher scores suggesting better performance.

### 5.2.2.3.1. The Mini Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975) was selected as a global measure of cognition (Appendix 3). This screening tool takes less than 10 minutes to administer and consists of 30 questions assessing domains of orientation, attention, memory and language. Specifically the MMSE assesses temporal orientation (10 marks) including location in time in space; registration (3 marks) by asking the participant to recall 3 words that have been given to them; attention and calculation (5 marks) by asking the participant to count backwards in 7s from 100 and spelling the word WORLD backwards; recall (3 marks) where a mark is given for each correct word recalled, object naming (2 marks) a mark is given for correctly naming a wristwatch and a pencil; repetition (1 mark) where the mark is given for repeating the phrase “No ifs, ands or buts”; comprehension (3 marks) the participant scores full marks for correctly understanding and following a set of verbal instructions, for example ‘Take the piece of paper in your right hand (1), fold it in half (1) and put it on the floor (1); reacting (1 mark) where the participant is asked to undertake a written command such as ‘Close your eyes’; writing (1 mark) by asking the participant to write a coherent sentence; and finally copying (1 mark) where the participant is asked to copy a picture of intersecting pentagons. Scores from each domain are assimilated to give the overall score for global cognitive function, with a maximum of 30.

### 5.2.2.3.2. The Short Cognitive Evaluation Battery (SCEB)

The SCEB (Robert et al., 2003, Girtler et al., 2012) was selected as it is sensitive to pathological changes and has minimal verbal involvement. This battery is comprised of four different aspects, Temporal Orientation, 5- word memory test (immediate and delayed recall), Clock- Drawing task and Category Fluency task (Appendix 4).

The Temporal Orientation task used was the Benton Temporal Orientation Test (Benton, 1983) which is a highly reliable measure of cognitive status. This test assessed knowledge of the month, date, year, day of the week and time of the day, with a graduated scoring system according to the degree of error. For example, getting the date wrong by one day would be -1, but by 10 days would be -10. The maximum total error score was -113.

The 5-word test is a version of the enhanced cued recall test, reflecting semantic immediate and long-term memory. A list of 5 words from different semantic categories was given to the participant who was asked to read the words aloud. The participant was then given a semantic cue and asked to identify each item. The list of words was then removed and the participant was asked to recall the 5 words in any order, where the cue was provided if any items were not spontaneously recalled. A non-semantic interference task was then undertaken (Clock-Drawing task) and following this, the 5 items were again asked to be recalled. Once more if any words were not recalled freely, the semantic cue was given. The score was recorded as the sum of the free and cued recall, to a maximum of 5.

The Clock-Drawing task was used as a measure of visuoconstructive abilities. The participant was given a piece of paper with a large circle, and asked to turn it into a clock, including all of the numbers and then set the time at 20 minutes to 4. The scoring procedure used was based on seven attributes, where one point was given for each correct portion, to a maximum of 7.

The Category Fluency task assesses semantic verbal ability and executive control in a single category of animals. The participant is asked to name as many animals as possible in 60 seconds. One point is given for each correct answer.

Scores from each part of the SCEB were summed, a higher score reflecting better cognitive performance.

### 5.2.2.3.3. Verbal Fluency Task

Two measures of verbal fluency were employed to assess verbal ability and executive control, the Category Fluency (semantic fluency) and Letter Fluency (phonemic fluency) tasks (Lezak, 2004) (Appendix 5). The participant is given the category or letter, and is asked to name as many words that fit into the category or begin with that letter in 60 seconds. There are three trials each, for semantic fluency categories were animals, cities and fruit and for phonemic fluency, the letters were p-, l- and f-. The participant is given one point for each correct word given.

### 5.2.2.3.4. Digit Cancellation

The digit cancellation task (Spinnler and Tognoni, 1987) was used to measure visual attention and speed of processing (Appendix 6). There are three progressive trials where participants are asked to put a line through (cancel) numbers, first one number (5) per trial and then two numbers (2, 6), and finally three numbers (1, 4, 9). The cut off was scored at 60 seconds and the number of correct responses in this time were recorded. After 60 seconds, the participant was allowed to continue (if needed) but correct responses were no longer recorded. Correct scores from each of the three matrices were summed to a maximum of 60.

### 5.2.2.3.5. House Visual Span

The House Visual Span (Cornoldi and Vecchi, 2004) assesses short and long-term visual memory and was translated onto a PowerPoint programme for ease of delivery. A paper version can be found in Appendix 7. Participants were presented with black and white line drawings of house shapes of various types, for one second. They were then asked to identify the houses they had initially seen from a larger set of houses. The span included sequences of houses of increasing length, up to 6, and there were three trials at each span level. When the participant reached the point where they did not get 2/3 for each trial correct, the task was concluded. The second part of this assessment included a 6-house recall. Participants were shown 6 houses on the screen all together for 30 seconds, and they were then asked to choose these 6 out of a possible 12 houses. All participants were then shown the same 6 houses for another thirty seconds, and were asked to recall them after 10 minutes. This was recorded as the long-term recall, again to a maximum of 6.

## 5.2.2.4. Data analysis

All statistical analysis was undertaken using IBM-SPSS statistics software, v22. Two-tailed hypotheses were tested, and a significant *p* value was set at .05, which was corrected to *p*= .008 using the Bonferroni factor to assess individual performance on the battery of cognitive tests.

Effect sizes are included for statistical comparisons to report information about the magnitude and direction of the difference or association between groups. Cohen’s *d* is usedfor comparisons between two means where effect sizes of *d*= 0.2, 0.5 and 0.8 represent small, medium and large effect size respectively. For non-parametric analysis between two groups, the Mann Whitney U test effect size *r* is presented, where 0.1, 0.3 and 0.5 represent small, medium and large effect sizes respectively. Odds ratio (OR) is used to describe the effect sizes between categorical variables, where OR=1.68 is equivalent to small, OR= 3.47 is equivalent to medium and OR= 6.71 is equivalent to large effect sizes.

A composite score of ‘Overall Cognition’ was created by averaging of the individual neuropsychological tests. First, each test was standardised into z-scores, using the formula:

As the contributions from each test were considered equal, the z-scores were summed to give the variable ‘Overall Cognition’. Subsequently, using a median split (median = 0.0375) was applied to convert Overall Cognition into a categorical Cognitive Performance level, with quantiles coded as ‘high’ and ‘low’ performers.

In order to explore the differences in demographic characteristics between groups of HL and normal hearing, the Kolmogorov-Smirnov test was chosen as a test of normality, and parametric and non-parametric independent samples analysis were decided on the basis of this test for continuous data, and χ² test was employed for categorical variables. As the aim of this experiment is to investigate the role of HL on cognitive performance, the need to minimise any other differences which could impact on the differences were investigated. Any demographic differences between the normal hearing and HL group were investigated using hierarchical multiple linear regression as an exploratory analysis. This would allow us to define how important each demographic factor was in predicting PTAv variance throughout the sample.

Hierarchical multiple linear regressions were subsequently performed to predict cognitive performance based on Age (Model 1) and including PTAv in Model 2, for Overall Cognition and the raw tests in which a significant difference between the 2 groups had been detected.

# Results

## Hearing assessment

Forty three participants (38%) reported a subjective HL, and the rest reported no hearing problems. PTAv thresholds varied between 20 dB and 66.25 dB in the better hearing ear. The prevalence of measured HL was 33% in the sample, with 37 participants screening positive for HL and 75 participants having normal hearing.

Participants were classified into two groups depending on their hearing status, hearing thresholds <25 dB HL were classified as normal hearing and ≥26 were classified as HL. The demographic characteristics of both groups are shown in Table 5.1. Participants with HL were more likely to be male, older, with CV risk factors and slightly fewer years of education.

As age, years of education and CV risks were different between the two groups (normal hearing and HL) it was investigated how these demographic factors could explain variance in PTAv scores, or whether as predicted, fewer years of education and higher CV risks may be present in the HL group as a result of the increased age. As expected, PTAv was highly correlated with age (*r*s = .630, *p* < .001) (Figure 5.1), and weakly correlated with years of education (*r*s = -.189, *p* = .046) and cardiovascular risks (*r*s = .305, *p* = .001). An exploratory hierarchical multiple linear regression was performed to investigate whether the associations with education and cardiovascular risks (Model 2) could explain any variation in PTAv over and above age (Model 1). The results showed no significant change in R² between Model 1 (R² = .295, *p* <.001) and Model 2 (∆R²= .009, *p* = .486), suggesting that the lower levels of education and higher levels of cardiovascular risk factors in people with higher PTAv thresholds, reflect the age related variance of these variables. Therefore, subsequently only age will be included as a potentially confounding factor with cognitive performance.

**Table 5.1.** *Demographic characteristics of the sample as a whole and of subsamples according to hearing status*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Demographic | Sample  (n=112) | Normal Hearing (n=75) | Hearing loss  (n=37 ) | Significance |
| Age | 64.93 [12.09] | 60.47 [10.41] | 73.97 [10.11] | **.001\*** |
| Education | 15.07 [3.20] | 15.49 [3.09] | 14.22 [3.28] | **.046\*** |
| Sex (M/F) | 44/68 | 22/47 | 22/21 | **.025\*** |
| Handedness (R/L) | 99/13 | 64/11 | 35/2 | .214 |
| Subjective Hearing Loss | 43 (38%) | 10 (13%) | 33 (89%) | **.001\*** |
| CV Risk Factors | 37 (33%) | 19 (25%) | 18 (49%) | **.019\*** |
| Depression | 3.86 [4.00] | 3.67 [3.74] | 4.24 [4.51] | .476 |
| Anxiety | 4.23 [4.73] | 4.19 [4.68] | 4.32 [4.88] | .886 |

NB. \*Significant at the *p*< .05 level. Age, education, depression and anxiety are mean scores and [SD] is reported in square brackets.



**Figure 5.1.** *Scatterplot showing the correlation between age and PTAv.*

## Neuropsychological performance

All individuals scored within the age appropriate normal range on the cognitive tests, demonstrating they were all a cognitively healthy sample (Table 5.2.)

**Table 5.2.** *Average (and variability) performance on the battery of neuropsychological testing* in the whole sample

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Neuropsychological test | Mean | (SD) | Median | (IQR) | Range |
| MMSE | 29.02 | (1.18) | **29.00** | **(1.00)** | 25 – 30 |
| SCEB | **34.37** | **(6.70)** | 34.00 | (9.00) | 21 – 50 |
| House Visual Span | 2.58 | (0.58) | **3.00** | **(1.00)** | 1 – 4 |
| 6-house recall | 5.20 | (0.85) | **5.00** | **(1.00)** | 3 – 6 |
| Category Fluency | **60.33** | **(14.58)** | 59.00 | (21.00) | 32 – 97 |
| Letter Fluency | **44.89** | **(10.93)** | 44.00 | (14.00) | 18 – 73 |
| Digit Cancellation | 55.96 | (3.62) | **57.00** | **(4.00)** | 35 – 60 |

NB. The average score reflects the mean (SD) for the Short Cognitive Evaluation Battery (SCEB) and Category and Letter Fluency, and the median (IQR) for the Mini Mental State Examination (MMSE), House Visual Span and Digit Cancellation.

### Neuropsychological assessment according to hearing groups

On average, there was a difference in cognitive performance between individuals with HL and normal hearing (Table 5.3). This difference between group scores was significant at the *p* <.008 corrected level for the Overall Cognition (*t* (110) = 3.28, *p*=.001, *d*=0.68) and raw scores on the MMSE (*U=* 884.00, *p*=.001, *r*= 0.31) and Category Fluency Task (*t* (110) = 2.88, *p*=.005, *d*=0.58).

To ensure that the group difference found between MMSE scores was not due to an artefact of the testing procedure, a corrected MMSE score was calculated (now out of 23) to remove any questions that would immediately be disadvantageous to the HL population. This included removal of Question 3, Registration of three words; Question7, Repetition (1 mark); and Question 8, 3-stage command (3 marks), see Appendix 3 for specific questions. The corrected scores no longer reflected a significant difference between normal hearing (Median = 23, IQR =1) and HL (Median=23, IQR=1), (*U*= 1175.00, *p=* .133, *r*= 0.14).

**Table 5.3.** *Neuropsychological performance according to hearing loss groups*

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Normal Hearing (n=75) | | | | | Hearing loss (n=37) | | | | |  |
| Cognitive Test | Mean | (SD) | Median | (IQR) | Range | Mean | (SD) | Median | (IQR) | Range | Significance |
| MMSE | 29.29 | (0.84) | **29.00** | **(1.00)** | 26-30 | 28.46 | (1.54) | **29.00** | **(1.00)** | 25-30 | **.001\*\*** |
| SCEB | **35.48** | **(6.12)** | 36.00 | (8.00) | 22-48 | **32.11** | **(7.33)** | 31.00 | (10.00) | 21-50 | .012\* |
| House Visual Span | 2.64 | (0.56) | **3.00** | **(1.00)** | 2-4 | 2.46 | (0.61) | **3.00** | **(1.00)** | 1-3 | .208 |
| 6-house Recall | 5.32 | (0.81) | **5.00** | **(1.00)** | 3-6 | 4.95 | (0.88) | **5.00** | **(2.00)** | 3-6 | .023\* |
| Category Fluency | **63.08** | **(14.18)** | 62.00 | (20.00) | 32-95 | **54.95** | **(13.83)** | 53.00 | (19.00) | 38-97 | **.005\*\*** |
| Letter Fluency | **45.52** | **(10.51)** | 45.00 | (12.00) | 21-73 | **43.95** | **(11.86)** | 43.00 | (17.00) | 18-71 | .476 |
| Digit Cancellation | 56.47 | (2.89) | **57.00** | **(5.00)** | 50-60 | 54.95 | (4.65) | **56.00** | **(4.00)** | 35-60 | .058 |
| Overall Cognition | 0.127 | (0.47) | 0.139 | (0.55) |  | -0.219 | (0.55) | -0.255 | (0.81) |  | .001\*\* |

NB. \* Significance at *p*<.05, \*\*Significance at p<.008. MMSE= Mini Mental State Examination, SCEB= Short Cognitive Evaluation Battery.

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### Age, hearing status and neuropsychological testing

As age had a significant effect on neuropsychological testing, and was highly correlated with ARHL, to measure which proportion of the variance in cognitive scores was due to HL unconfounded by age, a hierarchical multiple linear regression was undertaken for the cognitive tests which reported a significant difference between the normal hearing and individuals with HL (Table 5.4). Please note this was not included for the MMSE due to the confounding influence of verbal administration of the tests as outlined in 5.2.3.2.1.

Model 1 suggested that age accounted for 30.6% of the variance in Overall Cognition, and when PTAv was included in Model 2 there was no significant change in the prediction of variance (Table 5.4). Similar results were found for the linear model of predictors of Category Fluency performance, where there was no significant change in R² between Model 1 (R² = .203, *p* <.001) and Model 2 (∆R² = .013, *p* = .188).

**Table 5.4.** *Linear model of predictors of Overall Cognition*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | SE B | Β | *p* |
| Model 1 |  |  |  |  |
| Constant | 1.53 | .224 |  | <.001 |
| Age | -.024 | .003 | -.553 | <.001 |
| Model 2 |  |  |  |  |
| Constant | 1.47 | .222 |  | <.001 |
| Age | -.020 | .004 | -.473 | <.001 |
| PTAv | -.008 | .005 | -.148 | .119 |

NB R²= .306 for Model 1, ∆R² = .015 for Model 2 (p= .119)

### High and low performers

Overall the median split yielded 56 participants classed as high performers and 56 participants classed as low performers. Table 5.5 shows low performers were significantly older (*t* (110) = 6.35, *p* <.001, *d*= 1.23), had fewer years of education (*U* = 2291.50, *p* <.001, *r*=0.40) and a higher proportion of individuals with HL (χ² (1) = 6.82, *p* = .009) compared to the high performance group.

Therefore a larger number of people with HL were low performers (67.57%) and a larger number of people with normal hearing were high performers (58.67%) (Figure 5.2.), where the odds of being in the high performance group was 2.96 times higher for participants with normal hearing compared to those with HL.

**Table 5.5.** *Demographic differences between high and low performers on Overall Cognition*

|  |  |  |
| --- | --- | --- |
|  | Low performer (n=56) | High Performer (n=56) |
| Age | 71.16 (10.12) | 58.70 (10.65) |
| Years of education | 13.00 (6.00) | 17.00 (10.00) |
| Hearing loss | n=25 (44.64) | n=12 (21.43) |

NB. The average reflects the mean (SD) for age and the median (IQR) years of education. For hearing loss, n= reflects the number of participants, the proportion of individuals in each performance group, with hearing loss expressed as a percentage in brackets.



**Figure 5.2.** *High and low Cognitive Performance per hearing group.*

The 25 low performers with HL had an average hearing threshold of 32.50 dB HL (IQR =15.00) and the 12 high performers with HL had an average hearing threshold of 31.32 dB HL (IQR =11.00), suggesting that there was no difference in the severity of HL between high and low performers with HL, *U* = 98.00, *p* = .095, *r=* 0.28.

# Discussion

The prevalence of HL in our sample was 33%, which is in keeping with prevalence estimates for the mean age of 64.93 years (Lin et al., 2011c). Individuals with HL on average scored lower on Overall Cognition and specifically on the Category Fluency task, which could suggest that HL is associated with poorer cognitive performance. However, there is a large variation in age across the sample, and by definition, people with ARHL would be expected to be older. As age plays a major role in cognition and neuropsychological test performance, it was reported that after accounting for the effects of age, hearing thresholds did not significantly predict cognitive performance on any test. The second aim was to investigate which areas of cognition may be selectively affected in people with HL, but as there was no difference in any areas of cognition, this could not be undertaken.

Our findings are incongruent with other research that has reported lower neuropsychological scores for people with HL, including a renowned longitudinal study which presented people with HL had lower baseline performance and an increased risk of dementia over 12 years, which was linearly dependent on the severity of their HL (Lin et al., 2011b). This study reported as a limitation, that people with HL were significantly older than the normal hearing group, which could actually at least partially explain the variability in baseline performance and the increased risk of developing dementia over time. Another study reported a strong association between performance on speech in noise tests, using the Dichotic Digit Test and lower cognitive scores on a battery of cognitive tests (Moore et al., 2014), but also reported an independent association of age with both the Dichotic Digit Test and cognitive performance, which again could explain the association between the two factors.

Our findings are in keeping with previous research in cognitively healthy groups of elderly participants, where any apparent associations between HL and cognitive performance disappeared when controlling for age (Herbst and Humphrey, 1980, Gennis et al., 1991). Similarly, studying a narrow age cohort eliminates the confounding variable of ageing, and when investigating the association of auditory acuity and cognitive functioning in three cohort samples of 75 year old, it was found that PTAv was only very weakly correlated with cognitive performance (*r* ≤ .10) which the authors suggested was more indicative of common health or socioeconomic status rather than a true association (Hofer et al., 2003), once more supporting our findings.

The lack of association between PTAv and cognitive performance after controlling for age suggests that in our sample the severity of hearing thresholds does not predict neuropsychological testing, which is different from a retrospective longitudinal study which suggested at baseline, participants with HL had a significantly lower MMSE score after controlling for age, gender and education levels (Amieva et al., 2015). However, there were limitations to that study as HL was self-reported, and the actual difference in baseline scores across 3500 participants was marginal (mean difference of 0.69 points), so although statistically significant, it is unlikely to be clinically meaningful. Also, as previously mentioned, the MMSE may be highly influenced by auditory acuity (Jorgensen et al., 2016), as when questions which heavily rely on good audibility were removed, there was no longer a significant difference between MMSE scores for people with and without HL (5.2.3.2.1), despite the significantly higher age in the HL group and the strong influence age has on the MMSE performance (Crum et al., 1993). Therefore, the lower MMSE scores at baseline in the study by Amieva et al., (2015) could have been confounded by auditory acuity rather than a meaningful difference in cognitive performance. This may be a useful clinical criterion, and supports the notion that HL should be evaluated and acknowledged during cognitive assessments using verbally administered tests such as the MMSE.

One limitation of the present study is the methodology employed for the hearing assessment. Hearing levels and thresholds reported are not as a result of full audiological assessment by a qualified audiologist in a sound proof testing booth. Although training was given to the investigator, and steps were taken to minimise external noise that may confound the results, the hearing levels presented were as part of a single screening test. For example, there were no speech audiometry tests such as speech recognition threshold or speech in noise tests to validate the pure tone results (Kramer, 2014). Similarly an ear inspection was not carried out to inspect cerumen, which may be trapped in the ear canal and lead to a mild conductive HL (Kramer, 2014). Therefore people may be recorded as having HL which might not actually be there. However, it was demonstrated in 4.2.2.2.2 that the CE70 warbler was somewhat reliable and previous research has shown that the warble tone has strong test-retest reliability (Arlinger and Jerlvall, 1987), and the thresholds are directly comparable to pure tone thresholds (Dockum and Robinson, 1975).

To conclude, when using a battery of neuropsychological tests which aims to ameliorate the confounding effects of verbal administration, there is no difference in baseline performance of those with HL and normal hearing after controlling for the variance of age. These results are interesting, as they suggest that (after controlling for age) the presence of a HL does not influence baseline cognitive performance. Therefore, any changes or accelerated decline in cognitive performance over time in people with HL must be due to other factors.

# **Experiment 5.2 - Social and emotional associations of hearing loss and Cognitive performance in cognitively healthy adults**

# 5.3.1. Introduction

The psychosocial pathway linking HL and cognitive decline has been introduced in 2.3.3.3, where evidence was presented concerning the increased rates of depression, low self-esteem and social isolation in people with a HL (Strawbridge et al., 2000, Heine and Browning, 2002, Yueh et al., 2003); and how these factors lead to the increased risk of dementia (Wilson et al., 2007, Li et al., 2011).

The risk of dementia in people with HL is greatly increased by the severity of the HL (Lin et al., 2011b, Deal et al., 2016). A more severe and untreated HL is more likely to be associated with a more severe social isolation (Mick et al., 2014), and therefore the increased risk of cognitive decline and dementia in people with HL may be influenced by the psychosocial factors associated with HL rather than due to degeneration of the peripheral auditory system. The role of hearing aids is an interesting factor in this relationship, as epidemiological research has proposed that the treatment of HL by use of hearing aids can lead to a reduction in the risk of incident dementia compared to individuals with HL who remain untreated (Dawes et al., 2015b, Fritze et al., 2016). One cross sectional study found that hearing aid use was associated with better performance on a test of executive function (Lin, 2011), however, hearing aid use was only apparent in 13 participants and this was measured based on them wearing a hearing aid for at least one day in the past year, and so may not be representative of hearing aid users.

Although hearing aid adoption is generally low, there is evidence to suggest that hearing aid users are more likely to have a severe HL (Fischer et al., 2011), and therefore this might be a confounding factor, where individuals with severe HL are both more likely to develop dementia and have a reduced risk of dementia due to increased hearing aid use. However, although there was limited hearing aid data in both longitudinal studies, neither study reported any decreased risk in individuals who used hearing aids (Lin et al., 2011b, Deal et al., 2016).

Also, the poorer performance on cognitive tests reported for people with a HL could also be due to the complications or consequences of HL such as depression, social isolation and loneliness. People who are depressed tend to score worse on a large variety of cognitive tests (Crews and Harrison, 1995, Rabbitt et al., 1995). Similarly, the MMSE, the most widely used cognitive screening tool, shows sensitivity to low mood and depression (Girtler et al., 2012) and a high specificity to the severity of depression (Milian et al., 2013). Therefore, people who are highly restricted by their HL, regardless of hearing thresholds may perform worse during cognitive testing. To our knowledge, there are no studies which have investigated the influence of hearing disability directly on cognitive performance. Again, as hearing aid data is conflicting in terms of cognition it is not known how hearing aids may play a role in baseline cognitive testing, as hearing aids may help reduce perceptual effort during cognitive testing, or they may help to reduce the social and emotional disability associated with HL (Mick et al., 2014).

Inconsistent evidence surrounding the role of hearing aids on cognition, together with few studies addressing the indirect HL, psychosocial impairment and cognitive impairment pathway (Fulton et al., 2015) means the role of hearing disability cognition has not been investigated. Therefore, the aim of this study was to measure the influence of subjective hearing disability using the Social and Emotional Associations of Hearing loss (SEAH), to identify whether disability associated with HL has any (more of an) impact on cognitive performance than hearing thresholds alone. The secondary aim was to identify whether the use of hearing aids influences this association.

This experiment would help to identify whether the impoverished auditory signals coming into the brain were responsible for the evidence of decline in upstream cognitive processing or whether social isolation would be a more important factor linking the two. Investigating the role of hearing aids on this relationship would lead to further understanding of the psychosocial pathway linking HL and cognitive decline. The hypothesis is that for individuals with the same levels of HL, those with higher perceived levels of hearing disability would be more likely to perform lower on cognitive tests, and wearing hearing aids would lead to a reduction in hearing disability and thus mitigate any poorer performances.

# 5.3.2. Methods

## 5.3.2.1. Participants and procedure

The same participants were recruited as presented in Experiment 5.1, and the same general procedure was followed as described in 5.2.2.1 for collecting of demographic details, cognitive testing and hearing assessment.

In addition to this, all participants completed the SEAH questionnaire (Experiment 4.2 for validation), to measure their subjective feelings around their hearing abilities. Thresholds of >25% were set for hearing disability, with the greater the number, the more socially and emotionally impaired the individual felt.

Ethical approval was as described in 5.2.2.1. All participants gave their written informed consent.

## 5.3.2.2. Data analysis

Statistical analysis was undertaken using the same parameters defined in 5.2.2.4.

A correlation coefficient was used to investigate the association of SEAH with demographic variables such as age, PTAv, anxiety (GAD-7) and depression (PHQ-9) scores. This was undertaken to investigate whether the social and emotional associations of HL reported were specific to the hearing domain or could be more generalised to higher levels of depression and anxiety in individuals with high SEAH scores. The association between SEAH and hearing aid use and overall satisfaction was also investigated, to identify whether hearing aid use and perceived satisfaction had an influence on subjective hearing disability, and whether this related to the hours worn or overall satisfaction.

To identify whether the use and perceived satisfaction of hearing aids impacted subjective hearing-related disability, correlational analysis was undertaken to explore the relationships between hearing aid use, duration of use (as a percentage of 16 hours, used based on the assumption of awake hours) and perceived satisfaction (a score between 1 and 10). The non-parametric Mann-Whitney U test was utilised to investigate the effect of hearing aids on SEAH scores in the whole sample, and cognitive performance in a subsample of individuals with mild HL who were aided or unaided. This group could be used to investigate SEAH scores, hearing aid use and cognitive performance whilst controlling on the group level for the influence of hearing thresholds impacting the relationship.

To investigate how social and emotional associations of HL may impact on cognitive performance, participants were grouped according to their hearing disability status into the binary variable hearing disability. Classification of disability was SEAH scores ≥25%, and no subjective hearing disability was reported for participants scoring <25%. Parametric Independent Samples t-test and non-parametric Mann-Whitney U test were used to compare neuropsychological performance between the disability groups. Where equal variances were not assumed (age between groups) then the degrees of freedom were adjusted to reflect this.

Following this, χ² analysis was used to investigate any difference in disability between high and low performers (see 5.2.2.4), and subsequently hierarchical multiple linear regression was performed to evaluate whether SEAH scores measuring hearing disability (Model 2) could explain any of the variance in Overall Cognition after controlling for the confounding effects of Age on cognition (Model 1). To confirm the results, a sample of participants with normal hearing thresholds who reported hearing related disability’s cognitive performance was compared to a matched sample of individuals with no hearing disability. Similarly, the influence of hearing aids was investigated on cognitive performance by comparing the subsample of individuals with a mild HL with and without hearing aids.

# Results

## SEAH

Scores on the SEAH ranged between 0 and 80%, and as predicted, there was a significant correlation between PTAv and self-reported disability, (*r*s = .65, *p* <.001) (Figure 5.3). There was no association between scores on SEAH and scores on the anxiety scale GAD-7 (*r*s = .159, *p*= .093) or the depression scale PHQ-9 (*r*s = .082, *p* =.391), suggesting the reported social and emotional disability was due to HL alone and not a more generalised anxiety disorder or as a consequence of low mood. Table 5.6 shows the range and median SEAH scores for the normal hearing and HL groups. In this sample, 28 (25%) participants classified themselves as limited or restricted by their HL according to the SEAH, and 84 were functioning with their HL. It is shown in Table 5.6, that although disability levels were higher for the HL group, it is not only individuals with a measured HL that reported hearing disability, as 6 participants with normal hearing reported SEAH scores over 25%.



**Figure 5.3.** *Correlation between SEAH and PTAv thresholds.*

**Table 5.6.** *SEAH scores according to hearing loss group*

|  |  |  |
| --- | --- | --- |
|  | Normal Hearing (n=75) | Hearing loss (n=37) |
| Median SEAH (IQR) | 9 (14) | 30 (29) |
| Range SEAH | 0 - 45 | 4 - 80 |
| Hearing disability (%) | 6 (8%) | 22 (59%) |

NB Hearing disability (%) refers to the percentage of each hearing loss group who reported subjective hearing disability.

## Hearing aids and SEAH scores

Twenty-eight participants reported owning hearing aids, with a range of compliance and perceived satisfaction. Overall, people who wore hearing aids judged themselves as significantly more restricted on the SEAH (median= 35, IQR= 27) than individuals with HL who did not wear hearing aids (median= 14, IQR =10), *U* =322.5, *p* =.004, *r*= 0.44.

The percentage of hearing aid wearers was significantly different for mild and moderate to severe HL, (χ² (1) = 8.92, *p* = .003) with all of the moderate to severe group wearing hearing aids, reflecting the need for amplification and suggesting why SEAH scores were significantly higher (Table 5.7).

**Table 5.7.** *Percentage* *of participants with hearing loss who wore hearing aids*

|  |  |  |
| --- | --- | --- |
| Hearing loss severity | Aided | Unaided |
| Mild (n=28) | 68% | 32% |
| Moderate/Severe (n=9) | 100% | 0% |

As two thirds of the sample with a mild HL wore hearing aids, and another third did not, this group was used to test the hypothesis of hearing aids influencing perceived hearing disability. As shown in Table 5.8, there was no difference in mean age between those with a mild HL who wore hearing aids and those who did not wear hearing aids, *t* (26) = -.881, *p*=.386, *d* = 0.32. There was no difference in hearing thresholds between participants who wore hearing aids and those who didn’t, *U* = 119.00, *p*=.105, *r* =0.31. Finally, there was no difference between hearing related disability for aided and unaided participants (*U* = 101.00, *p*=.468, *r* =.014), although the median scores were higher for those with a hearing aid, which may reflect the higher hearing thresholds.

**Table 5.8.** *Demographic comparisons between participants with mild hearing loss who were aided and unaided*

|  |  |  |
| --- | --- | --- |
|  | Aided (n=19) | Unaided (n=9) |
| Age | 73.37 (7.97) | 69.67 (11.66) |
| PTAv | 32.50 (10.00) | 28.75 (6.00) |
| SEAH | 29.00 (25.00) | 18.00 (10.00) |

### Hearing aid use and hearing related disability

Hearing aid use (duration of wear) varied throughout the sample, with participants reporting wearing their hearing aids for between 0 hours and 16 hours (100% of the time) per day. There was a significant positive correlation between severity of HL and number of hours hearing aids were worn (*r*s = .587, *p* =.001) as shown in Figure 5.4, where participants who did not wear hearing aids all day tended to have a more mild HL. There was, however, no association between amount of time wearing hearing aids per day and SEAH scores (*r*s = .256, *p* =.173).



**Figure 5.4.** *The amount of time per day (%) hearing aids were worn according to hearing severity*

### Hearing aid satisfaction and hearing related disability

Overall satisfaction with hearing aids varied throughout the group, with participants reporting between 0/10 and 10/10 satisfaction with their aids. The group median was 7/10 (IQR 2), with most participants reporting satisfaction between 6/10 and 9/10. There was no association between perceived satisfaction and amount of time hearing aids were worn (*r*s = .288, *p* =.244), or between perceived hearing aid satisfaction and SEAH scores (*r*s = -.195, *p* =.319). However, this may be expected if people with more severe HL are the individuals wearing hearing aids.

## Neuropsychological performance according to SEAH

People who reported higher scores on the SEAH had on average lower performance on many of the cognitive tests (Table 5.9). There was a significant difference between performance on Overall Cognition for people who reported hearing disability compared to those who did not (*t* (110) = 2.86, *p*=.005, *d* = 0.65). Raw tests showed a significant difference between the number of houses recalled on the long-term recall section of the House Visual Span (*U* = 764.50, *p* =.003, *r* = -.28) where individuals with subjective hearing disability recalled significantly less houses.

**Table 5.9.** *Neuropsychological* *performance according to hearing disability*

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | No disability (n=84) | | | | | Hearing disability (n=28) | | | | |  |
| Cognitive Test | Mean | (SD) | Median | (IQR) | Range | Mean | (SD) | Median | (IQR) | Range | Significance |
| MMSE | 29.20 | (1.03) | **29.00** | **(1.00)** | 25-30 | 28.46 | (1.43) | **29.00** | **(1.00)** | 25-30 | .012\* |
| SCEB | **34.80** | **(6.77)** | 35.00 | (10.00) | 21-48 | **32.86** | **(6.42)** | 33.00 | (9.00) | 21-50 | .170 |
| House Visual Span | 2.58 | (0.59) | **3.00** | **(1.00)** | 1-4 | 2.57 | (0.57) | **3.00** | **(1.00)** | 1-3 | .893 |
| 6-house recall | 5.35 | (0.75) | **6.00** | **(1.00)** | 3-6 | 4.75 | (0.97) | **5.00** | **(2.00)** | 3-6 | **.003\*\*** |
| Category Fluency | **61.57** | **(14.27)** | 60.00 | (20.00) | 32-95 | **56.68** | **(15.12)** | 54.00 | (20.00) | 39-97 | .119 |
| Letter Fluency | **45.84** | **(10.35)** | 45.50 | (13.00) | 21-73 | **42.07** | **(12.26)** | 42.00 | (17.00) | 18-71 | .102 |
| Digit Cancellation | 55.93 | (3.80) | **57.00** | **(4.00)** | 35-60 | 56.07 | (3.07) | **57.00** | **(4.00)** | 48-60 | .818 |
| Overall Cognition | 0.077 | (0.48) | 0.121 | (0.62) |  | -0.235 | (0.55) | -0.281 | (0.55) |  | .005\*\* |

NB. \* Significance at *p*<.05, \*\*Significance at p<.008. MMSE= Mini Mental State Examination, SCEB= Short Cognitive Evaluation Battery.

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### High and low performers

The subjective hearing disability distribution throughout high and low cognitive performers was significantly different (χ² (1) = 6.857, *p* = .009). Figure 5.5 shows the group percentage for individuals based on their hearing disability status. The odds of high cognitive performance was times higher for people who did not report a subjective hearing disability compared to those who did, OR= 3.25. For people with no hearing disability, 42.9% were low cognitive performers, and 57.1% were high cognitive performers. Conversely, 71.4% of individuals who reported hearing disability were low performers, compared to 28.6% who were high cognitive performers.



**Figure 5.5.** *Overall Cognition and subjective hearing disability according to the SEAH*

NB. HD= hearing disability

### Age, neuropsychological performance and hearing disability

Due to the high correlation between PTAv and SEAH (5.3.3.1), and PTAv and age (5.2.3.1), there was a significant difference between the mean ages between groups with no hearing disability and those who reported subjective hearing related disability. Individuals reporting hearing disability were significantly older than those who reported no hearing related disability, as shown in Table 5.10 (*t* (73.05) = -5.80, *p*<.001, *d= 0.70*). There was also a significant difference between males and females, where the odds of males reporting subjective hearing disability was 2.66 times higher than the odds for females (χ² (1) = 4.99, *p* = .025), however this might be exaggerated by the increased ratio of males with a HL compared to those with normal hearing. There was no difference between education levels for those who reported subjective hearing disability and those who did not (*U* = 1042.00, *p* =.365, *r*=-.08). Therefore, age may be confounding the association between hearing disability status and cognitive performance.

**Table 5.10.** *Demographics according to subjective hearing disability*

|  |  |  |
| --- | --- | --- |
|  | No disability (n=84) | Hearing disability (n=28) |
| Age (SD) | 62.10 (11.99) | 73.43 (7.67) |
| Years of education (IQR) | 16.00 (5.00) | 15.50 (7.00) |
| Gender M/F | 28/56 | 16/12 |

The results from the hierarchical multiple linear regression suggested that age (Model 1) accounted for 30.6% of the variance in overall cognitive performance, and when SEAH is included as a predictor at Model 2, there is no significant change in the prediction of variance (Table 5.11). Therefore, after controlling for the effects of age, subjective hearing disability has no association with cognitive performance.

**Table 5.11.** *Linear model of predictors of Overall Cognition*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | b | SE B | β | *P* |
| Model 1 |  |  |  |  |
| Constant | 1.53 | .224 |  | <.001 |
| Age | -.024 | .003 | -.553 | <.001 |
| Model 2 |  |  |  |  |
| Constant | 1.43 | .238 |  | <.001 |
| Age | -.021 | .004 | -.497 | <.001 |
| SEAH | -.003 | .003 | -.109 | .241 |

NB R²= .306 for Model 1, ∆R² = .009 for Model 2 (p= .241)

### Subjective hearing disability, normal hearing and cognition

The six individuals with normal hearing who subjectively reported hearing disability were compared to six age, gender and education matched participants with normal hearing who reported no hearing disability. There were no demographic differences between the groups (Table 5.12).

Similarly, there was no difference in Overall Cognition or the raw scores on any of the neuropsychological tests between participants with or without hearing related disability (Table 5.13), suggesting that subjective hearing disability did not influence cognitive performance in this sample of cognitively healthy controls with no HL.

**Table 5.12.** *Demographic characteristics of matched samples according to hearing disability*

|  |  |  |  |
| --- | --- | --- | --- |
| Demographic | No disability (n=6) | Hearing disability (n=6) | Significance |
| Age | 67.00 (6.95) | 68.00 (5.44) | .787 |
| Education | 15.50 (3.39) | 16.17 (3.55) | .746 |
| Gender (M/F) | 3/3 | 3/3 | 1.00 |
| PTAv | 20.00 (1.00) | 23.00 (3.00) | .310 |
| GAD-7 | 7.67 (7.31) | 3.33 (2.81) | .205 |
| PHQ-9 | 4.83 (5.10) | 3.33 (2.42) | .523 |

NB. \* Significance at *p*<.05. The mean (SD) is reported for age, years of education, GAD-7 and PHQ-9 scores, and the median (IQR) is reported for PTAv.

**Table 5.13.** *Neuropsychological* *performance according to subjective hearing disability of matched sample*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | No disability (n=6) | | | Hearing disability (n=6) | | |  |
| Cognitive Test | Average | | Range | Average | | Range | Significance |
| MMSE | 30.00 | (1.00) | 29-30 | 28.50 | (1.00) | 26-30 | .065 |
| SCEB | 32.00 | (8.49) | 23-48 | 32.17 | (5.81) | 23-37 | .969 |
| House Visual Span | 3.00 | (1.00) | 2-4 | 3.00 | (1.00) | 2-3 | .485 |
| 6-house Recall | 5.00 | (2.00) | 3-6 | 4.50 | (3.00) | 3-6 | .598 |
| Category Fluency | 58.50 | (19.66) | 37-95 | 62.67 | (17.04) | 39-85 | .703 |
| Letter Fluency | 44.67 | (15.64) | 30-72 | 42.17 | (13.83) | 24-66 | .775 |
| Digit Cancellation | 56.00 | (2.97) | 52-60 | 56.67 | (3.67) | 51-60 | .736 |
| Overall Cognition | 0.051 | (0.62) |  | -0.168 | (0.76) |  | .602 |

NB. \* Significance at *p*<.05, \*\*Significance at p<.008. The average reflects the mean (SD) for the Short Cognitive Evaluation Battery (SCEB), Category and Letter Fluency tests, Overall Cognition composite *Z* score and the Digit Cancellation, and the median (IQR) for the Mini mental state examination (MMSE) and House Visual Span.

### Hearing aids and neuropsychological performance

Comparisons in cognitive performance between the hearing aid users and non-hearing aid users were undertaken in the subsample of age matched individuals with mild HL. There was no difference in years of education between those who were aided and those who were unaided (*U* = 132.00, *p* =.654, *r* =.08). Similarly, there was no difference in neuropsychological performance between the groups (Table 5.14), suggesting that rehabilitation with hearing aids did not affect cognitive performance in this sample of cognitively healthy individuals with a mild HL.

**Table 5.14.** *Neuropsychological* *performance according to hearing aid use for participants with a mild hearing loss*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Aided (n=19) | | | Unaided (n=9) | | |  |
| Cognitive Test | Average | | Range | Average | | Range | Significance |
| MMSE | 29.00 | (2.00) | 25-30 | 29.00 | (1.00) | 27-30 | .332 |
| SCEB | 33.16 | (7.23) | 22-50 | 32.56 | (8.25) | 21-43 | .605 |
| House Visual Span | 3.00 | (1.00) | 1-3 | 3.00 | (1.00) | 2-3 | .629 |
| 6-house Recall | 5.00 | (2.00) | 3-6 | 6.00 | (2.00) | 4-6 | .285 |
| Category Fluency | 57.00 | (14.74) | 38-97 | 55.56 | (13.30) | 44-76 | .805 |
| Letter Fluency | 44.84 | (10.43) | 26-66 | 44.78 | (12.43) | 29-60 | .989 |
| Digit Cancellation | 56.00 | (3.00) | 35-60 | 57.00 | (6.00) | 53-60 | .699 |
| Overall Cognition | -0.19 | (0.53) |  | -0.34 | (0.54) |  | .476 |

NB. \* Significance at *p*<.05, \*\*Significance at p<.008. The average reflects the mean (SD) for the Short Cognitive Evaluation Battery (SCEB), Category Fluency test, Letter Fluency test and Overall Cognition, and the median (IQR) for the Mini Mental State Examination (MMSE), House Visual Span and Digit Cancellation.

# Discussion

In the present study, subjective hearing disability was relatively low, 25% of our population reported hearing disability as measured by the SEAH, which correlated significantly with hearing thresholds. Only 59% of the HL group reported subjective hearing disability, which indicates that not all individuals are disturbed by their hearing impairment, in keeping with previous findings (Quaranta et al., 2014). In this sample, the use of hearing aids did not influence the limitations or restrictions associated with HL, and in fact subjective hearing disability was higher in individuals using hearing aids. Neither level of hearing disability nor the use of hearing aids had any influence on the variation in cognitive scores.

Due to the high correlation between SEAH scores, age and hearing thresholds, the lower performance reported for the Overall Cognition and the 6-house recall test were confounded by the significantly older age of the group reporting hearing disability. After age was accounted for, SEAH scores did not predict any more of the variance in cognitive performance. This change suggests that subjective hearing related disability had no direct influence on cognitive performance, in this sample of cognitively healthy participants, regardless of hearing thresholds.

As expected, the SEAH was highly correlated with levels of HL, suggesting the worse the hearing the more limitations and restrictions the individual felt. However, there was also some variability within the sample for both people with and without HL as a small number of individuals who screened negative for a HL reporting hearing related disability. This finding is supported by another study which reported a high proportion of individuals misperceive their degree of hearing disability (Moore et al., 2014) and as already alluded to in Chapter 4, a mild HL can impart a heavy burden and vice versa (Ewertsen and Birk-Nielsen, 1973). To investigate whether hearing disability was more important than hearing thresholds alone, the cognitive profiles of participants with normal hearing who reported disability were compared to that of age matched controls with normal hearing and no subjective hearing related disability. No difference in cognitive performance between individuals reporting subjective disability was found (Table 5.12), suggesting that subjective hearing disability alone had no influence on cognitive performance. A recent study has found higher levels of stress and anxiety to be associated with overestimation of HL (Kim et al., 2017), although in our sample (not statistically significant) lower rates of anxiety and depression were reported for the individuals with higher SEAH scores and therefore these factors cannot be used to try to explain this difference. The individuals who reported a hearing disability had slightly higher hearing thresholds which were still within the normal range and thus there may be to some extent, a ‘hidden’ HL. Hidden HL is a loss of high threshold auditory nerve fibres which does not affect absolute sensitivity and therefore is undetectable using pure tone audiometry (Plack et al., 2014).

Our second aim was to investigate the influence of hearing aids on hearing related disability and cognitive performance, and it was hypothesised that people with HL who wore hearing aids would report lower rates of hearing disability on the SEAH as it has been extensively reported in the literature that the use of hearing aids enhance quality of life, depressive symptoms and socialisation of the elderly (Mick et al., 2014, Acar et al., 2011, Gopinath et al., 2009). However, in our study, there was a significantly higher disability reported for individuals with hearing aids compared to those with HL who did not wear hearing aids, but this finding was confounded by the much increased severity of HL reported for the individuals who wore hearing aids compared to those who were unaided. There was also a strong positive correlation between the severity of HL and the duration the hearing aids were worn for throughout the day, but no association between the duration they were worn for and the perceived benefit or the reduction in hearing disability. This might help to explain why there was no influence of hearing aids on SEAH scores as originally predicted. A large epidemiological study investigating the role of self-reported hearing aid use on social handicap reported that hearing aid use was associated with marginally higher levels of isolation than those with HL who did not wear hearing aids (Dawes et al., 2015b), which could reflect a difference in hearing severity in those with hearing aids, corroborating our findings.

Similarly, other studies have reported hearing related disability to be higher in individuals who wear hearing aids (Quaranta et al., 2014), reflecting that the self-perception of hearing disability is an important factor to seeking hearing aid rehabilitation. Similar results were found in this study, when severity of HL was controlled for, by comparing SEAH scores between aided and unaided individuals with mild HL. There was no significant difference in hearing disability between the two groups, although the median scores were higher for the aided group suggesting they reported more hearing related limitations and restrictions. As the SEAH is a self-report questionnaire, the possibility of social desirability bias may be used to interpret this finding. It has been extensively reported that HL is untreated in the general population, which may be due to the stigma surrounding hearing aids (Kochkin, 2009). People with a mild HL who seek out hearing aids may have accepted the challenges that are associated with HL and are happy to report they have some difficulty with hearing. In the same way, people who are in denial about their HL may report that their hearing is not bad or underplay the difficulties associated with their increasing hearing thresholds.

The use of hearing aids had no influence on neuropsychological performance in our sample, after controlling for age and hearing severity. Previous results from a cross sectional sample of cognitively healthy adults reported the same findings, where use of hearing aids was not associated with higher scores on any of the cognitive tests (Lin et al., 2011a). Choi et al., (2011) reported that administration of hearing aids improved retest performance on the visual verbal learning test and words in noise test six months later, which suggests that as the speech related cognitive function improved with hearing aids this was more simply due to the fact they could hear the tests better.

Taken together this suggests that in this sample of cognitively healthy adults with and without HL, perceived hearing disability levels and the use of hearing aids did not influence cognitive performance. In the same way, there is no evidence that hearing aids influence the perceived disability associated with HL. The lack of correlation between subjective hearing disability and number of hours hearing aids were worn each day, or the perceived overall satisfaction of hearing aids suggests that the use of hearing aids alone cannot mitigate all of the challenges associated with a HL, and there must be other influencing factors.

# **Experiment 5.3 - Hearing loss, subjective hearing disability and hearing aids; their influence on cognitive change**

# 5.4.1. Introduction

When investigating the relationship between two factors, it is most interesting to see whether the association changes over time. Due to the highly confounding nature of age on both the prevalence of HL and lower cognitive scores, it is hard to separate out whether HL may independently contribute to the age related variability in cognitive performance. Experiments 5.1 and 5.2 reported the lack of influence of peripheral hearing thresholds, subjective hearing disability and hearing aids on cognitive performance in a sample of cognitively healthy adults. Therefore, it was suggested that there may be no true association between HL and poorer cognitive performance in a cognitively healthy sample of adults, when using a neuropsychological battery of cognitive tests which does not heavily rely on auditory perceptual processing. However, despite no baseline difference, there is still some evidence that HL is associated with accelerated rates of decline in test performance over time (Lin et al., 2013) and a higher risk of incident dementia (Lin et al., 2011b, Fritze et al., 2016).

As introduced in Chapter 2, previous research investigating the associations between HL and cognitive performance over time has reported varied and inconsistent findings. Lin et al., (2013a) found even after controlling for possible confounders and demographic risk factors, people with HL between the ages of 70 to 79 years old had accelerate rates of cognitive impairment compared to normal hearing participants. However, the opposite has also been shown (Gennis et al., 1991) and a recent longitudinal study following people over 10 years reported that compared to individuals with no sensory impairment, HL was not significantly associated with cognitive decline or a greater decline in MMSE scores at 5 or 10 years (Hong et al., 2016). The HL was measured using PTA but HL was categorised as being >40 dB HL in the better or worse ear (neither made a difference) and therefore some people with a mild HL may have been in the control group when in fact they have a HL, which could explain no associations. However, if the relationship between HL and cognitive decline is reflected by the severity of HL (Lin et al., 2011b, Deal et al., 2016) one might still expect to see an association. Therefore, discrepancies in the outcomes are heavily dependent on the methodology and the tools used to measure both HL and cognition. The limited battery of cognitive tests used and over reliance on the MMSE means the results are not easily generalisable, as discussed earlier there are many factors which can influence MMSE performance. Similarly, how cognitive decline and dementia are defined in these studies can influence the conclusions, as a decrease in 1.5 points on the MMSE over 25 years (Amieva et al., 2015) does not indicate a cognitive impairment or an increased risk of dementia, rather reflects the natural association of age on MMSE performance (Crum et al., 1993).

According to the sensory degradation hypothesis, HL drives cognitive impairment, or the common cause theory where there is another common factor leading to declines in hearing acuity and cognition, one might expect the progression of HL to predict the decline in cognition. Many of the studies have employed self-report measures of HL and even those with full audiometric batteries have reported HL at baseline only, and therefore it is not known how hearing thresholds change with cognitive performance.

Therefore it remains to be investigated whether HL and subjective hearing disability may influence changes in cognition over time and whether decline in cognitive performance is associated with the decline in hearing thresholds, in the same cognitively healthy sample. This would help us to understand whether the increased rate of cognitive decline reported for people with HL can be identified as short-term effects of normal ageing, or whether this is associated with pathological cognitive decline as it has been previously reported. The primary outcomes of Experiment 5.3 were to identify a change in cognitive performance over a one year period due to an interaction between a) HL groups, b) decline in hearing thresholds, c) hearing disability scores, and d) whether the use of hearing aids has any influence on cognitive change.

Due to the short follow up time within the constraints of the PhD, much variation in cognitive performance between baseline and the follow up retesting would not be expected. Therefore, for the HL group a difference between high and low performers with HL will be expected, as the hypothesis is that if there were a decline in cognitive performance, this would be more prominent in the group with the lowest cognitive scores at baseline. In keeping with the sensory deprivation hypothesis, it would be expected that people with HL would decline over time compared to those with normal hearing, and therefore a secondary hypothesis states that there will be a decline in cognitive scores in the Low performance, HL (Low, HL) group relative to the three other groups. Similarly, to investigate the common cause hypothesis, it is proposed that hearing decline will be associated with cognitive decline rather than baseline hearing performance. When investigating the indirect impact of hearing related disability on cognition, the hypothesise is that hearing disability will be associated with decline in performance over time, but due to the results of Experiment 5.2, it is not expected that hearing aids will have any influence on the relationship.

# 5.4.2. Methods

## Participants and procedure

Only 101 of the 112 participants recruited to Experiment 5.1 (5.2.2.2) consented to be approached to repeat testing at approximately 12 months follow up. Eighty four participants (83% of original sample) were included in the follow up analysis, reason for drop out reported in 5.4.3.1. The interval between baseline and retesting ranged between 11 and 13 months, with the majority of patient’s second assessment being 12 months post initial assessment.

The protocol for neuropsychological assessment was as described in 5.2.2.3, hearing assessment as described in 5.2.2.2 and the SEAH was administered as described in 5.3.2.1. Ethical approval was as described in 5.2.2.1. All participants gave their written informed consent.

## Data analysis

Statistical analysis was undertaken using the same parameters defined in 5.2.2.4.

In order to compare the differences between participants who were followed up and those who dropped out, the Kolmogorov-Smirnov test was chosen as a test of normality, parametric and non- parametric independent samples analysis was employed for continuous data, and χ² test was employed for categorical variables.

Parametric or non-parametric repeated measures analysis was employed to compare performance between Time 1 (T1) and Time 2 (T2) for the three measures of neuropsychological assessment, hearing thresholds (PTAv) and subjective hearing disability (SEAH). A series of mixed factorial ANOVAs were then undertaken to investigate any interactions with the variable of interest and neuropsychological performance over time.

For cognitive performance, Mixed Factorial ANOVA was conducted for the tests which showed a graphical difference between T1 and T2, with ‘Time’ as the within groups variable and ‘Group’ as the between groups variable. Time consisted of two levels (T1 and T2) and group was four levels (as defined in 5.2.2.3.3, High H, High HL, Low H, Low HL). Age was included as a covariate. The threshold for significance was adjusted to correct for multiple comparisons between the 4 groups to *p* < 0.0125.

To try to explain why differences were reported for interactions with group and time, post hoc analysis was conducted to investigate the effects of education using the non-parametric Kruskal Wallis H- Test with pairwise comparisons between the 4 groups, and One-way ANOVA with Bonferroni correction to compare age between the 4 groups.

Secondly, to identify whether decline in hearing thresholds was associated with a decline in cognition, a Mixed Factorial ANOVA was conducted to compare the main effects of Time (within groups variable) and Hearing Decline (between groups variable) and the interaction effect between Time and Hearing Decline on cognitive performance, when age was included as a covariate. Again, Time consisted of two levels (T1 and T2) and Hearing Decline consisted of two levels, no decline (less than 5 dB change in threshold) or decline (>5 dB increase in PTAv threshold).

To identify whether subjective hearing disability had any influence on cognition, a third Mixed Factorial ANOVA was conducted to compare the main effects of Time (within groups variable) and Hearing Disability (between groups variable) and the interaction effect between Time and Hearing Disability on Overall Cognition, with age as a covariate. Again, Time consisted of two levels (T1 and T2) and Hearing Disability consisted of two levels, presence or absence of hearing disability as defined at T1.

Lastly, to investigate the role of hearing aids on cognition, controlling for the effects of age and hearing levels, the fourth Mixed Factorial ANOVA compared the main effects of Time (within groups variable) and Hearing aid use (between groups variable) and the interaction effect between Time and Hearing aid use on Overall Cognition for participants in the mild HL group.

# Results

## Participants

The reasons for the drop out are shown in Table 5.15 below. There were no differences in demographics between participants who were recruited to the follow up and those who dropped out (Table 5.16). However, as shown in Table 5.17, there was a significant difference in terms of dropout rates between high and low performers at T1 (χ² (1) = 5.95, *p* = .015), where the odds of dropping out was 4.38 times higher for low performers compared to high performers.

**Table 5.15.** *Reasons for non-follow up*

|  |  |
| --- | --- |
| Reason for drop out | Number of participants |
| No reply- no reason given | 5 |
| Not contacted | 1 |
| Could not contact (change of contact details) | 4 |
| Not well enough (change in health status) | 5 |
| Refused (worried about results) | 2 |
| Total | 17 |

**Table 5.16.** *Demographic differences between the participants who were followed up and not*

|  |  |  |  |
| --- | --- | --- | --- |
|  | Drop out (n=17) | Follow up (n=84) | Significance |
| Age | 66.35 [13.42] | 65.57 [11.67] | .825 |
| Education | 14.41 [3.64] | 15.32 [3.16] | .348 |
| Gender (M/F) | 5/12 | 33/51 | .443 |
| Handed (R/L) | 14/3 | 75/9 | .420 |
| Subjective Hearing loss | 8 (47%) | 32 (38%) | .491 |
| CV risk factors | 5 (29%) | 30 (36%) | .618 |
| Depression | 4.88 [4.94] | 3.62 [3.71] | .329 |
| Anxiety | 5.94 [5.70] | 3.93 [4.44] | .184 |
| SEAH | 21.41 [19.53] | 19.06 [17.97] | .651 |
| Hearing Loss | 9 (53%) | 31 (37%) | .218 |

N.B. \*Significant at the *p*< .05 level. Standard deviation [SD] is reported in square brackets

**Table 5.17.** *Follow up and dropout rates for high and low performers*

|  |  |  |  |
| --- | --- | --- | --- |
|  | Dropout | Follow up | Total |
| High Performer | 4 | 47 | 51 |
| Low Performer | 13 | 37 | 50 |
| Total | 17 | 84 | 101 |

## Test Performance over time

### Neuropsychological performance

On average, there was a trend for the same or improved performance on the cognitive testing at T2 compared with scores at baseline (Table 5.18). Overall, there was no significant difference between performance at T1 and T2, except for the Letter Fluency task where performance was significantly higher at T2, *t* (83) = -6.16, *p*<.001, *d* =.41.

**Table 5.18**. *Paired samples showing differences in average performance on tests over time*

|  |  |  |  |
| --- | --- | --- | --- |
| Cognitive test | Time 1 | Time 2 | Significance |
| MMSE | 29.00 (1.00) | 29.00 (2.00) | .034\* |
| SCEB | 34.90 (6.82) | 35.27 (7.52) | .488 |
| House span | 3 (1.00) | 3 (1.00) | .160 |
| House recall | 5 (1.00) | 6 (1.00) | .043\* |
| Category Fluency | 61.88 (15.03) | 62.92 (15.70) | .191 |
| Letter Fluency | 45.05 (11.06) | 49.54 (11.55) | **<.001\*\*** |
| Digit Cancellation | 57 (3.00) | 57 (4.00) | .691 |
| Overall Cognition | 8.23 x10¯4 (0.55) | 14.29 x10¯4 (0.57) | .942 |

NB. \* Significance at *p*<.05, \*\*Significance at p<.008. The average reflects the mean (SD) for the Short Cognitive Evaluation Battery (SCEB), Category and Letter Fluency tests and the Overall Cognition composite *Z* score, and the median (IQR) for the Mini Mental State Examination (MMSE), House Visual Span and Digit Cancellation.

### Hearing assessment

Over the 12 month period, as expected, there was a decline in hearing acuity across the sample resulting in increased PTAv thresholds. These thresholds increased between 0 and 23.75 dB, with 9 participants classified as having hearing decline (threshold increase ≥5 dB) and thus 75 participants hearing thresholds remaining stable. Individuals whose hearing declined were significantly older (Mean= 77.22 years, SD= 4.84) than individuals whose hearing remained stable (Mean= 64.17, SD=11.47), *t* (82) = -3.36, *p* =.001, *d* =1.48, and had higher baseline hearing thresholds. As expected, there was a significant interaction between HL group and decline in hearing thresholds over time (F (1, 82) = 18.47, *p*< .001), reflecting the progressive nature of ARHL.

### Subjective hearing disability- SEAH

There was a strong positive correlation between scores on the SEAH at T1 and T2 (*r*S = .902, *p*< .001) as shown on Figure 5.6. The difference in scores between T1 and T2 ranged between -39 and +19, with a median difference of 0, IQR = 8. However, this difference was not uniform for participants with and without HL, where there was a significant interaction between HL group and change in SEAH scores over time (F (1, 82) = 4.36 , *p*= .040). This interaction was not in keeping with the decline in hearing thresholds, and showed that subjective hearing disability levels for people with normal hearing remained relatively stable or increased slightly between T1 and T2, and people with HL were more likely to report lower levels of disability at T2 compared to T1. For example, the red circles on Figure 5.6 show two individuals who felt the disability associated with their HL had dramatically improved, due to new hearing aids.



**Figure 5.6.** *The relationship between SEAH scores at Time 1 and Time 2*

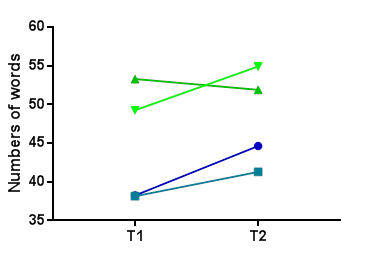
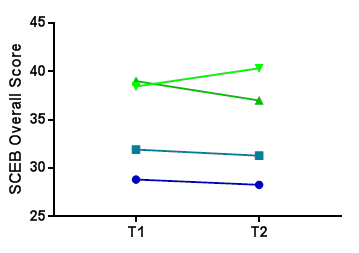
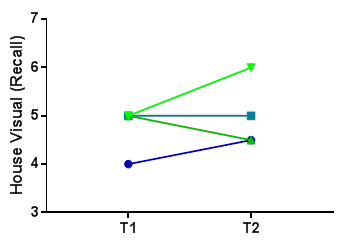
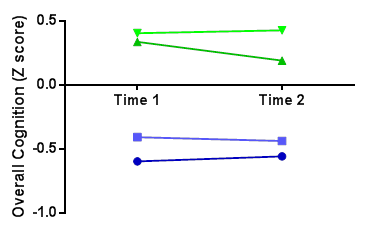
NB. The red circles represent participants with hearing loss whose subjective disability improved dramatically due to new hearing aids between T1 and T2.

## Interactions with hearing and neuropsychological performance over time

### 5.4.3.3.1. High and low performers, per hearing loss group and cognition

Although overall there was no difference in performance on the cognitive tests between T1 and T2 (Table 5.17), there was an inconsistent pattern across the four groups of high and low performers with and without HL. For most of the groups there was a trend which reflected the overall outcome of very similar or slightly increased performance between T1 and T2, however the high performance group with HL (High, HL) tended to show a decline in performance between T1 and T2 on many of the tests, as shown in the interaction graphs (Figure 5.7 A-D). This trend was most clearly seen for the Overall Cognition (Figure 5.7A), SCEB (Figure 5.7B), House Visual Span recall (Figure 5.7C) and Letter Fluency Task (Figure 5.7D).

The results of the Mixed Factorial ANOVA showed a significant interaction between time and group for the Letter Fluency task only, after controlling for MMSE levels. There was a significant main effect of time (F (1, 79) =18.62, *p*<.001, *r*=.43), indicating the significant improvement in performance at T2 compared to T1 overall. In addition, there was a significant main effect of group on overall Letter Fluency, (F (3, 79) = 10.39, *p*=<.001). Pairwise comparisons revealed significant differences between Letter Fluency performance between high performers and low performers with and without HL (all *p* <.0125). There was a significant interaction effect between Group and Letter Fluency performance over time, indicating a non-uniform pattern throughout the groups (F (3, 79) = 3.99, *p*= .011). This interaction effect can be clearly seen in Figure 5.7D, where all groups increased performance between T1 and T2, but the High, HL groups overall performance decreased at T2.



**A**

**B**

**C**

**D**



**Figure 5.7.** *Difference in neuropsychological performance between Time 1 and Time 2 for the four groups*

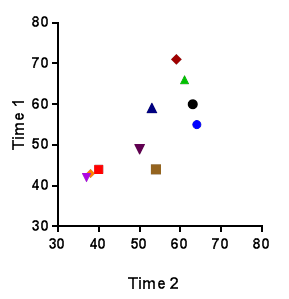
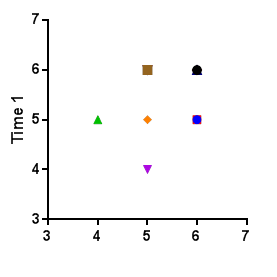
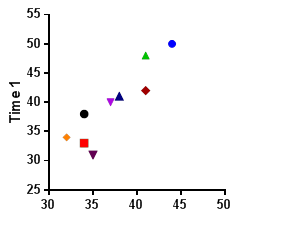
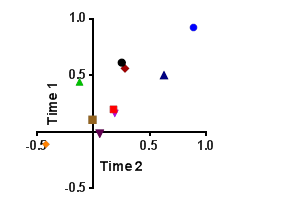
NB. A) Overall Cognition (composite z-score), B) Short Cognitive Evaluation Battery (SCEB) C) *House Visual recall D) Letter Fluency Task.*  Key: Low = low performance, High = high performance, HL = hearing loss, H = hearing.

To investigate why individuals in the High, HL group declined between T1 and T2, further analysis was undertaken. As reported in Table 5.5, high performers were significantly younger with more years of education than the lower performers. Investigating age and education for the four groups (Table 5.19) showed the same result, there was a significant difference for age (F (3) =25.39, *p<.001)* and years of education (*U* = 14.67, *p* = .002), between the four groups. However Bonferroni post hoc comparisons showed that there was only a significant difference between the age of High, H and all of the other three groups, and similarly pairwise comparisons showed that there was only a significant difference in years of education between High, H and both of the low performance groups. Therefore, although people in High, H group were significantly younger than those in the High, HL group there was still a significant interaction after controlling for the effects of age. Although on average, years of education were higher for the High, HL group, there was no significant difference in years of education compared to any of the other groups and therefore suggesting that years of education could not account for the difference in performance over time.

**Table 5.19.** *Range and average age and education for the four groups*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Mean Age (SD) | Age range | Median Education (IQR) | Education range |
| Low, HL (n=22) | 76.32 (7.42) | 62-93 | 12.5 (6) | 9-20 |
| Low, H (n=14) | 69.64 (7.99) | 53-80 | 13.5 (6) | 10-19 |
| High, HL (n=10) | 68.10 (8.95) | 55-80 | 17 (2) | 12-18 |
| High, H (n= 38) | 57.18 (9.12) | 41-73 | 17 (4) | 11-21 |

To evaluate whether the decline was associated with certain individuals rather than on the group level, scatterplots were produced for the four tests previously reported to show the trend with decreased performance between T1 and T2 for the 10 participants in the High, HL group, Figure 5.8 shows that on the individual level, there is no participant(s) who continuously decline across all of the tests more than others.



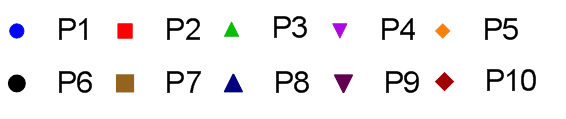
**A**

**B**

**C**

**D**





**Figure 5.8.** *Individual performance from High, HL group on Time 1 and Time 2*

NB. A-D shows performance on individual cognitive tests where A) Overall Cognition, B) Short Cognitive Evaluation Battery (SCEB), C) Visual House Recall, D) Letter Fluency. P refers to each participant. All participants scored within normal limits for each test at Time 1 and Time 2.

### Decline in hearing thresholds and cognition

The results of the Mixed Factorial ANOVA after controlling for age, showed there was no significant interaction between hearing decline and time (F (1,82) = 2.36 , *p*= .128), suggesting that there was no difference in change in Overall Cognition over time for those whose hearing declined or remained stable (Figure 5.9). Therefore although individuals whose hearing declined had lower performance at baseline and follow up, the decline in hearing thresholds did not predict decline in cognitive performance in this sample.



**Figure 5.9.** *Difference in Overall cognitive performance between Time 1 and Time 2 for two groups whose hearing remained stable or declined over time.*

The variance in hearing decline was great throughout the sample, as reported earlier, between 0 and 23.25 dB. The mean increase in hearing thresholds for each group is shown in Table 5.20, where on average participants increase in thresholds was 2.03 dB (SD= 3.37). However, the range of decline was up to 23.25 dB for the Low, HL group, where 2 participants hearing declined significantly more than the mean, 13 and 22 dB respectively. Figure 5.10 shows their individual performance (A and B) on each of the raw tests, where there was a decline in performance on Category Fluency and Digit Cancellation for participant A (shown in pinks), and the MMSE, SCEB, House Recall, Category Fluency and Digit Cancellation for participant B (shown in greens). Therefore individuals, whose hearing declined more rapidly, may show a change in cognitive performance.

**Table 5.20.** *Mean decline in hearing (increase in thresholds) for the four groups*

|  |  |  |
| --- | --- | --- |
|  | Decline (SD) | Range |
| Low, HL (n=22) | 5.07 (4.96) | 0-22 |
| Low, H (n=14) | 1.11 (1.62) | 0-5 |
| High, HL (n=10) | 1.90 (1.97) | 0-5 |
| High, H (n= 38) | 0.64 (1.36) | 0-6 |

NB. The increase in hearing thresholds is measured in dB.



**Figure 5.10.** *Cognitive Performance at Time 1 and Time 2 for the two participants (A and B) whose hearing thresholds declined significantly.*

NB. Neuropsychological tests where House= House Span Recall, CF= Category Fluency, LF= Letter Fluency and Digit= Digit Cancellation. T1= Time 1, T2= Time 2.

### Subjective hearing disability and cognition

As there was no change in overall SEAH scores between T1 and T2 (5.4.3.2.3.), a change in cognitive scores between T1 and T2 was compared between individuals who reported hearing disability on the SEAH at T1 and those who reported no hearing related disability. There were 21 participants in this sample who reported subjective hearing disability at T1 (27 in total at T1 but 6 dropped out), and therefore 63 who reported no debility. There was no significant interaction between time and hearing disability (F (1, 81) = 0.399, *p*= .530), suggesting that there was no difference in Overall Cognition over time for those individuals who reported higher levels of hearing disability at baseline. Therefore, subjective hearing disability did not influence cognitive change.

### The use of hearing aids and cognition

To investigate the effects of hearing aid use on neuropsychological performance over time, hearing aid wearers with mild HL were compared to the group of matched unaided participants with mild HL. Twenty four out of the thirty one participants with mild HL were followed up, so at T2, there were 14 hearing aid users and 10 non hearing aid users. There was no interaction between hearing aid use on Overall Cognition over time, (F (1, 22) = 1.40, *p*= .250), suggesting that the use of hearing aids did not influence change in cognitive performance.

# Discussion

In this sample as a whole, there was no difference in cognitive performance between baseline and at 1 year follow up, except for a significant improvement on the letter fluency task. These findings were expected, as one would presume a practice effect to have an influence on repeat neuropsychological testing within the limited follow up period (Salthouse, 2016). As the influence of practice effects on cognitive tests have been shown to be global, and not related to any demographic characteristics (Duff et al., 2012), it would be expected that these would apply to the sample as a whole. However, a difference in change in performance over time for the high performer with HL (High, HL) group was observed, which yielded a significant interaction (*p* <.0125) between group and time on performance during the Letter Fluency Task (Figure 5.10).

This finding was contrary to the hypothesis, that low performers with HL would be more likely to decline compared to low performers with normal hearing or high performers at baseline. Although the same trend was shown for many of the cognitive tests, the report of a significant interaction for the Letter Fluency task suggests that there may be some difference or decline in the executive abilities of members of this group (Shao et al., 2014). A recent study found that education has an influence on both category and letter fluency performance, which is more apparent or pronounced in individuals with HL compared to normal hearing participants (Santos et al., 2014). Similarly, age has an influence on processing speed abilities which can lead to declines in verbal fluency tasks (Elgamal et al., 2011). However, in our study, age and education levels were not significantly different between the High, HL group compared with other groups suggesting that age and education do not influence change in performance in our sample. Similarly it is unlikely that the results could be explained simply as a regression towards the mean, as this same trend would not be expected for most of the tests (Figure 5.7 A-D) in the High, HL group only. The High, HL group also reported lower performance on the MMSE over time (results not shown) suggesting a more global deterioration rather than the effects of chance on any of the tests.

A prospective cohort study intending to identify factors associated with successful ageing in elderly adults reported similar findings (Tomioka et al., 2015). A highly functioning subsample of older adults who at baseline reported the maximum score on activities of daily living, intellectual activity and social role were investigated over a five year period, to examine whether self-reported HL was associated with a decline on any of the above scales, after controlling for demographic differences and geriatric syndromes, including depressive symptoms, cognitive impairment, falls and visual impairment amongst other variables. The authors reported that there was no difference in decline on activities of daily living between those with and without HL (OR= 1.07, 95% CI= 0.76 – 1.48), however there was a statistically significant difference in the likelihood of experiencing decline in intellectual activity (OR= 1.39, 95% CI= 1.04 – 1.86) and social role (OR= 1.34, 95% CI= 1.02 – 1.76), (Tomioka et al., 2015), therefore showing over 5 year period, high performers with HL are likely to decline more than high performers without HL. Unfortunately, the authors did not publish the findings relating to low performers with and without HL, but the decline with time in high performers with HL is in keeping with our results.

Due to the fact there is no difference in age, education, subjective hearing disability or increased rate of hearing decline in this group compared to the others, this finding is hard to interpret over a one year follow up. The possibility that this group difference may be influenced by one or a few members declining and thus affecting the group average was discarded, as in Figure 5.8; there was no consistent decline in performance in any of the members of the High, HL group. One possible explanation could be that over 75% of participants who dropped out before T2 were low performers and therefore there might have been a difference in performance of the Low, H or Low, HL groups had the complete sample been followed up. However, as only 2 individuals in the High, HL group dropped out, it is unlikely there would have been a difference in performance between T1 and T2 in this group.

As HL is a progressive disorder, a decrease in hearing thresholds was expected to have been observed in this population over the 12 month follow up.In this sample, there was an average decline in hearing thresholds of 2.03 dB which is in keeping with the literature (Lin et al., 2011b, Kiely et al., 2012). There was a significant interaction between group and time on cognitive performance; however, this suggested that the group whose hearing declined actually improved between T1 and T2, rather than declined. Therefore, decline in hearing levels were not related to a decline in cognition in our sample.

However, two participants with HL (A and B) had a decline in hearing much larger than expected over the one-year period, and this reflected a decline on many of the cognitive tests (Figure 5.10). It has been previously reported that decline in hearing thresholds were related to a decline in cognitive performance (Lin et al., 2011b), where individuals who developed dementia had a greater yearly decline in hearing ability. Similarly, Kiely et al., (2012) suggested that probable cognitive impairment predicted annual rates of change in hearing thresholds, where hearing decline was much more severe in individuals with cognitive impairment. Therefore the larger decline in these participants in relation to the decline in cognitive performance could suggest that in these individuals another common or pathological factor was the decline of both processes, therefore lending evidence to the common cause hypothesis. However, as there were only two participants and the reduction in hearing acuity was so large for such a short amount of time, the influence of experimental error cannot be discounted. As already discussed in 5.2.4, problems with the methodology used to measure hearing may account for some of this variance between thresholds.

Other areas of interest were to investigate the role of subjective hearing disability and hearing aid use on cognitive function over time. It was observed over the 1 year study period that there was no significant change or decline in SEAH scores, despite the decline in hearing levels. In fact, many individuals with a HL actually reported lower SEAH scores at T2. There was no interaction between subjective hearing disability and time on Overall Cognition, suggesting that subjective hearing disability did not influence cognitive performance for these tests, in this sample.

In our sample, there was no difference in cognitive performance over time in the group of individuals with mild HL who were aided or unaided, suggesting that hearing aids did not have an effect on cognitive performance in our battery of tests. However, as there was not much change in cognition over time, the benefits may be underrepresented and again a longer follow up would help to ensure results are generalisable. Although hearing aid influences on cognitive tests are inconsistent, there are reports of an improvement on cognitive function in adults with HL (Choi et al., 2011). However, as the cognitive test employed by Choi et al., (2011) was one of auditory verbal learning, these results may be confounded by the fact that improved scores may reflect the ability to better hear the words with hearing aids.

To summarise, HL had an influence on decline in cognitive performance in individuals who were high performers at baseline compared to low performers or those with normal hearing. Decline in hearing levels did not significantly predict decline in cognition and subjective hearing disability, and the use of hearing aids had no influence in cognitive performance. Taken together, it could be that HL alone may lead to a reduction in cognitive scores, but a longer follow up period is needed to ensure results are generalisable.

# General Disussion

Our findings suggest that in a group of cognitively healthy adults, the presence of HL did not influence cognitive function when using a battery of tests designed to decrease perceptual effort and the overreliance on auditory abilities. Similarly, subjective hearing disability and the use of hearing aids had no influence on cognitive testing. However, over a one year follow up, after controlling for age, a decline in performance was reported on a few cognitive tests for individuals with HL, who were high performers at baseline. Therefore, due to ensuring that people with HL are not being disadvantaged by the testing procedure it is assumed that this difference is a real finding and something related to their HL, or a common factor driving a lower cognitive performance.

There was no difference in cognitive performance in the volunteer sample at baseline, which is contrary to some published literature with much larger population sizes (Lin, 2011, Lin et al., 2013). For example, a study by Lin et al., (2011a), reported after controlling for age, education and other demographic variables, HL was independently associated with tests of memory (Free Recall) and executive function (the Stroop Test) in a cognitively healthy sample of 347 participants. However, the effect sizes were rather small; suggesting that a 10 dB increase in HL would lead to -0.58 point reduction on the Free Recall and -0.91 point reduction on the Stroop Test, with *p*-values that were not corrected for multiple comparisons (Lin et al., 2011a). They included ten different tests of cognitive function in the battery and thus the corrected threshold should have been set at *p* <.005 (Benjamini and Hochberg, 1995), whereas these reported *p* values were *p* <.05 and *p* <.01 respectively. Therefore, there is a chance that the results reported are due to a type one error.

It is interesting that the link was with executive function, as also reported by Lin (2011), although different measures were used, the follow up study found a decreased performance on the Letter Fluency Task which encompasses some aspects of executive function. Due to the larger sample sizes it could be that these results are more in keeping with those of the general population, and due to the cross sectional nature, the participants with HL who performed lower on the tests could have had similar profiles to those reported here, but they might have been at a later stage in their cognitive trajectory. There is some evidence to suggest that declines in executive function may precede dementia by 2-3 years (Grober et al., 2008) and may be an early manifestation of preclinical AD (Chen et al., 2001). Unfortunately, our follow up period is too short and the authors above have not published any longitudinal data on these cohorts and so decline in individual performance cannot be assumed, but the individuals who performed lower may be the ones at risk of cognitive impairment.

Another cross sectional study of 459 participants over the age of 85, aimed to investigate the link between cognitive function (using the MMSE and a small battery of tests which assessed memory, executive functioning and speed of processing) and HL. Over 85% of the sample screened positive for a HL, and the authors reported that severe hearing impairment (>64 dB HL) was associated with significantly lower MMSE performance compared to participants with normal hearing or mild HL, but no association was found on any other tests (Gussekloo et al., 2005). The authors proposed that this association between sensory impairment and cognitive function as described by the MMSE, may be partly based on the practical disadvantages of sensory impairments (Gussekloo et al., 2005), and the problems with the MMSE which have already been alluded to in previous sections. Therefore, these results are in keeping with our cross sectional findings, that people with HL do not perform differently on any of the cognitive tests, and perhaps after controlling for the questions which are reliant on hearing acuity, the association with the MMSE might also disappear. Therefore, if any differences occur over time, this may indicate a pathological factor over and above the normal age associated declines in hearing acuity and cognitive abilities.

In terms of the main hypotheses proposed to link HL and cognition, our findings do not directly support nor discount any. For example, the information degradation hypothesis would expect people with HL of the same age to perform worse on the cognitive tests due to more effortful processing, limiting the resources available to undertake the cognitive task (Peelle et al., 2011). However, taking into account the non-verbally reliant nature of the tasks and the average levels of HL in this sample, it can be assumed that peripheral deficits were not so severe to increase processing demands at the detriment of cognitive function. This interpretation is supported by a recent study which stated that although HL limits the resources available for language comprehension on various tasks, (DeCaro et al., 2016) the regression analysis showed hearing acuity only contributed a significant variance to performance under the more challenging processing situations, i.e. the more complex linguistic tasks, presented at a below normal speech conversational level (DeCaro et al., 2016). In this study, although the level of presentation was not recorded, normal speech level is approximately 65 dB (Kramer, 2014), so it is assumed there were no increased perceptual demands on the individuals with HL, and thus cognitive performance would not be affected. Therefore, if care is taken to administer cognitive tests without an overreliance on auditory perception, there should be no difference in baseline cognitive performance of people with and without HL of the same age and thus limiting the possibility of overdiagnosis of cognitive impairment. Further evidence to support this notion comes from hearing aid studies which suggest that over a limited follow up, people with HL when aided appear to improve their cognitive scores (Acar et al., 2011). Although not directly tested, there was no difference in cognitive performance across the sample for people with and without hearing aids, even after controlling for age and hearing levels, again suggesting that perceptual demands were not increased for those without a hearing aid.

In our study there is evidence to support the sensory deprivation hypothesis, as people with HL at baseline had decreased cognitive performance over time, however only in a sample of individuals who were initially higher performing. Due to the fact that there was no difference in baseline characteristics between the groups, the lower performance at T2 might be more likely explained by the common cause hypothesis. Therefore this difference in performance in one group only could occur due to a common factor leading to a change in the normal hearing and cognitive trajectories in this group of people, which may alter and increase the risk of clinical cognitive decline in the future. However, to support the common cause hypothesis completely one might expect that there would be a linear association between decline in hearing thresholds and decline in cognition over time, which was not seen in this sample.

These results do not provide any evidence for the indirect mechanism of the psychosocial hypothesis, as there was no difference in cognitive performance at baseline or over time in individuals with higher SEAH scores, where subjective disability scores were unrelated to cognitive function after controlling for hearing levels. There is no association between SEAH scores and the questionnaires of depression and anxiety, showing the SEAH is a very selective tool for measuring hearing related dysfunction. However, this was a volunteer sample and so the low levels of depression and anxiety reported could be due to the motivation of the participants to take part in research (King et al., 2015), which could explain the lower levels and lack of association, between these factors. In this study, subjective hearing disability was suggestive of a more severe HL and the presence of hearing aids. Direct comparisons could only be drawn between disability and hearing aid use in a sample of individuals with a mild HL and thus the influence of subjective disability and depression in individuals with a more severe HL might be underestimated. However, recently a large epidemiological study has published similar results suggesting that HL is not necessarily associated with higher levels of depression (Fritze et al., 2016) and thus our sample might actually be more representative of general cases of HL in the elderly population. It would be interesting to investigate subjective hearing disability and the associations with cognitive performance in a group of participants with subjective memory complaints, to establish whether subjective hearing difficulties play any role in every day cognitive functioning.

There are some limitations to the methodology and sampling methods used in these three experiments. Firstly, many neuropsychological tests are not an ideal way to investigate cognitive differences between cognitively healthy individuals, as the raw scores are often an integer of a determined range, where a healthy population will elicit a skewed distribution towards the upper end of the range leading to ceiling effects concealing any potential differences between groups (Uttl, 2005). There is a minimal variation in the cognitive scores, and due to these ceiling effects it may not be possible to distinguish a true difference between the groups with and without HL, or decline in performance over time. If there is a small decline in cognition in a group, to be statistically significant this would have to be observed in a relatively large sample to have power. Also, as the theory was to investigate which areas individuals with HL may selectively decline in, multiple tests were utilised to assess different domains of cognition, and therefore the correction for multiple comparisons for the battery of tests may further reduce potential significant effects. For example, another longitudinal study which followed participants over 10 to 12 years found that people with HL at baseline (which was based on observations of hearing difficulties during the testing or interview) had a faster decline of 0.26 points on the 3MS-R per year compared to individuals with normal hearing. This study lends support to our findings that there was a marginal decline in performance which might not be significant in other tests for the High, HL group.

Similarly, other limitations are with the equipment used to assess hearing levels, as described in 5.2.4. Although the warble tone has strong test-retest reliability (Arlinger and Jerlvall, 1987), the large decrease in hearing levels between T1 and T2 for two individuals may reflect a problem with the testing procedure at one of the stages, as it is unlikely that hearing would decline that dramatically over a one year period. It is interesting that there was a decline on many of the cognitive tests as shown in Figure 5.10, which if hearing thresholds were correct could imply some evidence to support the common cause hypothesis. Again, it would be useful to follow the participants up for a longer period of time to establish further changes in hearing and cognitive performance.

As with any volunteer sample, there are differences between the personalities and universal health status between the sample and the general population (King et al., 2015). Similarly, volunteer samples traditionally have higher levels of education (Ganguli et al., 1998) which is in keeping with these results. As the sample was highly educated and due to the influence education has on cognitive performance and cognitive reserve (as reported in 1.4.1.1) our results may not be directly generalisable to wider population. However, the demographics associated with HL in this sample, such as increased age, male prevalence and increased numbers of cardiovascular risk factors support the current literature proposing the risk factors for ARHL (Agrawal et al., 2008, Lee, 2013) and are in keeping with many other cross sectional population studies (Lin et al., 2011b) Therefore, it may be suggested that this sample of individuals with and without HL are representative of the differences found within the wider population, and therefore our results regarding similarities and differences in cognition would be a reliable indicator of cognitive performance in the general population.

As age has such an influence on cognitive performance, a prospective case control methodology in hindsight might have allowed us to gleam more information about hearing levels and their direct association with cognition and the risk factors for cognitive decline. However, as ARHL by definition is associated with ageing, matching groups may not be easy to accomplish for the younger or older extremes which have been presented here.

To summarise, after taking age into account, no differences in baseline cognitive performance between people with HL and normal hearing were reported, regardless of level of subjective hearing disability and the use of hearing aids. A suggestion is that other studies which have found the contrary in cognitively healthy participants may be overestimating the influence of HL, as these individuals may be disadvantaged by the testing procedures, most commonly the MMSE or auditory verbal tests. Alternatively, cross sectional studies are not ideal to study healthy cognition, as it is not known who may be in the prodromal stages of pathological cognitive impairment, which may confound the associations. A difference in cognitive performance over time for individuals with HL who performed above average at baseline was found at the one year follow up when compared to individuals with normal hearing and low performers at baseline with HL. However, the conclusion is not one of cognitive decline in these individuals, as their performance was still above average and in keeping with age norms, thus a longer follow up would be needed to establish the foundations behind this group difference. Self-reported hearing disability and the use of hearing aids did not influence any change in performance at baseline nor over time, and similarly a decline in hearing did not predict decline in cognitive performance.

# Chapter 6: Central auditory processing and the links with cognition

# Introduction

Typically, presbycusis was believed to be solely due to degeneration of the peripheral hearing structures, where most commonly loss of outer hair cells or atrophy of the stria vascularis is found (Liu and Yan, 2007), (see Chapter 5 for a detailed description). However, animal model studies have also shown age related degeneration of the central components of the auditory system (Hoeffding and Feldman, 1988), which can be found secondary to peripheral presbycusis or in the absence of any peripheral deficits (Willott, 1996, Walton et al., 2002). Individuals with advanced presbycusis may also report difficulty hearing in noisy environments or difficulty with sound localisation, which can occur regardless of whether they have normal peripheral hearing threshold levels (Gates, 2012b). Central presbycusis is epitomised by difficulty with speech comprehension against a noisy background and difficulties in shifting or sustaining attention (Gates et al., 2002, Gates, 2012a, Gates, 2012b), but it is not as clearly understood as peripheral HL, and is only recently gaining recognition for its importance in ageing, auditory dysfunction and links with executive functioning.

## 6.1.1. The structure and function of the central auditory processing pathway

The structure and function of the human central auditory processing pathway has not been as well defined as the other sensory processing systems, such as the visual and somatosensory pathways (Langers et al., 2005). Functional MRI techniques and PET scanning have helped us to understand the functional interactions between the subcortical auditory nuclei up to the primary auditory cortices (Barrett et al., 2016). Afferent neurons of the cochlear branch of the vestibulocochlear nerve run from the organ of Corti, exiting the inner ear through the internal auditory canal and laterally entering the brainstem and the pontomedullary junction (Kramer, 2014). There are five pairs of primary auditory nuclei, the cochlear nucleus (CN), superior olivary complex (SOC), lateral lemniscus (NLL), inferior colliculus (IC) and the medial geniculate nucleus (MGN) of the thalamus. These afferent fibres from the cochlea first synapse with the CN on the ipsilateral side. The majority of neural output from the CN travels to the contralateral NLL or IC, whilst some synapse with the ipsilateral or contralateral SOC (Langers et al., 2005, Kramer, 2014). Signals from the SOC ascend both ipsilaterally and contralaterally to the IC, where they then leave the midbrain and continue via the MGN to stimulate the primary auditory cortex (Kramer, 2014, Barrett et al., 2016), located in Heschl’s gyrus of the temporal lobe (Morosan et al., 2001). Auditory information is processed in the primary auditory and auditory association areas of the cortex to mediate conscious awareness and perception of sound (Hackett, 2015). Although the functional roles of the human auditory cortices remain poorly defined, and the exact location of the auditory cortical areas are not yet known (Hackett, 2015), evidence from non-human primate studies have helped to understand the auditory cortex is largely confined to the superior temporal gyrus. Cytoarchitectonically, the primary auditory cortex is defined as Brodmann area 41, in the depth of the sylvian fissure, occupying most of Heschl’s gyrus and surrounded by the auditory association cortex, Brodmann areas 42 and 22 (Brodmann, 1909, Cechetto and Topolovec, 2002).

Interestingly, although the auditory cortices appear very structurally similar, the left auditory cortex is consistently larger (Geschwind and Levitsky, 1968, Bonte et al., 2013) underlying the hemispheric specialisation (Barrett et al., 2016). The right auditory cortex is mainly responsible for processing music, tonal and vocal sounds and the left for processing language (Belin et al., 2000, Hickok and Poeppel, 2000, Rogalsky et al., 2011, Evans et al., 2014). Right and left auditory cortices are connected by the corpus callosum so further information can be exchanged via this pathway (Kramer, 2014).

## 6.1.2. Age related changes to the central auditory system

With ageing, there is a change in the integrity of the central auditory processing pathway. Central presbycusis refers to these age related changes in the auditory components of the central nervous system, which negatively impact auditory perception and speech communication (Humes et al., 2012). A reduction in the size of the cells in the auditory nuclei, and numbers of neurons making up the central auditory pathway has been reported in mouse models of presbycusis (Willott, 1996). These changes have been proposed to occur secondary to the ageing or dysfunction of the peripheral auditory system, causing impoverished signals leading to downstream neuronal decline or changes in the tonotopic organisation of the central auditory regions (Willott, 1996). For example, an fMRI study monitored the functional changes in language driven brain activity in a group of older adults with varying degrees of HL, whilst they undertook language comprehension tasks with various linguistic demands. The language driven activity was defined as increased activation during the complex sentences compared to the simple sentences. A whole brain correlational analysis showed poorer hearing was associated with lower levels of activation in the superior temporal gyri bilaterally, including the left primary auditory cortex, thalamus and brainstem (Peelle et al., 2011). There were no regions where there was increased activation for people with HL, suggesting that there is a down regulation of neural activity during processing of higher level aspects of speech in people with a HL, which may be secondary to the impoverished signals coming in (Peelle et al., 2011). As there were no differences in overall performance on the language comprehension tasks, the authors reported that peripheral HL may lead to a change in recruitment of brain regions for linguistic processing (Peelle et al., 2011).

Therefore, if central presbycusis is driven by peripheral deficits, it may be plausible that the use of hearing aids may help maintain involvement of the central auditory system, as input from the cochlea would be sustained. However, reports have stated that the use of hearing aids or cochlear implants cannot correct or bring benefit for central auditory processing dysfunction (Parham et al., 2013), and therefore it is likely that central presbycusis involves an interaction or the coexistence of peripheral presbycusis and independent age related degeneration of the central auditory system (Willott, 1996, Humes et al., 2012).

In keeping with this, another study has reported changes in diffusivity of the white matter in the auditory processing pathway between the IC and the white matter under Heschl’s gyrus. In older subjects compared to younger subjects this is accompanied by grey matter reduction in Heschl’s gyrus and auditory association areas (Profant et al., 2014). The authors reported no differences in age matched subjects with mild HL or a more severe HL (Profant et al., 2014), suggesting the morphometric changes in the auditory processing areas are due to ageing rather than peripheral hearing levels alone.

## 6.1.3. The prevalence of central presbycusis

Despite widely available and easy to administer tests of central auditory function (Parham et al., 2011), to date, they are not included in the routine HL diagnostic process (Beck and Nilsson, 2013), and thus prevalence estimates are inconsistent which may be due to the wide plethora of tools aiming to assess central auditory function in different populations.

Large population studies have reported a high prevalence of central auditory processing abnormalities, with rates ranging from 22.6% to 76.4%, where the incidence increases with increasing age (Stach et al., 1990, Cooper and Gates, 1991, Golding et al., 2004). Thus, classifications of central auditory processing dysfunction are varied throughout studies due to the lack of clinically defined parameters. Gates et al., (2008b) investigated the extent of auditory dysfunction in a cognitively healthy sample of older adults by testing the peripheral and central auditory abilities. They found in persons over the age of 70, central auditory dysfunction contributed as a major component of presbycusis. This central dysfunction was regardless of, or in addition to, any peripheral HL, and they reported central auditory abilities declined at a faster rate than peripheral hearing levels (Gates et al., 2008b).

The links between central auditory dysfunction and age were investigated by a large scale retrospective study, which analysed clinical data from 700 audiology patients, 100 patients every half decade between the ages of 50 to 80, and then 100 cases from the over 80 population. The authors reported both PTAv and speech understanding abilities declined with age, and there was a prevalence of auditory dysfunction in 17% of patients between the ages of 50 to 54, increasing systematically to 95% of patients over the age of 80 (Stach et al., 1990). Central presbycusis was defined based on a specific pattern of results from the Synthetic Sentence Identification Test and phonetically- balanced word test. To control for the confounding effects of peripheral hearing levels with increasing age, Stach et al (1990) analysed a subsample of participants from each of the half decade groups who had normal peripheral hearing (PTAv of 20 dB). They found that the prevalence of central presbycusis still dramatically increased with age regardless of these normal hearing thresholds. To ensure the results were generalisable, the authors compared these rates with a group of volunteer participants not recruited from the audiology clinics, and found that, although there was a consistently lower prevalence for each age decade (ranged between 0 and 72%), the prevalence was still very high in the older population (Stach et al., 1990). The authors did not comment on or present the degree of central presbycusis and therefore it is not known whether the severity of central presbycusis is affected by age or hearing levels. Nevertheless, the frequentness of central auditory dysfunction highlights the prominence of declining abilities with increasing age and thus suggests a case for routine central auditory testing to be undertaken. Current hearing rehabilitation technologies (such as hearing aids and cochlear implants) do not often take central auditory dysfunction into account and people with auditory dysfunction often report no benefit from amplification (Chmiel and Jerger, 1996), and thus may better benefit from auditory training (Ferguson et al., 2014).

# **Experiment 6.1 – Central auditory processing and cognitive function**

# Introduction

Although central presbycusis can be secondary to, and is closely linked to peripheral HL, if speech comprehension is notably impaired only in noisy situations, it is likely to be due to a central auditory processing disorder (Parham et al., 2011). The indications of central auditory disorders are commonly reported in the elderly population, including finding difficulty in noisy situations, and symptoms of poor auditory memory, distractibility and poor attention (Kramer, 2014). Therefore, lesions in the central auditory processing pathway may lead to misrecognition of cognitive dysfunction.

The association between cognition and auditory processing are not entirely defined, but it has been well established that top down cognitive processes are involved in the processing of speech (Eysenck and Keane, 2005), and thus central auditory functions are closely linked with higher order cognitive functions (Ronnberg et al., 2011). Due to age related changes in the auditory system and cognitive processes, it is not easy to separate the effects of ageing of these systems in isolation, and therefore to what extent central auditory and cognitive changes are involved in the misunderstanding of speech perception remains to be elucidated.

Therefore, it is likely that auditory decline with age is related to cognitive decline; however, linking central auditory function to cognitive decline hasn’t been as well researched as the links with subjective or peripheral HL. There is some evidence to suggest that measures of auditory processing rely heavily on working memory (Pichora-Fuller et al., 1995, Akeroyd, 2008, Souza and Arehart, 2015), but depending on the test used to assess central auditory function and speech understanding, there have been links to executive functioning, attention, speed of processing and frontotemporal integrity (Hugdahl, 1988, Jerger et al., 1991, Humes, 2005, Lee, 2015). Therefore, even after controlling for the effects of peripheral hearing levels, age related slowing or cognitive declines may confound the abilities to perform on many of these tests. For example, speech in noise tests (SiN) are a measure of central auditory function and determine the ability to hear speech against a background noise, symptoms commonly reported in presbycusis. A review of research studies which include tests of both SiN and cognitive function (Akeroyd, 2008) reported that although there appears to be a connection between cognitive function and SiN performance, there are not any cognitive tests which consistently correlate with SiN tests, although tests of working memory are most closely related (Akeroyd, 2008).

In terms of auditory dysfunction with neurodegeneration, studies have reported disruption of auditory processing in individuals with AD, although this is often not found for SiN tests (Belleville et al., 2003). Idrizbegovic et al., (2011) described no difference on measures of SiN for patients with MCI and AD compared to cognitively healthy participants after controlling for peripheral hearing levels. Therefore, SiN tests which are heavily confounded by peripheral hearing levels (Akeroyd, 2008), and have shown inconsistent evidence in relation to working memory (Fullgrabe and Rosen, 2016) may not be the best method to measure speech processing or the integrity of the auditory processing system alone in relation to cognition.

Further complications to understanding this relationship arise from the impact of the symptoms of central auditory dysfunction (Kramer, 2014). Tests of central auditory function are highly correlated to the levels of hearing disability using the HHIE-S (Gates et al., 2008b) and social isolation leads to poorer central auditory performance (Cacioppo et al., 2000), and therefore auditory processing may also help to explain the link between severity of HL and cognitive function.

The increased risk of cognitive impairment and dementia with the increasing severity of HL (Lin et al., 2011b, Deal et al., 2016) could be indicative of the severity of auditory processing dysfunction, which may be more likely to reflect a change in the integrity of neural networks than peripheral hearing thresholds. As the sensory systems are vulnerable to the effects of ageing (Rogers et al., 2016), via the common cause mechanism, impending neurodegeneration could disrupt auditory processing or exacerbate auditory dysfunction already present due to peripheral presbycusis, thus leading to an earlier manifestation of hearing deficits resulting in the temporal arrangement of HL prior to the onset of cognitive impairment.

Therefore, due to the confounding associations with age, peripheral hearing levels and different cognitive functions it is still unknown to what extent cognitive processes influence speech understanding in noise, and thus which specific cognitive aspects are selectively involved with decline in speech processing or central auditory dysfunction. Therefore, utilising a paradigm which reflects auditory function and cognitive function may help to understand further the link been HL and cognitive decline in ageing and pathology (Humes et al., 2012).

## 6.2.1.1. Dichotic listening

A group of tests commonly used to measure central auditory processing integrity are the dichotic speech tests, one of which, the dichotic listening paradigm, will be described below.

Dichotic listening is the auditory process of listening with both ears, and the dichotic listening paradigm thus involves simultaneous presentation of different sounds to both ears (McCullagh, 2013). The brain cannot easily process the two signals simultaneously (Hallgren et al., 2001) and thus the model involves binaural separation, where the brain has to perceive the signal in one ear and ignore the other (McCullagh, 2013).

A method of dichotic listening is the consonant-vowel (C-V) forced- attention paradigm (Hugdahl and Andersson, 1986). Syllables of C-V pairs are presented to both ears under two conditions, free recall and forced listening conditions. During the free recall condition, the participant is asked to recall the one C-V pair that is heard the most clearly, and under the forced conditions, the participant is asked to recall the stimulus from the right or left ear only, ignoring the other one. Thus, dichotic listening has been used to investigate structural language laterality under the non-forced (NF) conditions, and the top down manipulation of the structural laterality by selective attention and inhibition in the auditory processing pathway under the forced attention conditions (Hugdahl, 1988).

During the NF condition, where participants freely recall the stimulus, more correct responses from the right ear are typically reported relative to the left ear, resulting in a right ear advantage (REA) (Hugdahl and Andersson, 1986, Hugdahl et al., 2001, Foundas et al., 2006, Zenker et al., 2007, Takio et al., 2009, Saetrevik, 2012). This reflects the contralateral anatomical arrangement of the auditory system and dominant left hemisphere for linguistic processing (Kimura, 1961). The classical model suggests that contralateral auditory ascending pathways are stronger than ipsilateral pathways, and thus the REA ensues as there is a direct link to the speech processing centres in the left temporal lobe, where information from the left ear must first cross the corpus callosum (Hugdahl et al., 1999). These lateralisation effects have been corroborated by fMRI using sound stimuli (Langers et al., 2005). However, the C-V dichotic listening paradigm does show that responses from the left ear are being processed as there are relatively high correct responses from the left ear under the NF conditions, suggesting that there is a slower and less accurate processing from the left ear (Asbjornsen and Hugdahl, 1995).

Under the forced attention situations, healthy participants are expected to be able to modulate their attention and thus increase, during the forced-right (FR) condition, or decrease during the forced-left (FL) condition, the bottom up- driven REA. The success of this, however, may be dependent on the age of the participants (Takio et al., 2009). Older adults report stronger cases of REA and a reduction in inhibition of the REA under the FL condition (Hugdahl et al., 2001, Takio et al., 2009). Therefore, this form of dichotic listening task has been regarded as an excellent way to examine age related and pathological cognitive decline, as performance in the elderly is reduced compared to younger subjects and further reduced in individuals with AD (Bouma and Gootjes, 2011).

Due to the forced attention tasks requiring effective management of competing signals, cognitive processes such as short-term memory, shifting attention and competitive inhibition are utilised (Gates et al., 2008a). Furthermore, the neural processing demands differ under the forced conditions, where there is a stronger activation of the prefrontal cortex and caudate nucleus under the FL task compared to NF and FR conditions (Kompus et al., 2012), suggesting the involvement of different cognitive processes. Thus, the C-V dichotic listening paradigm involves examination of three different auditory-cognitive processes: firstly, lateralised perceptual processing under the NF condition, attention processing under the FR condition and executive cognitive control processing during the FL condition (Hugdahl et al., 2009).

This paradigm has been developed and translated onto an app, the iDichotic (Bless et al., 2013) for ease of administration on a mobile device, which has high reliability and validity when compared with lab based tests. The creation of the app has enabled a global investigation into language laterality across different languages and cultures, which has reported the REA as a global phenomenon (Bless et al., 2015). This paradigm is useful for exploring auditory processing function in healthy subjects due to the absence of ceiling effects (Hallgren et al., 2001).

Although the aspects of attention have been studied using the dichotic listening paradigm under the forced conditions, to our knowledge there is no reported evidence linking laterality to cognitive performance, or any other demographics than age and peripheral hearing levels. Therefore, the main aim of Experiment 6.1 is to identify whether performance on the iDichotic is related to demographic features and cognition in a sample of cognitively healthy individuals, regardless of age and peripheral hearing thresholds. The hypothesis includes that the NF condition would not be related to any demographic or cognitive features, the FR condition would be associated with attention measured by performance on the Digit Cancellation Task and the FL condition would reflect Overall Cognition and might be selectively associated with other cognitive tests. The secondary aim was to investigate whether any differences in NF condition were related to the ability to shift attention during the FR and FL tasks. The third aim was to investigate whether subjective hearing disability, measured by the SEAH, was associated with iDichotic performance to establish whether reduction in central auditory processing might too be linked with the social and emotional consequences of HL.

# Methods

## Participants and procedure

The participants and procedure are the same as reported in Chapter 5, Experiment 5.1 (5.2.2.1). In addition to the procedure described, participants also undertook a test of central auditory processing. Although the exclusion criteria were the same for this experiment, there was one addition; participants could not have more than a 10 dB difference in PTAv threshold between the right and left ears. One participant did not fulfil the criteria and was subsequently removed from this analysis, leaving 111 participants included in this study. The remaining participants ages ranged from 41 to 93 years, with a mean age of 64.91 (SD= 12.14). There were 43 (39%) males and 68 (61%) females in this sample. On average, participants were highly educated, with the number of years of formal education ranging from 8 to 23 years, with a mean of 15.11 years (SD= 3.19). The majority of participants were right-handed (R=98, L=13). Hearing status and neuropsychological assessment was recorded for all participants as described in 5.2.2.2 and 5.2.2.3.

Ethical approval was obtained from the University of Sheffield Medical School (ref: 002853) and NRES Committee North East- Newcastle and North Tyneside (ref: 170445, 15/NE/0152). All participants gave their written informed consent.

## Central auditory processing assessment

Central auditory processing was measured using the iDichotic app (Bless et al., 2015), a C-V dichotic listening paradigm, which has high reliability and validity when compared with lab based tests (Bless et al., 2013). The app was presented on an iPad tablet with a set of JVC circumaural headphones. Minimum hearing levels for each ear were designated and adjusted by the participant before starting the trial, where they were directed to slide the tone until the sound became inaudible for both ears separately, to ensure the volume was appropriate for both ears if there were any discrepancy in PTAv threshold.

The auditory stimuli were groups of consonant-vowel pairs, which were ba, da, ga, pa, ta and ka. The stimuli were simultaneously presented to the right and left ears using all possible combinations chosen at random. As described in 6.2.1.2, there were three conditions, the Non Forced (NF), a non-directional condition where the participant was asked to listen to the stimuli and chose the most dominant sound from either ear. This score was used to work out baseline laterality, based on the number of correct responses from the right and left ear over 30 trials. Ear advantage was calculated as the correct number of syllables chosen for the right ear – correct for the left ear/the total number of correct syllables chosen for any ear. There were then two forced conditions, Forced Right (FR), and Forced Left (FL), where participants were directed to attend selectively to the right or the left ear and report only the stimuli heard in this ear. Here again, the correct responses were recorded for each ear and a shift in laterality could be determined. The NF condition was always presented first, and the FR and FL were randomly allocated. Testing of all three conditions took approximately 10 minutes.

Laterality was defined for each participant by plotting the percentage of responses from the left ear on the vertical (y) axis, and percentage of right ear responses on the horizontal (x) axis. A line which has an intercept at 0.0, and a slope of 1 (45° angle) would signify an equal percentage of correct responses from the right and left ears, suggesting dichotic listening symmetry and no lateralisation (Foundas et al., 2006). The degree of lateralisation is defined as the linear distance from the line no symmetry line, which can be calculated using the following formula:

The maximum distance from this line, and therefore the laterality, could range between -70.71, and 70.71, negative numbers represented left laterality and positive reflected right laterality.

## Data analysis

All statistical analysis was undertaken according to the parameters defined in 5.2.2.4.

In order to explore demographic differences in the sample, for continuous variables, the Kolmogorov- Smirnov test of normality was undertaken and parametric and non-parametric analysis was chosen to compare differences across the three ear advantage groups. For categorical data such as differences in gender, handedness and HL was analysed using Pearson’s χ2.

Parametric Pearson’s correlation coefficient or Spearman’s Rho correlational coefficient if assumptions of normality and linearity were violated, were used to explore the associations between laterality under the three conditions and the associations with age, PTAv and SEAH scores.

The overall performance on iDichotic could be assessed by averaging the outcomes for FR and FL tasks. Spearman’s Rho correlational coefficient was again used to explore associations with iDichotic and continuous demographic variables. The differences in iDichotic performance between the ear advantage groups was explored using the nonparametric Kruskal Wallis H test, and pairwise comparisons with adjusted *p* values were used to measure differences between each group respectively. Wilkinson signed ranks related samples test was used to investigate the difference in laterality between NF laterality and FR and FL laterality respectively.

A one-way ANOVA was used to compare the shift in attention to the right between the different ear advantage groups. Levene’s test of Homogeneity of Variances indicated that the assumption of homogeneity was not met, F(2, 108) = 3.28, *p*= .041 and therefore Welch’s adjusted F ratio is reported. The Kruskal Wallace H test was used to compare shift in attention to the left between the different ear advantage groups, and pairwise comparisons to look for differences specifically between the groups. As shift is a continuous measure, it was dichotomised into Attend or not Attend by taking the arbitrary threshold of 10% (-7.07) as previously reported (Foundas et al., 2006), so participants could be classified as able to Attend to the directed ear.

The χ² test was used to identify any significant differences in the ability to Attend Left between the three ear advantage groups. Post hoc analysis involved transforming the adjusted residuals to create precise estimated *p* values for each group (Beasley and Schumacker, 1995). After adjusting for multiple comparisons between the three groups, the corrected *p* value was *p*< .008.

Due to the hypothesis of interest described in 6.2.1.1, associations between NF laterality and cognitive performance were assessed using the Spearman’s rho nonparametric correlation coefficient. For the FR condition, the Mann Whitney U test was performed to investigate median differences in the Digit Cancellation scores between participants who were able or unable to Attend Right. Finally, the difference in average scores for Overall Cognition and the raw cognitive tests were assessed using the Independent Samples T-Test, or the non-parametric equivalent the Mann Whitney U test, to compare between participants who could and could not attend left.

To ensure that the Attend Right and Left were reflecting the ability to attend to the dominant and non-dominant ear as described in 6.2.1.2, the analysis was repeated for Attend to non-dominant side and influence on cognition, thereby controlling for the confounding effects of non-left dominant hemisphere for linguistic processing in those with a LEA.

# Results

## Hearing assessment

As reported in 5.2. PTAv thresholds varied between 20 and 66.25 dB HL, 75 participants had normal hearing (68%), and 36 had HL (32%). SEAH scores ranged between 0 and 80%, with a mean score of 18.42 (SD= 17.77), which was highly correlated with PTAv as described in Figure 5.3 (5.3.2.1).

## Central auditory processing

### Non forced condition

NF laterality ranged between -42.43 and 51.62. Positive laterality reflects right ear dominance and negative laterality reflects left ear dominance. A REA was most commonly found, where 72 (65%) participants reported more correct responses from the right ear compared to the left ear, 24 (21%) reported no ear advantage and 15 (14%) reported a left ear advantage (Figure 6.1). There was no correlation between NF laterality and age (*r*s= -.118, *p=* .218), PTAv (*r*s= .017, *p=* .857) (Figure 6.2), or SEAH scores (*r*s= -.058, *p=* .546) (Figure 6.3). Thus suggesting that the age, HL or hearing disability did not influence the lateralised perceptual processing.

In terms of demographic characteristics, there was no significant difference between the three ear advantage groups (Table 6.1); therefore, the complete sample was included for subsequent analysis.



**Figure 6.1.** *Number of correct right and left ear responses under the non-forced condition*

NB. X and Y axis show the number of correct responses to the left and right ear, to a combined maximum score of 30. Green represents individuals who chose more answers from the right ear (REA), blue represents the participants who scored equal numbers of right and left responses (NEA) and red represents individuals who reported more from the left ear compared to the right (LEA).



**Figure 6.2.** *A scatterplot of Non Forced Laterality and Hearing thresholds showing no correlation*



**Figure 6.3.** *A scatterplot of Non Forced Laterality and Social and Emotional Association of Hearing loss (SEAH) scores showing no correlation*

**Table 6.1.** *Demographic characteristics of participants according to their ear advantage groups*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Demographic | Neither  (n=24) | Right Ear (n=72) | Left Ear  (n=15) | Significance |
| Age | 68.00 (10.68) | 62.99 (12.20) | 69.20 (12.67) | .072 |
| Education | 15.00 (6.00) | 16.00 (5.00) | 16.00 (6.00) | .351 |
| Handed (R/L) | 19/5 | 66/6 | 13/2 | .251 |
| Gender (M/F) | 9/15 | 31/41 | 3/12 | .264 |
| PTAv | 23.50 (15.00) | 20.00 (9.00) | 22.00 (20.00) | .352 |

NB. The average score reflects the mean (SD) for age, and the median (IQR) for years of education and PTAv thresholds.

### Forced conditions

Overall scores on the iDichotic ranged from 13 to 83% with a mean score of 42.41% (SD = 10.88). There was a significant correlation between overall score and age (*r*= -.531, *p*< .001), education (*r*= .317, *p*= .001), PTAv (*r*s= -.541, *p*< .001) and SEAH (*r*s= -.333, *p*< .001) ; suggesting that age, number of years of education, HL and subjective hearing disability had an impact on overall performance and the ability to shift attention during the dichotic listening task.

Overall iDichotic scores varied for the ear advantage groups, as shown in Figure 6.4 below. This difference was significant (*H* (2) = 10.63, *p* =.005). Pairwise comparisons with adjusted *p* values reported a significant difference between the NEA and REA group (*p* =.006, *r* =.32), but no differences between REA and LEA (*p* =.336, *r* =.17) or LEA and NEA (*p* =1.00, *r* =.13).



**Figure 6.4.** *Median performance on the iDichotic for each ear advantage group*

NB. \* *p* <.05, ns= not significant. Error bars reflect the upper quartile.

#### Forced- Right

Although the range of laterality did not change from the NF laterality (between -42.43 and 51.62), asking participants to attend to the right ear caused a significant positive shift in laterality (*T* = 3765.5, *p*<.001, *r* =.36) where 66 participants (60%) increased their laterality towards the right ear. Figures 6.5 to 6.7 show that participants from all three ear advantage groups shifted their laterality to the right when directed to (middle section), shown by an increase in correct scores from the right ear compared to the NF condition. Results from the one-way ANOVA showed there was no significant difference between the ability to shift to the right between the three groups (*Welch’s F* (2, 29.08) = .543, *p*= .587).

Overall, the amount that participants were able to shift to the right under the FR condition significantly correlated with age (*r*= -.215, *p*= .023) and PTAv (*r*s= -.313, *p*=.001), but there was no significant correlation with years of education (*r*s= .055, *p*=.564) or SEAH scores (*r*s= -.141, *p*=.139). This suggests that regardless of baseline laterality, older age and more severe hearing thresholds were associated with the amount of shift to the right. Using the arbitrary values described in 6.2.2.3, 49 participants (44%) could attend to the right ear when directed to. In keeping with the correlations described above, participants who could attend to the right were younger (Mean= 62.65, SD= 11.80) than participants who could not attend to the right (Mean= 66.69, SD=12.20) although this difference was not significant. There was a significant difference between HL in the two groups, where participants who could attend to the right had significantly lower hearing thresholds than participants who could not attend (*U*= 1130.00, *p*=.014, *r=* .23).

#### Forced- Left

Overall, there was a shift in laterality to the left under the FL condition. FL laterality ranged between -54.45 and 63.64, increasing the range of laterality in both directions from the NF condition. Asking participants to attend to the left side caused a significant negative shift in laterality (*T* =1041.00, *p*<.001, *r* =.54), where 79 participants (71%) shifted their laterality towards the left. Figures 6.5 to 6.7 show that in all ear advantage groups, on average participants could increase the correct responses from the left ear and decrease the responses from the right ear relative to the NF condition (last and first column).

The amount participants were able to shift attention to the left varied between the ear advantage groups (*H* (2) = 11.49, *p*= .003), pairwise comparisons with adjusted *p*-values showed a significant difference between REA and NEA groups (*p*= .002, *r*= .34), but no significant differences between REA and LEA (*p*=.665, *r*= -.13) or LEA and NEA (*p*= .539, *r*= .21). Thereby suggesting that participants with NEA could not shift their attention to the left as much as participants with REA.

Overall, the amount that participants were able to shift to the left under the FL condition significantly correlated with age (*r*s= .223, *p*= .019), but there was no association between the degree of shift to the left ear and PTAv (*r*s= -.123, *p*=.200), SEAH scores (*r*s= .162, *p*=.089) or years of education (*r*s= -.068, *p*=.476). This suggests that the degree of shifting attention to the left side negatively correlated with age but hearing thresholds, subjective disability and education had no association with the ability to shift to the left.

In terms of ability to attend to the left side, 59 participants (53%) could attend to the left ear. Although the degree of shift to the left overall correlated with age, Table 6.2 shows that there was no difference in age or demographic characteristics of participants who could and could not attend to the left side. However, there was a significant difference in ability to attend to the left side between the different ear advantage groups, (χ² (2) = 11.23, *p* = .004), shown in Table 6.3. The null hypothesis was there would be no difference in numbers of participants who could attend left in each group. Post hoc analysis and generation of precise estimated *p* values suggest that there was a significant difference between participants with REA (*p* =.002) and participants with NEA (*p*= .002) but not for participants with a LEA (*p*=.59), therefore suggesting participants with REA were significantly more likely to be able to attend Left, and participants with NEA were significantly less likely to be able to Attend Left.

**Table 6.2.** *Demographic characteristics of participants who can and cannot attend to the left under the FL condition*

|  |  |  |  |
| --- | --- | --- | --- |
| Demographic | Attend Left (n=59) | Not Attend (n=52) | Significance |
| Age | 63.34 (12.57) | 66.69 (11.50) | .147 |
| Education | 16.00 (5.00) | 16.50 (5.00) | .475 |
| Hearing Loss | 20 | 22 | .362 |
| Normal Hearing | 39 | 30 | .362 |
| Gender (M/F) | 25/34 | 18/34 | .402 |
| SEAH | 11.00 (16.00) | 15.00 (29.00) | .091 |

NB. The average scores reflect the mean (SD) for age and the median (IQR) for years of education and Social and Emotional Associations of Hearing loss (SEAH).

**Table 6.3.** *A cross tabulation of ability to attend left for the three ear advantage groups*

|  |  |  |  |
| --- | --- | --- | --- |
| Ear Advantage | Attend Left | Not Attend | Total |
| None | 6 | 18 | 24 |
| Right | 46 | 26 | 72 |
| Left | 7 | 8 | 15 |

**A**



**B**

**C**

**Figure 6.5.** *Correct responses from the right and left ears under the three conditions for individuals with A) no ear advantage (blue), B) right ear advantage (green) and C) left ear advantage (red)*

NB. The graph shows the mean correct responses, and error bars represent SD. On the X axis, R= right ear and L= left ear. The three different conditions are separated by a dotted line.

## Neuropsychological assessment, laterality & ability to shift attention to the left

The scores on the battery of neuropsychological tests were the same as reported in 5.2.2.3., reflecting a cognitively healthy sample.

### Non-forced condition and neuropsychological assessment

There was no association between the NF laterality and Overall Cognition, or on any of the raw neuropsychological assessments (Table 6.4).

**Table 6.4.** *Correlation between NF laterality and performance on neuropsychological assessment*

|  |  |  |
| --- | --- | --- |
| Cognitive test | *rs* | Significance |
| MMSE | .043 | .652 |
| SCEB | -.142 | .138 |
| House span | -.033 | .731 |
| House recall | -.003 | .976 |
| Category Fluency | -.052 | .591 |
| Letter Fluency | -.051 | .593 |
| Digit Cancellation | -.004 | .963 |
| Overall Cognition | -.025 | .796 |

NB. MMSE= Mini Mental State Examination, SCEB= Short Cognitive Evaluation Battery.

### Attend right and digit cancellation

Despite the older age and presence of peripheral HL in the participants who could not Attend Right, there was no significant difference in the attention abilities measured using the Digit Cancellation between individuals who could and could not Attend Right (U= 1403.50, *p* = .489, *r* = -.07). Both groups obtained median scores of 57, reflecting high performance.

### Attend Left and neuropsychological assessment

Participants who could Attend Left had, on average, higher scores on raw cognitive tests and Overall Cognition compared to participants who could not. This trend is shown in Figures 6.6 to 6.8, however, the difference between group performance was only significant for the House Span (Recall), where performance was greater for people who could attend to the left side (median 6, IQR=1) compared to those who couldn’t attend to the left side (median 5, IQR=2), *U*= 1953.5, *p*=.008, *r=* .25.

### Attend to non-dominant ear and neuropsychological assessment

There were no significant associations between the ability to attend to the non-dominant ear and neuropsychological testing, where the association between Attend Left and a significant difference on the House Visual Span recall was no longer significant at the corrected level (results not shown).



**Figure 6.6**. *Mean scores (z score) on the overall cognition for participants who can and cannot Attend Left*



**Figure 6.7**. *Median scores on the House Span recall for participants who can and cannot Attend Left*



**Figure 6.8**. *Mean scores on the Phonemic Fluency for participants who can and cannot Attend Left*

# Discussion

Under the NF conditions, a predominant right ear advantage was reported for 65% of the sample, in keeping with the current literature and predictions of structural laterality. However, this percentage is lower than other reports of REA, where some cases have found a prevalence of REA to be between 75 to 90% (Hugdahl et al., 2001, Hugdahl, 2011). The NF laterality and thus ear advantage in our sample, was not associated with peripheral hearing levels, age or any other demographics including subjective hearing disability, suggesting that under free recall conditions, these demographical factors have no impact on undertaking the dichotic listening task or the lateralised perceptual processing.

In this experiment the aim was to identify whether there was a difference in cognitive performance consistent with performance on the auditory processing task, iDichotic. The overall iDichotic scores significantly correlated with age, levels of education, hearing thresholds and SEAH scores, reiterating the contribution of ageing, cognition and peripheral hearing on tests of auditory processing.

Under the FR condition, there was a significant increase in the number of correct responses from the right ear (60%) relative to the NF condition, although the amount to which participants could attend to the right side was weakly associated with age and more moderately correlated with hearing levels, suggesting that the ability to Attend to the right ear was dependent on age and hearing abilities. These results are supportive of the hypothesis that the FR condition reflects attention processing (Hugdahl et al., 2009), which is decreased for older adults relative to younger adults, as shown in measures of attention throughout the ages (Hugdahl et al., 2001). However in our study, the Digit Cancellation test, a task of visual search attention reported no associations with performance and the ability to Attend, despite the older age of the participants who could not Attend Right. Due to the high performance and little variance throughout the sample, the lack of association could be due to ceiling effects of the Digit Cancellation in a healthy population.

When directed to shift attention to the left, under the FL trial, 71% of participants could increase their correct responses to the left ear, relative to their NF condition. This was 11% higher than the right, which is likely to be due to an already strong REA seen for the majority of the sample, reflecting the abilities to modulate attention to the non-dominant side. In general, the degree of shift to the left side weakly correlated with age, suggesting older participants could not shift their attention by as much. However, taking the arbitrary value of 7.07, to distinguish participants that could and could not Attend Left, Attend Left was unrelated to any of the demographic variables (Table 6.2) and therefore ideal to evaluate the relationship between cognition on this task of central auditory processing.

A trend was found between lower Overall Cognition and Letter Fluency scores for people who could not Attend compared to those who could, although these mean differences did not reach significance. A significant difference was reported for individuals on a task of visual-recall, the House Visual Span, where participants who could Attend Left could recall significantly more houses. This finding is interesting as this is a test of visual memory which is not influenced by hearing levels, and similarly due to the single category of stimuli, which all share the same verbal label - houses, the effects of verbalisation in the task are reduced (Cornoldi and Vecchi, 2004). One mechanism which could be used to explain the association of lower performance on both the iDichotic and the house visual span is due to distraction, for example, during the house span test, the participants had to recall the 6 houses from a larger sample of 12 houses, including 6 other house shapes which are very similar looking and thus distractors. During the FL condition, participants are asked to report answers from the left side and consequently ignore the distracting stimuli from the right side. Therefore in both circumstances, participants are using attentional resources to block out the unwanted stimulation and thus fewer resources are able to supply performance on the main task (Craik, 2014). This might be a marker of attentional difficulties, where individual differences in attention lead to poorer performance on the iDichotic task regardless of age and peripheral hearing levels. Changing the parameters to Attention to the non-dominant side rather than FL or FR showed a reduction in the significance level to below the corrected threshold. Therefore, the observation of no significant association with performance on the Digit Cancellation task with Attend Right, significance only on the House Visual Span for Attend Left, of minimal variability in cognitive performance throughout the sample, could indicate possible ceiling effects of the neuropsychological tests and suggest the iDichotic is more sensitive to minor deficits in attention and cognitive control.

The secondary aim was to investigate whether baseline laterality affected the performance during the forced listening conditions. This present experiment provided evidence of group differences between the ability to modulate attention, where people with a REA could shift their attention significantly more than the participants with NEA (Figure 6.4). This introduces the possibility that there might have been problems in the auditory processing (regardless of cognition) in individuals who reported no baseline laterality under the NF conditions. Due to a left dominant hemisphere for language processing which receives stronger activation from contralateral stimulation (Langers et al., 2005), a lack of asymmetrical response may suggest disruptions in the ascending tracts. This was supported by the finding that participants could shift to the right more easily than the left, although only 42% could Attend Right, and could be reflexive of the structural make-up of the auditory system. The fact that there were no associations between NF laterality and cognitive performance again might reflect the minimal involvement of cognitive processing under this condition further supporting this proposition.

Therefore, disrupted auditory processing may impact the ability to modulate attention rather than the cognitive abilities, or may suggest that a common factor leads to disruption of both auditory and cognitive processing regardless of age.

Previous research has demonstrated that there is a difference in laterality and the ability to shift attention between right and left-handers (Foundas et al., 2006). Foundas et al., (2006) reported that right-handed individuals were better able to shift their attention than left-handers. Similarly, left-handed individuals had a less dramatic REA and were not able to shift their attention as much as the right-handers (Geffen and Quinn, 1984). In our sample there was no significant difference between right and left-handers in terms of NF laterality (ear advantage) although Table 6.1 shows that 38% of left-handed individuals had NEA, which could support this finding of a reduced REA. When the analysis was restricted to right-handed individuals only, the prevalence of REA in the sample did not significantly increase (from 65 to 67%), and the results from the forced conditions remained unchanged, except for the Letter Fluency Task, which suggested that participants who could Attend Left, produced on average higher numbers of words during the FL task, although this difference was only significant at the uncorrected level. Therefore, is unlikely that handedness had an influence on our findings linking auditory processing and cognition.

The final aim of this Experiment was to investigate the influence of subjective hearing disability on dichotic performance. As expected, there was no association between SEAH scores and NF laterality. There was no association between the severity of self-reported disability and amount that attention was shifted to the right or left under the forced listening trials, suggesting that the significant correlation between overall iDichotic performance and SEAH scores was due to the confounding features of hearing severity and their associations with subjective hearing disability, as reported in Figure 5.3. Therefore it is concluded that subjective hearing disability is not associated with auditory processing scores as measured by the iDichotic, and thus any associations with cognitive performance are not through the psychosocial pathway.

There are limitations to this study including the ceiling effects of the cognitive tests which has already been mentioned. There is also some recent evidence which suggests that the eardrum moves in conjunction with shift in eye movements (Gruters et al., 2017), therefore if participants shift their eyes to the forced direction, there may be better auditory priming of that ear, making it easier to recall the stimulus. During the dichotic listening testing, it was noted that some participants did shift their eyes to the directed side also; therefore this may be introducing a bias into the results. However, an older study reported that when requesting groups of participants to direct their head or eyes for example to the right, there was no significant increase in correct responses from the right ear, where in fact the REA was strongest under the standard NF where participants were given no instructions on head or eye movement (Asbjørnsen et al., 1990). This suggests perhaps that dichotic performance is not influenced by the cued attention to either side in space.

To conclude, in our cognitively healthy sample, there was a high rate of participants who could attend to their non-dominant ear, i.e. the situation of cognitive conflict, suggesting that auditory processing abilities and cognitive control were intact. There was some indication even in the cognitively healthy sample that the dichotic listening paradigm tapped into the attentive and cognitive control aspects of cognition as shown by associations of performance on both tasks. No relationship with subjective hearing disability was observed, however there was a difference in the attention abilities of individuals with NEA. It could, therefore, be concluded that individuals with NEA may have problems in auditory processing abilities regardless of age, peripheral or cognitive hearing status.

# **Experiment 6.2 - Can central auditory dysfunction predict cognitve decline?**

# Introduction

Due to the fact that there are common age related declines in the central auditory processing abilities of people with normal hearing and HL (Fullgrabe et al., 2014, Stach et al., 1990), there are no standardised measures which separate what is regarded as ‘normal’ auditory processing from dysfunction or pathology.

In the early stages of neurodegeneration, it is often hard to distinguish pathological ageing from normal age related declines using the current neuropsychological tests. However, alterations in episodic memory performance are often suggested as the earliest signs of neurodegeneration (Salmon, 2012). In Experiment 6.1 a significant difference between the numbers of houses recalled during the long term portion of the House Visual Span was reported, which could suggest that inability to Attend Left is associated with the early stages of episodic memory impairment. However, as this was a cross sectional study, where the scores were still within the clinically healthy range, one must be cautious not to assume that a lower performance is suggestive of deficits in episodic memory.

Unlike the compensatory abilities of the brain to the effects of ageing or pathology, presented in 1.2.1, the auditory system may be unable to disguise the effects of neurodegeneration and thus performance on central auditory tasks may be reduced. Therefore tests to distinguish auditory processing abilities may be invaluable as a marker of cognitive ageing, as suggested by Gates et al., (2002) where they reported auditory dysfunction may precede dementia and be more sensitive to subclinical deficits in cognitive function (Gates et al., 2010, Gates et al., 2011). However, as the prevalence of auditory processing deficits are so high in the general population and even higher in individuals with HL (Stach et al., 1990) (discussed in more detail in 6.1.3), the implications must be treated with caution. For example, Stach et al., (1990) found that 95% of people with a peripheral HL over the age of 80 had auditory dysfunction, and it is not plausible to assume that all of these participants had impeding neurodegeneration, which raises the question of how sensitive these measures are. It could be that the levels of central dysfunction are overestimated in the studies due to the lack of available norms and thus monitoring longitudinal performance over time may be more effective measure.

To our knowledge there are no studies which have reported the monitoring of dichotic listening performance over time, with the exception of those investigating childhood language laterality. Therefore the interactions between performance on iDichotic and cognition over time are yet to be elucidated. Due to the C-V dichotic listening paradigm measuring different central audio-cognitive abilities, it is hypothesised that the iDichotic may be a more sensitive measure to subtle changes in cognitive and underlying neuronal function, thus deficits may manifest earlier than shown in the current neuropsychological tests. This could then help to explain the temporal relationship of both peripheral and central HL to decline in cognitive function over time (Gates et al., 2002, Lin et al., 2011b, Lin et al., 2013, Deal et al., 2016).

In this experiment, the aim is to identify if there would be a difference in the iDichotic performance over time, and if this correlated with changes in cognitive function. Reported in Experiment 6.1, laterality and ear advantage reflected differing abilities to Attend Left, which was hypothesised to show disruption of the auditory processing pathway. In this experiment the secondary aim is to investigate whether the ability to Attend Left could predict changes in cognition, thereby suggesting a pathway where declines in central auditory function might predict changes in cognitive performance on neuropsychological assessment and the ability to modulate attention on the iDichotic.

# Methods

## Participants and procedure

Participants were recruited via the same process as reported for Experiment 5.3 (5.4.4.1). The 84 participants recruited for follow up in Experiment 5.3 were approached and consented for testing at approximately 12 months. Due to a unilateral decrease in PTAv, 6 participants were excluded from the subsequent analysis, leaving 78 participants. The participants’ age ranged from 41 to 87 years, with a mean age of 64.37 (SD= 11.01). There were 27 (35%) males and 51 (65%) females in this sample. On average, the sample was highly educated, with mean years of education of 15.63 (SD= 3.01) ranging from 10 to 21 years. The majority of participants were right-handed (R=69, L=9).

All participants had repeat neuropsychological assessment (first described in 5.2.2.3), hearing assessment (first described in 5.2.2.2) and central auditory processing as described in 6.2.2.2.

Ethical approval was as described in 6.2.2.1. All participants gave their written informed consent.

## Data analysis

All statistical analysis was undertaken according to the parameters defined in 5.2.2.4.

The Pearson’s Correlation coefficient was used to investigate the relationship in performance at T1 and T2, and the Spearman’s Rho Correlational coefficient was used when the data violated the assumptions of normality. Similarly, the paired samples t-test was used to compare the change in performance over time in terms of laterality, where the non-parametric equivalent Repeated Samples Wilcoxon Signed Ranks test was used to evaluate change in performance on the iDichotic overall score.

To investigate if there was any difference in ability to Attend Left at T1 and T2, a cross tabulation was undertaken. Thus four groups were created dependent on abilities to Attend Left under both times of participation. A One way ANOVA was then used to investigate demographic differences between the groups who remained constant or changed performance over time, and Bonferroni pairwise comparisons to investigate where the specific differences between the groups occurred.

The Mixed Factorial ANOVA was utilised to measure an interaction effect between Time and Group on the neuropsychological tests. The within-groups variable was Time, which consisted of two levels T1 and T2, and the between-groups variable was Group, which consisted of firstly two levels, Attend Left or Not Attend Left at T1, and then was repeated for the interaction between the four groups of change in Attend abilities (Attend both T1 and T2, Attend neither T1 or T2, Attend T1 not T2 or Attend T2 not T1). Age was used as a covariate for both sets of Mixed Factorial ANOVAs.

# Results

## Hearing assessment and baseline scores

PTAv thresholds varied between 20 and 74, 47 participants had normal hearing (60%), and 31 had HL (40%). When measured at T1, from this sample, 52 participants had a REA (67%), 11 participants had a LEA (14%) and 15 participants had NEA (19%). Forty two participants could Attend Left and 36 participants could not Attend Left. There was no significant difference between age (*U* = 632.5, *p*= .215, *r* =.14) or education (*U* = 702.50, *p*= .589, *r*= .06) between these groups.

## Dichotic listening over time

### 6.3.3.2.1. Non forced condition

The NF laterality ranged from -42.43 to 35.36 at T1, and at T2, there was an increase in both right and left laterality as the range was from -47.38 to 47.38. This small change in laterality was not significantly different as correlation reported *r* = .654, *p* <.001, and the paired samples *t*-test reported no significant change in laterality between T1 and T2 (*t* (77) = -.594, *p* =.554, *d=* 0.06).

The overall percentage of participants with a REA, LEA and NEA did not change, however only 60% of participants reported the same ear advantage in T2 as T1 (Table 6.5), therefore suggesting that NF laterality had changed for 40% of the sample.

At T2, there was again no significant difference between age (*H=* 4.48, *p*= .106), education (*H* = 3.71, *p*= .157) or PTAv (*H=* 4.66, *p*= .097) between the ear advantage groups.

**Table 6.5.** *Ear advantage groups at Time 1 and Time 2*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | NEA | REA | LEA | Total |
| NEA | 3 | 7 | 5 | 15 |
| REA | 10 | 40 | 2 | 52 |
| LEA | 2 | 5 | 4 | 11 |
| Total | 15 | 52 | 11 | 78 |

### 6.3.3.2.2. Forced conditions

Over the twelve month period, there was a significant positive correlation between Overall performance at T1 and T2, rs= .732, *p* <.001 (Figure 6.9). However median scores marginally but significantly improved at T2, (*Z* =1791.50, *p*<.001), from 43.00 (IQR= 9) to 45.00 (IQR=14).

Ability to attend to the Left (Attend Left) at T1 and T2 is described in Table 6.6 below, and data show that the abilities to Attend for the majority of people remained the same, they could either attend both or neither times, but 34.6% of peoples abilities changed between T1 and T2, where 15.38% declined in the ability to Attend, and 19.23% gained the ability to attend. The results of the ANOVA suggested that there was a significant difference in age between the different groups of Attend Left, (F (3) =3.50, *p* =.020), and Bonferroni corrected post hoc multiple comparison’s reported a significant difference between the ages of participants who could Attend both times and those who could not attend either time, suggesting that ability to attend to the left might be influenced by age. Although at T1 no differences in average age were reported for individuals who could and could not attend to the left (Experiment 6.1, Table 6.2).

**Table 6.6.** *Ability to Attend Left at Time 1 and Time 2*

|  |  |  |
| --- | --- | --- |
| Attend Left | Count | Age |
| T1 = 1, T2 = 1 | 30 | 60.97 (10.68) |
| T1 = 0, T2 = 0 | 21 | 69.33 (9.26) |
| T1 =1, T2 = 0 (decline) | 12 | 68.00 (11.70) |
| T1 = 0, T2 = 1 (improve) | 15 | 61.33 (10.85) |

NB, T1=0, participants could not attend left at T1, T1=1, participants could attend left at T1. T2=0, participants could not attend left at T2, T2=1, participants could attend left at T2.



**Figure 6.9.** *Scatterplot showing performance of participants on Overall Score at T1 and T2*

## Neuropsychological assessment

In keeping with the results presented in Experiment 5.3 (5.4.4.2.1), there was little change in cognitive performance in this sample between T1 and T2 (Table 6.7), although there was a significant increase in the mean number of words recalled at T2 compared to T1 on the Letter Fluency Task, *t* (77) = -6.01, *p*<.001, *d* = .37.

**Table 6.7.** *Paired samples showing differences in average performance on tests overtime*

|  |  |  |  |
| --- | --- | --- | --- |
| Cognitive test | Time 1 | Time 2 | Significance |
| MMSE | 29.00 (1.00) | 29.00 (2.00) | .039\* |
| SCEB | 35.32 (6.82) | 35.83 (7.52) | .363 |
| House span | 3.00 (1.00) | 3.00 (1.00) | .105 |
| House recall | 5.00 (1.00) | 6.00 (1.00) | .070 |
| Category Fluency | 63.28 (1.90) | 63.97 (15.68) | .363 |
| Letter Fluency | 45.37 (11.25) | 49.54 (11.55) | **<.001\*\*** |
| Digit Cancellation | 57.00 (4.00) | 57.00 (4.00) | .841 |
| Overall Cognition | 9.52 x10¯4 (0.68) | 38.37 x10¯4 (0.67) | .947 |

NB. \* Significance at *p*<.05, \*\*Significance at p<.008. The average reflects the mean (SD) for the Short Cognitive Evaluation Battery (SCEB), Semantic and Phonemic Fluency tests and the Overall Cognition composite *Z* score, and the median (IQR) for the Mini Mental State Examination (MMSE), House Visual Span and Digit Cancellation.

## Attend left at baseline and neuropsychological performance

Although neuropsychological performance remained constant on the whole, there was a slight variation in trend with performance over time between the participants who could attend L and those who could not attend Left, Figure 6.10 shows that Overall Cognition and performance on the SCEB and Category Fluency Task increased for the group who could Attend Left, and decreased for those who could not attend. There was no difference in performance on the other raw tests over time (results not shown). For the House span recall, although the group who could attend had significantly higher performance, scores did not deviate from baseline for either group.

The results of the mixed factorial ANOVA report no significant main effect of Time, Group or no significant interaction effect for Overall Cognition or the Category Fluency Task. There was no significant main effect of Time (F (1, 76) = 0.56, *p* =.455), or Group (F (1, 76) = 1.12, *p* = .293) on SCEB performance, but there was a significant interaction effect for Group and Time on the SCEB (F (1, 76) = 6.182, *p*= .015), which however this did not survive the adjusted threshold for multiple comparisons (*p*<.008).

**A**



**B**



**C**



**Figure 6.10.** *Difference in A) Overall cognitive performance, B) Short Cognitive Evaluation Battery and C)**Category Fluency, between Time 1 and Time 2 for participants who could and could not attend left at Time 1.*

## Change in the ability to attend left and neuropsychological performance

To identify if there were any difference in performance between individuals whose ability to attend changed over time, the interaction effects was repeated for the four groups controlling for the effects of age. The interaction graph for Overall Cognition (Figure 6.11A), shows that all participants remained relatively stable overall, but there was a decline in the participants who attended at T1 and not at T2, and i.e. they declined in the ability to Attend Left over time. This interaction however was not significant after controlling for the effects of age (F (3, 73) = 1.07, *p*= .366). Figure 6.11B shows that the significant interaction remained between SCEB performance and ability to attend over time (F (3, 73) = 4.18, *p*= .008), where there was a significant improvement on scores for the participants who could attend to the left both times, and a stable or slight decline in performance for the other groups. Again, although performance for the House Recall was higher for participants in the T1=1 T2=1 group, there was no deviation from baseline scores for any of the groups.

**A**



**B**

**Figure 6.11.** *Difference in A) Overall Cognition and B) Short Cognitive Evaluation Battery (SCEB) between Time 1 and Time 2 for participants with varying attend left abilities.*

NB, T1=0, participants could not attend left at T1, T1=1, participants could attend left at T1. T2=0, participants could not attend left at T2, T2=1, participants could attend left at T2.

# Discussion

In this experiment, a marginal improvement on overall iDichotic scores from T1 to T2 was reported, which was expected due to the influence of practice effects. However, unexpectedly a change in NF laterality was found for almost 40% of the sample between T1 and T2. This again might be due to practice effects and a deeper understanding of the test, where participants might have (unconsciously) modulated their attention to either or both sides. This may suggest that the C-V dichotic listening paradigm is not a highly reliable measure of language laterality. Previous measures of the reliability of dichotic listening have varied consistency, which may be due to the different methods and techniques probing language laterality (Blumstein et al., 1975, Gadea et al., 2000). However, the same test as used in this experiment has previously shown a moderate test-retest reliability over a two week period (Hugdahl and Hammar, 1997), although the authors reported that the lowest coefficient (*r*= .61) was for the NF condition, in keeping with our suggestion that participants performance may be affected by attention under the NF condition. An earlier study by Porter et al., (1976) found changes in dichotic listening performance over an 8-week period, but reported that participants have a more consistent pattern of performance after 300-400 trials. Therefore, to improve the reliability and minimise the confounding influence of practice effects, more C-V trials could be employed in the future.

The main aim of the study was to investigate whether there was any decline in cognitive performance over time relating to the ability to Attend Left. There was an interaction between Attend and performance on the SCEB, where participants who could Attend at T1 improved performance on the SCEB, and those who could not Attend at T1 declined on the SCEB between T1 and T2, although this was only significant at the uncorrected level.

The ability to Attend left at T2 was measured to ensure that there was no change in performance. Again, unexpectedly, there was a change in the ability to Attend left between T1 and T2 in 35% of the sample. Taking these four groups into account (Table 6.6) and controlling for the effects of age, a significant interaction was observed at the corrected level between Group and Time on the SCEB, where participants who could Attend both times performed better on the SCEB at T2 compared to T1. There was also an interesting result where participants who could not attend either time declined on Overall Cognition between T1 and T2, reflecting a decline on aspects of all of the cognitive tests although this was not significant after controlling for the effects of age.

However, it can be concluded with some confidence that the ability to Attend Left was associated with a decline in scores between T1 and T2 for the SCEB. It would be interesting to extend the follow up time to understand fully the change in performance over time and investigate any other influences on cognition.

To conclude, the iDichotic may be a more sensitive measure to changes in the brain, and it would be interesting to follow participants over a longer period of time to investigate whether the iDichotic can act as a marker of cognitive function and thus predict cognitive decline. However, on the individual level, this test may not be suitable or specific enough, due to the lack of consistent results in NF laterality between T1 and T2.

# General Discussion

The findings from Experiments 6.1 and 6.2 suggest that the iDichotic was associated with cognitive performance in a sample of cognitively healthy adults. In Experiment 6.1, a significant difference in the number of houses that were able to be recalled was reported for individuals who could Attend and could not Attend Left. Experiment 6.2 reported a significant association between declines in performance on the SCEB and inability to consistently Attend Left, and no change in performance on the House Visual Span recall. It was also postulated that participants without a REA may be experiencing central auditory dysfunction, which then had a knock on effect in their abilities to modulate attention during the forced listening tasks. However, the test-retest reliability of ear advantage under the NF condition was low which raised caution for the generalisability of these findings, and the short follow up meant the trajectories of individuals with NEA could not be properly investigated over time.

The interaction with a decline on the SCEB and ability to Attend Left over time is suggestive of a decline in semantic and executive function, which is relatively preserved in healthy ageing and declines during the early stages of Alzheimer’s disease (Förstl and Kurz, 1999, Wakefield et al., 2014). Therefore this is in accordance with our hypothesis that lack of cognitive control on the iDichotic (not being able to Attend Left) may earlier predict declines in cognitive function which may have an underlying neurodegenerative basis. It was expected that the participants who could not Attend at T1 would decline in performance over time, and although this was found, the interaction was not significant at the corrected level. This was also confounded by changes in ability to Attend at T2, and as the interaction graph (Figure 6.11B) implies an increased performance of individuals who could Attend, but a very marginal decline in SCEB for individuals who could not Attend Left either time. It is difficult to speculate at this stage whether it can be assumed this could be used as a marker of cognitive decline. It can be, however, suggested with some certainty, that performance on the iDichotic was associated with cognitive function over and above attention, hearing levels and age.

A possible limitation to both experiments is the practice effects and acclimatisation needs of tests of dichotic listening. There is some evidence to suggest that elderly people require practice lists before undertaking the dichotic listening experiment (Feeney and Hallowell, 2000). Therefore, the lower or inconsistent performance of the older participants may be due to lack of complete understanding of the test and thus suggests that provision of sufficient practice trials may improve the reliability and validity of the scores. Similarly, other studies have reported auditory processing measures using a battery of auditory processing tests (Gates et al., 2008b, Gates et al., 2010, Gates et al., 2011) which may again yield more reliable results. However, it has also been shown that laterality changes are dependent on the dichotic listening measure used to evaluate them (Jancke et al., 1992) and thus monitoring performance over one test may be better than group of tests which all measure slightly different things and may further complicate the interpretation of any findings.

As peripheral hearing levels may confound the performance on measures of auditory processing, it would be more useful to investigate the differences in a sample of participants of the same age with varying levels of HL, and central auditory processing abilities. This would then help to identify the mechanism, for example if peripheral hearing levels were associated with poorer auditory processing measures and cognitive function or whether auditory processing dysfunction were related to poorer cognitive performance regardless of peripheral hearing levels. This could elucidate whether central auditory processing problems which are associated with cognitive decline are caused by peripheral HL.

To utilise this test further to explore whether the iDichotic could in fact predict cognitive performance, normative data from all age ranges would be needed, as this is only available for large samples up to the age of 59 (Hugdahl, 2011). This could then be used to establish norms for each age decade to distinguish properly degrees of auditory dysfunction, which can then be used longitudinally to measure the influence of changes in central auditory processing and cognitive control.

# Chapter 7: Hearing loss with cognitive impairment and dementia

# Introduction

As introduced in Chapter 2, there is conflicting evidence surrounding the associations of HL on the risk and progression of cognitive impairment and dementia. Earlier this year, a commissioned article by the Lancet reported that HL is a preventative risk factor for incident dementia, with a population attributable risk of 9% (Livingston et al., 2017). However, to date, the information reported regarding the use of hearing aids and interventions on cognitive profiles have been inconclusive and thus it is not possible to tell whether by treating HL, the risk of dementia would decrease. Similarly, there is an inconsistent association of HL in the dementia population, where not everyone with cognitive impairment has HL and not everyone with HL will develop cognitive impairment.

If HL is a risk factor for dementia, and it has the potential to be modified, then identification and treatment of HL in the general population should be a public health priority. Similarly the overlapping symptoms of untreated HL and the early stages of cognitive impairment could complicate diagnosis, and as reported in Chapter 5, people with HL may be disadvantaged by the testing procedures. These factors coupled with shared risk factors may put people with HL at risk of an over diagnosis of cognitive impairment (Jorgensen et al., 2016). Understanding the cognitive profiles of individuals with HL and dementia may further the understanding of the links between the two factors.

A recent study reported a higher prevalence of both peripheral and central auditory impairment in patients with MCI and AD dementia compared with controls (Quaranta et al., 2014). The prevalence of peripheral impairment was 35% in the healthy sample, 50% in MCI patients and 75% in the patients with AD. However, due to the significantly older age of MCI and dementia patients, after controlling for the effects of age and levels of education, there was no association of increased peripheral HL in the dementia group compared with the controls. Therefore, it is unlikely that HL independently increases the risk of cognitive impairment and dementia. Quaranta and colleagues did report that the prevalence of auditory dysfunction still remained after controlling for age, education and gender, where the odds for central impairment was 4.2 for AD group, and 2.0 for MCI compared with healthy controls. Thus suggesting that after adjusting for age and peripheral hearing levels, there is still disrupted central processing in people with cognitive impairment. Whether this is a consequence of disrupted cognition or auditory processing is difficult to tell, as the measurement of auditory processing is confounded by cognitive and peripheral aspects. The prevalence of AD pathology in the auditory processing pathways (Ohm and Braak, 1989, Sinha et al., 1993), however, may suggest that this could be influenced by both aspects.

Conversely, other researchers have reported no such association with dementia and auditory processing dysfunction (Krishnamurti et al., 2011, Idrizbegovic et al., 2011). Krishnamurti et al., (2011) reported no clear difference in tests of auditory processing between individuals with AD and controls, suggesting the decline of central auditory function is related to ageing rather than cognitive impairment (Krishnamurti et al., 2011). However, this sample only included 9 individuals with probable AD and 9 controls, some of whom scored 23 on the MMSE which could reflect the presence of some cognitive impairment in some of these people. At the same time, controls had slightly higher hearing thresholds at 500, 1000 and 2000 Hz which could be responsible for lower task performance and the lack of differences.

There is limited evidence linking HL to other types of dementia than AD, and most often associations are drawn for HL leading to a general cognitive decline by measurements using global screening tests. However, the study by Lin and colleagues (2011b, concluded that HL is an independent risk factor for dementia, as there was a linear increase in risk of incident dementia with increasing HL severity. The authors did not comment on the aetiologies of dementia, except that 64% of cases were AD. They did include however, that when taking solely AD cases into account, the results were no longer significant (Lin et al., 2011b). This disparity could be due to the study being underpowered, or suggests that there is no reason to believe HL is an independent risk factor for AD and it is unlikely that HL would increase the risk of all of the dementias with different aetiologies, driven by different pathological factors.

Similarly central auditory processing has not been studied in other causes of dementia, but studies have reported reduced central auditory function in other neurodegenerative conditions such as Parkinson’s disease and Huntington’s disease (Guehl et al., 2008, Claus and Mohr, 1996, Profant et al., 2017). This may suggest involvement of a common factor leading to both HL and neurodegeneration. Due to the lack of consistent evidence for hearing declines in AD, it was hypothesised that this increased risk or association may not be due to AD alone, but any neurodegenerative condition.

Studies of ageing using imaging techniques have reported little involvement of auditory areas in ageing or AD (Resnick et al., 2003, van der Vlies et al., 2013), although a longitudinal study has reported that HL is associated with accelerated rates of right temporal lobe and whole brain atrophy (Lin et al., 2014) which could help explain the link between reduced cortical volumes in people with HL and dementia. This will be discussed in more detail in 7.4.1.

# **Experiment 7.1 - Peripheral presbycusis and the psychosocial association in MCI and dementia**

# Introduction

There is inconsistent evidence suggesting that neurodegeneration is associated with increased levels of HL. For example, studies have reported higher rates of peripheral HL in Parkinson’s disease (Vitale et al., 2012, Lai et al., 2014), Huntington’s disease (Lin et al., 2011e) and AD (Uhlmann et al., 1986, Teipel et al., 2015), although other studies have reported no significant differences compared to controls after accounting for age and demographic factors (Idrizbegovic et al., 2011, Folmer et al., 2017, Profant et al., 2017).

It has also been reported that the progression of dementia is more rapid in people with HL (Peters et al., 1988, Uhlmann et al., 1989a), which supports the role of HL as an independent risk factor for dementia, but also supportive of the cognitive load on perception model. To reiterate, due to reduced hearing acuity, people with HL may rely more on intact cognition for efficient speech perception (CHABA, 1988), cognitive decline may reduce the resources available for auditory perception and thus increasing the effects of HL which may further exacerbate a decline in cognition.

Likewise, the behavioural features of dementia may be exacerbated in people with a HL (Umeda-Kamwyama et al., 2014). The behavioural and psychological symptoms associated with dementia were assessed in 99 patients with differing dementia aetiologies. The reported prevalence of these symptoms were 68% in people with a HL and 32% in people with no HL (Umeda-Kamwyama et al., 2014), suggesting that behavioural issues may occur more frequently in patients with a HL which could be due to increased difficulty with communication. Although the authors did not comment on dementia severity, as behavioural and psychological symptoms increase with disease progression in AD (Hashimoto et al., 2015), it is likely that people with HL may also have a more severe dementia.

It has been reported that hearing aid uptake and use is low in patients with dementia (Cohen-Mansfield and Infeld, 2006), although little evidence has suggested any improvements in cognitive function or behavioural features with the use of them (Allen et al., 2003), and thus lack of effectiveness may be a reason for low uptake.

The aim of Experiment 7.1 was to identify the prevalence of self-reported and measured HL in a sample of cognitively impaired patients, and to identify whether the cognitive profiles of individuals with HL were more severe depending on the severity of their HL. The hypothesis was that the severity of HL would be related to the severity of cognitive impairment. The second aim was to identify if subjective hearing disability was exacerbated in people with HL and cognitive impairment, as a way to identify whether HL indirectly leads to exacerbated cognitive decline through the psychosocial pathway. It was also investigated whether patients with MCI and dementia reported using hearing aids, and whether the perception of hearing aid benefit was different for controls and patients.

# Methods

## Participants and procedure

Thirty-five patients with neurodegenerative cognitive impairment were recruited to this study from the memory and dementia clinics at the Royal Hallamshire Hospital. The clinic typically sees between 3 and 6 new patients per week. All patients visiting the clinics between 1st September 2016 and 1st May 2017 were screened for eligibility by their clinician. Inclusion criteria included mild to moderate typical cases of neurodegenerative cognitive impairment, including both patients with a diagnosis of MCI and those with dementia. Exclusion criteria included cognitive impairment with suspected functional, vascular or secondary aetiology, severe behavioural cases or MMSE scores below 15, who were deemed to be too severe. Four patients were excluded based on their diagnosis, leaving 31 participants in the subsequent analysis.

Patients were further categorised into MCI or dementia. There were 18 patients with amnestic or non-amnestic MCI and 13 with dementia. The dementia patients included diagnoses of AD (n=7), dementia with Lewy bodies (n=2), frontotemporal dementia (n=3) and corticobasal degeneration (n=1). Patients were diagnosed based on multidisciplinary evidence and according to standard clinical criteria for AD (McKhann et al., 2011), dementia with Lewy bodies (McKeith et al., 2005), frontotemporal dementia (Lund-Manchester, 1994) and MCI (Albert et al., 2011).

Patients were 20 males (64.5%) and 11 females (35.5%), aged between 49 and 88 years with a mean age of 67.94 years (SD= 9.67). They reported between 10 and 18 years of formal education, with a mean duration of 12 years (SD= 2.34). All were right-handed except one who was left-handed. All patients underwent clinical assessment and completed neuropsychological testing for diagnostic purposes, which were retrospectively analysed. Patients were split into MCI and dementia groups and compared to 31 age, gender and education matched controls that were recruited as part of the cohort described in 5.2.2.1.

Ethical approval was obtained from the University of Sheffield Medical School (ref: 002853) and NRES Committee North East- Newcastle and North Tyneside (ref: 170445, 15/NE/0152). All participants gave their written informed consent.

## Neuropsychological testing

All patients undertook an extensive battery of neuropsychological testing for clinical purposes by a Professor of Neuropsychology to establish correct and differential diagnosis. The battery was chosen as it focused on areas most affected by pathological ageing. A sub-sample of neuropsychological tests were chosen to be retrospectively analysed as they are the most sensitive to change and disease progression, without overreliance on verbal instructions. These tests included the MMSE (Folstein et al., 1975) as a measure of global cognitive function, the WMS-III Verbal Paired Associates Test (Wechsler, 1997) as a measure of verbal episodic memory, the delay component of the Rey Complex Figure Test (Rey, 1941) to assess long- term visuographic memory, a modified version of the Stroop Task (Venneri et al., 1992) to measure executive function and finally, the Digit Cancellation (Spinnler and Tognoni, 1987) which assessed speed of processing and visual attention.

The controls undertook neuropsychological testing as described for section 5.2.2.3.

## Hearing assessment

### Peripheral hearing thresholds

Pure tone average hearing thresholds were established for all of the patients and controls as described in 5.2.2.2.

### Subjective hearing disability

The SEAH was also administered to all patients and controls as described in 5.3.2.1.

## Data analysis

Statistical analysis was undertaken using the same parameters defined in 5.2.2.4.

In order to explore differences in demographic characteristics between patients with both MCI and dementia and controls, the Kolmogorov-Smirnov test was chosen as a test of normality. Independent samples Mann Whitney U test was performed to establish any differences between age, level of education and global level of cognition (MMSE) for controls and patients, and Pearson’s χ² was used to test for any gender differences. Mann Whitney U test was used to compare differences between patients and controls on scores of subjective hearing disability using the SEAH. Spearman’s Rho correlation coefficient was used to analyse the association of subjective hearing disability to hearing thresholds in each group.

Due to unequal sample size between the three groups of MCI, dementia and controls, bar graphs are expressed with relative percentage rather than count.

As the data violated the assumptions for Pearson’s χ² test, Fisher’s exact test was used to identify any significant differences between ability to ‘Attend’ to the right and left between the groups. The adjusted residuals were transformed to create estimated *p* values for each group (Beasley and Schumacker, 1995), after adjusting for multiple comparisons between the three groups, adjusted *p* value *p*< .008.

# Results

## Participants

There was no difference in demographic characteristics between patients and controls (Table 7.1). The difference in average MMSE scores demonstrates the different cognitive profiles of patients and controls, where patients were significantly more impaired in terms of global cognition.

**Table 7.1.** *Demographic characteristics of patients and controls*

|  |  |  |  |
| --- | --- | --- | --- |
|  | Patients (n=31) | Controls (n=31) | Significance |
| Age | 67.94 (9.67) | 68.97 (10.53) | .526 |
| Gender M/F | 20/11 | 18/13 | .795 |
| Education | 12 (2.34) | 13 (2.50) | .054 |
| MMSE | 24.39 (4.88) | 28.90 (1.04) | **<.001\*** |

NB \* significant at *p* <.05. MMSE= Mini Mental State Examination.

## Peripheral hearing levels

In the whole sample, PTAv ranged from 20 dB to 68 dB, with 28 (45%) participants being classified as having a HL. The prevalence of HL was greater in the patients than controls, with 16 people with HL in the patients (52%), 10 with MCI and 6 with dementia, and 12 people with HL in the control group (39%). This difference was not significant, χ² (1) = 3.81, *p*= .283. HL severity was relatively similar across patients and control groups (Figure 7.1). The profile of controls and patients was the same, where normal hearing was reported for the majority of people, followed by mild HL with a few cases of moderate HL, and severe for both MCI and dementia patients (Figure 7.1).

**Figure 7.1.** *Overall percentage of cases of hearing status (normal, mild, moderate or severe hearing loss) per patient and control group.*

### Self-report hearing loss

There was no difference in the number of participants who self-reported HL between patients and controls, where in both groups, 15 participants reported HL and 16 reported no HL. Table 7.2 shows the count of participants in each group with and without a measured HL, which shows that patients may be more likely to report no HL in cases where they do have one and controls may be more likely to report difficulties hearing when they don’t have any.

**Table 7.2.** *The number of participants in each group self-reporting hearing loss according to their behavioural hearing measurements.*

|  |  |  |  |
| --- | --- | --- | --- |
|  | | Controls (n=31) | Patients (n=31) |
| Normal Hearing | No SRHL | 15 | 12 |
| SRHL | 2 | 0 |
| Hearing loss | No SRHL | 1 | 4 |
| SRHL | 13 | 15 |

NB. SRHL= Self-reported hearing loss

### Demographic differences between Patients with and without hearing loss

MCI patients with HL were on average older than MCI patients with normal hearing, this mean difference of 8.08 years was significant (*t* (12.42) = -1.84, *p*=.024), however there was no difference in years of education or mean MMSE scores between the groups (Table 7.3).

There were no significant demographic differences between patients with dementia with and without HL, although on average participants with HL were older compared to those with normal hearing (Table 7.4).

There was no difference in the neuropsychological profiles of patients with and without HL. The results are shown in Table 7.5 for MCI patients and Table 7.6 for dementia patients.

**Table 7.3.** *Demographic characteristics of MCI participants with and without hearing loss*

|  |  |  |  |
| --- | --- | --- | --- |
|  | Normal hearing (n=8) | Hearing loss (n=10) | Significance |
| Age | 59.38 (5.15) | 69.90 (9.55) | **.013\*** |
| Years of education | 12.00 (1.64) | 11.40 (1.71) | .486 |
| MMSE | 26.13 (2.59) | 26.25 (2.79) | .893 |

NB. All results are mean and SD. \*Significant at *p*<.05. MMSE= Mini Mental State Examination.

**Table 7.4.** *Demographic characteristics of dementia patients with and without hearing loss*

|  |  |  |  |
| --- | --- | --- | --- |
|  | Normal hearing (n=7) | Hearing loss (n=6) | Significance |
| Age | 70.43 (8.81) | 73.17 (10.03) | .610 |
| Years of education | 12.57 (3.26) | 12.33 (2.94) | .893 |
| MMSE | 21.43 (5.35) | 22.33 (7.47) | .804 |

NB. All results are mean and SD. \*Significant at *p*<.05. MMSE= Mini Mental State Examination

**Table 7.5.** *The neuropsychological profiles of patients with MCI with and without hearing loss*

|  |  |  |  |
| --- | --- | --- | --- |
| Test | Normal hearing (SD) (n=6) | Hearing loss  (SD) (n=12) | Significance |
| Mini Mental State Examination | 26.13 (2.59) | 26.63 (3.02) | .893 |
| Raven’s Progressive Matrices (PM47) | 28.88 (3.60) | 28.38 (5.13) | .544 |
| Digit Cancellation | 41.00 (8.11) | 48.88 (5.19) | .070 |
| Confrontational Naming | 19.13 (1.36) | 19.38 (0.52) | .478 |
| Verbal Paired Associates | 9.88 (2.85) | 10.88 (3.68) | .442 |
| The Pyramids & Palm Trees Test | 50.50 (1.51) | 51.13 (0.83) | .409 |
| Rey Complex Figure Test: |  |  | |
| Copying | 27.94 (7.05) | 31.38 (5.80) | .408 |
| Delayed (10 minutes) | 10.94 (5.14) | 12.06 (5.14) | .837 |
| Category Fluency | 41.13 (11.73) | 34.38 (7.48) | .168 |
| Letter Fluency | 36.00 (14.94) | 32.50 (7.95) | .330 |
| Digit Span (Forward) | 6.13 (1.46) | 6.13 (1.64) | .897 |
| Digit Span (Backward) | 4.25 (0.89) | 4.25 (1.04) | .952 |
| The Stroop Test: |  |  | |
| Time Interference Effect | 24.44 (5.80) | 39.06 (26.46) | .528 |
| Error Interference Effect | 2.19 (2.99) | 3.88 (6.73) | .149 |
| Visuoconstructive Apraxia Test | 12.39 (1.60) | 10.88 (2.30) | .094 |
| Token Test | 33.42 (1.11) | 33.25 (1.51) | .977 |
| WAIS- Similarities | 19.00 (7.33) | 19.08 (5.01) | .829 |
| Logical Memory: |  |  | |
| Immediate | 9.50 (3.66) | 11.63 (2.91) | .210 |
| Delayed (10 minutes) | 11.00 (6.65) | 14.88 (2.75) | .101 |

NB. SD = standard deviation. \*Significant at *p*<.05.

**Table 7.6.** *The neuropsychological profiles of patients with dementia with and without hearing loss*

|  |  |  |  |
| --- | --- | --- | --- |
| Test | Normal hearing (SD) (n=7) | Hearing loss  (SD) (n=6) | Significance |
| Mini Mental State Examination | 20.00 (5.79) | 25.00 (4.06) | .804 |
| Raven’s Progressive Matrices (PM47) | 20.60 (12.99) | 22.40 (5.46) | .952 |
| Digit Cancellation | 30.60 (20.31) | 41.20 (10.38) | .340 |
| Confrontational Naming | 13.80 (6.69) | 19.20 (0.84) | .089 |
| Verbal Paired Associates | 6.00 (2.00) | 9.00 (2.55) | .079 |
| The Pyramids & Palm Trees Test | 47.20 (3.96) | 48.80 (2.28) | .720 |
| Rey Complex Figure Test: |  |  | |
| Copying | 19.80 (17.20) | 26.30 (8.73) | .490 |
| Delayed (10 minutes) | 4.50 (3.69) | 8.80 (6.66) | .375 |
| Category Fluency | 25.20 (12.79) | 25.08 (7.91) | .903 |
| Letter Fluency | 28.60 (14.48) | 19.60 (11.91) | .317 |
| Digit Span (Forward) | 5.20 (1.10) | 5.20 (0.84) | .756 |
| Digit Span (Backward) | 3.60 (0.89) | 3.20 (0.84) | .341 |
| The Stroop Test: |  |  | |
| Time Interference Effect | 24.30 (21.73) | 35.20 (23.51) | .055 |
| Error Interference Effect | 17.90 (13.41) | 13.42 (13.79) | .227 |
| Visuoconstructive Apraxia Test | 7.40 (5.13) | 10.00 (1.22) | .175 |
| Token Test | 28.40 (6.44) | 29.20 (3.21) | .980 |
| WAIS- Similarities | 12.60 (4.28) | 17.20 (9.31) | .345 |
| Logical Memory: |  |  | |
| Immediate | 6.20 (2.17) | 7.00 (2.74) | .724 |
| Delayed (10 minutes) | 6.20 (4.71) | 9.00 (5.19) | .499 |

NB. SD = standard deviation. \* Significant at *p*<.05.

## SEAH

SEAH scores ranged from 0 to 89, with patients reporting on average higher subjective hearing disability (Median =20, IQR= 34) compared to controls (Median= 11, IQR =29), although this was not significantly different (*U* = 568.5, *p*= .214, *r* = .16). Overall 24 participants were classed as having a hearing disability, 10 controls and 14 patients (9 MCI and 5 dementia).

There was a significant correlation between PTAv and SEAH for the controls (*r*S = .743, *p*<.001) and although the correlation between PTAv and SEAH was still significant for patients, the association was weaker (*r*S = .434, *p* =.015) (Figure 7.2). Figure 7.2 shows that some participants with normal hearing (PTAv <25 dB) reported high levels of hearing disability in the absence of measured HL which was more common for the patients.



**B**



**A**

**B**

F**igure 7.2.** *Scatterplot showing the association between Social and Emotional Association of Hearing loss (SEAH) scores and hearing thresholds for A) patients and B) controls*

### 7.2.3.3.1. The use of hearing aids

Seven controls and twelve patients (8 MCI, 4 dementia) with HL reported wearing hearing aids for varying amounts of time and with various perceived benefits (Table 7.7). There was no difference in PTAv hearing thresholds between participants with HL who wore hearing aids and those who didn’t (*t* (26) =-.742, *p* =.465, *d*= 0.28), suggesting in this instance that hearing severity was not linked with wearing hearing aids. There was no difference in the amount of time patients and controls wore their hearing aids for, with both groups reporting a median of 14 hours (out of a possible 16) per day. On average, patients reported more perceived satisfaction from their hearing aids (Median= 8/10) in comparison with controls (Median=6/10).

**Table 7.7.** *Hearing aid use, compliance and benefit*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Aided | | Hours worn per day | | | Perceived satisfaction | |
|  | **(n)** | **(%)** | **MDN** | **IQR** | **Range** | **Range** | **average** |
| Patients | 12 | 63% | 14 | (8) | 0-16 | 0-10 | 8 |
| Controls | 7 | 50% | 14 | (11) | 4-16 | 4-10 | 6 |

NB. (%) refers to the percentage of participants in each group with HL who wear hearing aids. Perceived satisfaction ranges between 0 and 10 and is a question included in the SEAH questionnaire (Appendix 2).

# Discussion

A higher prevalence of HL was reported for patients compared with matched controls, although this was not significantly different. The non-significant higher prevalence is in keeping with the literature (Idrizbegovic et al., 2011) and could reflect the shared risk factors for dementia and HL such as higher blood pressure, although this was not directly measured. There was however, no relationship between the degree of peripheral HL and level of cognitive impairment; the neuropsychological profiles of patients did not differ between HL groups. Therefore, this suggests in our sample, cognitive impairment was not exacerbated by HL, as patients with HL did not report more severe deficits on any of the neuropsychological tests (Tables 7.5 and 7.6). However, in Table 7.5 there is a moderate difference in scores for patients with MCI with normal hearing and those with HL on the Category Fluency task (7.5 words); and shown in Table 7.6, patients with dementia and HL scored 10.6 points higher on the digit cancellation, and on average 9 words lower on the Letter Fluency tasks. Due to the small sample sizes across the patient groups, statistically significant differences may not be detected due to lack of power. Future studies are required to increase the sample sizes and split groups according to differential diagnosis. This would help to understand if HL associated with any specific disease leading to dementia.

Peters et al., (1988) suggested that patients with AD and HL had faster rates of decline after adjusting for age, compared to AD patients without HL. However, in this current study, cognitive decline was not measured longitudinally, nor was time from diagnosis reported, and thus there is a possibility that HL could lead to an exacerbated phenotype in dementia if these participants have had the disease for a shorter duration. However, this sample did include a mix of MCI and mild dementia cases, and therefore disease severity was controlled for in the selection criteria.

If HL was a driving factor behind the disease severity, the identification of a higher prevalence of HL in the dementia population relative to MCI and controls would be expected, but this was not observed (Figure 7.1). In fact, MCI patients had on average worse hearing than the dementia patients, which does not support the independent risk factor hypothesis, nor is it in keeping with evidence to suggest that severity of HL can predict risk of dementia. As cognitive impairment and HL are progressive, participants with dementia would be expected to have the most severe cases of HL. However, due to the cross sectional methodology, it is hard to infer causality and thus larger samples are needed to be explored over a longer period of time. From these current results no comment regarding whether a HL would lead to a more rapid conversion to dementia can be made, but this would be an interesting factor to follow up.

There was no significant difference between subjective hearing disability for patients and controls, although on average higher levels of disability were reported by patients. Similar results have previously been reported (Strouse et al., 1995), and therefore it is unlikely that the subjective disability associated with HL increased the risk for dementia. Interestingly, the correlation between SEAH and PTAv was a lot weaker for the patient group compared to the controls (Figure 7.2), suggesting that patients with normal hearing may tend to overestimate their hearing disability to a higher degree than controls.

The secondary aim was to investigate the use of hearing aids across the sample, as it has historically been reported that patients with dementia do not use hearing aids. In this sample however, a higher prevalence of hearing aid use was found in patients relative to controls, both patients and controls reported wearing their hearing aids for a significant period of time each day, and patients reported more benefit from their hearing aids. Therefore, this suggests that hearing aid use does not mitigate all of the effects of HL on cognitive impairment risk. Although not tested in this sample, there is evidence that HL may exacerbate the symptoms and have an impact on quality of life in people with dementia (Umeda-Kameyama et al., 2014) and therefore treatment of HL in dementia may be important and should be encouraged. Allen et al., (2003) reported that hearing aids were tolerated well in patients, and both patients and their families felt an improvement in hearing disability with the use of them (Allen et al., 2003).

A limitation to this experiment is that PTAv specificity may be reduced in patients with cognitive impairment, as they may have difficulty following instructions and thus scores may be unreliable (Villeneuve et al., 2017). Therefore, other physiological tests which may be more objective may be better, for example tympanometry, acoustic reflexes or auditory brainstem responses (Kramer, 2014) which may be more useful indicator of true hearing levels in people with cognitive impairment. However, PTAv is recommended for children as young as 5 years old and due to our sample including patients with MCI to mild dementia, it is a suitable measure in our sample. To strengthen the case, the patients sample reported higher numbers of hearing aid users, so can be confident that the HL reported was in fact correct.

# **Experiment 7.2 - Hearing loss: an under-recognised cause of subjective memory problems masquerading as Alzheimer’s Disease**

# Introduction

As introduced in Chapter 1, AD is one of the leading causes of disability in older life, and is associated with a negative prognosis, owing to an often late diagnosis and the lack of available disease modifying treatments. The current licenced therapies have shown a moderate effect in slowing the progression of AD in the earliest stages (O'Brien et al., 2016), and early diagnosis is key for access to these therapies, but also other benefits, such as ability for forward planning to ensure patients and their families feel more prepared and supported (Prince et al., 2011), increased patient safety and postponement of institutionalisation (Dubois et al., 2015). For these reasons, there has been increased attention and motivation around an early diagnosis (Chinthapalli, 2012).

This increased awareness may also lead to increased anxiety in elderly people who are living with symptoms or the risk factors for AD (Corner and Bond, 2004, Cutler, 2015). A large proportion of individuals who present with subjective cognitive complaints to the memory clinics do not necessarily have dementia, but rather are depressed, have a pseudo dementia or have a functional cognitive disorder (Blackburn et al., 2014). Functional cognitive disorder can be defined as subjective cognitive difficulties which cause distress and functional impairment, but which have no underlying neurodegenerative basis (Pennington et al., 2015).

Over the past 6 years, in the UK, there has been a 56% rise in dementia diagnosis (reported by ARUK). Studies investigating the tools used for diagnosis of dementia have reported the MMSE as the most commonly used diagnostic measure (Shulman et al., 2006, Jorgensen, 2012). However, many factors other than cognitive abilities, such as low mood, education and socioeconomic status can have an effect on MMSE performance (Brayne and Calloway, 1990, Rabbitt et al., 1995). According to DSM-IV criteria, the MMSE alone is insufficient to diagnose AD and therefore should not be used as a substitute for systematic evaluation. This was also reiterated by Folstein, the original author of the MMSE, in a response to a Letter to the editor (Folstein et al., 2007). This suggests that if subjective memory difficulties and MMSE performance are taken as diagnostic criteria, these new diagnostic estimates may be overinflating the true number of dementia cases. This was found by a group of Danish researchers, who reviewed medical records to establish the validity of each dementia diagnosis against the ICD-10 and/or DSM-IV criteria. The authors found that the diagnoses were correct in 85% of elderly patients (Phung et al., 2007) and only 58% of cases of early onset dementia (Salem et al., 2012), providing strong evidence for mis- or overdiagnosis. An over- or misdiagnosis of any life threatening disease is costly to both the patient and also to the institution (Welch and Black, 2010), which is why dementia screening is not recommended in the UK (The UK National Screening Committee, 2015). Patients are exposed to treatment harms and the detrimental effects on quality of life that arises from a diagnosis of dementia (Manthorpe et al., 2013).

Due to the insidious onset of HL in the ageing population, it is often under recognised and remains undiagnosed until the later stages (Wallhagen and Pettengill, 2008). People adapting to a HL may commonly report symptoms such as distraction, lack of concentration or confusion and they may appear more forgetful (Dalton et al., 2003), mimicking the symptoms seen in the early stages of AD. A diminished ability to hear and communicate can be frustrating, thus HL is often associated with depression, social isolation, poor self-esteem and communication dysfunction (Mulrow et al., 1990). These confusion-like behaviours, together with the functional disability and low self-esteem, often raise a concern for the individual and family members, and with the increased awareness of cognitive decline in the ageing population, may shift the diagnostic process towards dementia rather than addressing issues with hearing (Jorgensen et al., 2016).

This present study contributes to the current understanding of the links between HL and changes in cognition by reporting the over diagnosis of a gentleman in his 70s, GP, who presented to a memory clinic in another Institution with subjective memory problems and low mood and left with a diagnosis of AD.

# Methods

## Case report

GP, a right-handed male, with 11 years of formal education, presented himself as a volunteer for a feasibility study piloting neuropsychological evaluation in people with and without HL. GP was 76 at the time of first assessment, in September 2015. Of relevance in his background, there was a preliminary diagnosis of early AD, identified by his local memory clinic in 2013. This was based on GP and his wife’s reports of a significant short-term memory decline over the last 12 months, including often forgetting relevant items, such as his wallet when going shopping, or camera when going out for photography. He had a recent lack of understanding of finances and on more than one occasion left the gas cooker turned on. He was still a keen golfer, and no problems were reported playing golf, driving or with personal care, and he often went out alone with no trouble finding his way home. The examination case report stated GP had appropriate behaviour, with normal speech and no flight of ideas. He scored 30/30 on the MMSE, and had insight into his memory impairment. The radiology report stated the MR brain scan showed slight atrophy in the temporal lobes and subsequently the diagnosis of early AD was given. Following this, GP was started on Donepezil medication which he subsequently stopped taking due to side effects.

During the course of research participation, it was noted that there was also a history of depression, apathy and excessive sleeping during the day. He described his current mood levels as bad and memory as average, with periods of absentmindedness and lack of initiative and motivation. GP reported a profound HL, which had been diagnosed about 14 years before, for which he wears two hearing aids. GP noted that his hearing was getting worse and stopping his enjoyment of music, which had previously been a big part of his life. Both GP and his wife described the HL to be more debilitating than the memory problems or AD. During the course of brief neuropsychological testing, GP’s neuropsychological profile showed normal performance on all cognitive tasks, according to neuropsychological norms. GP was then asked to return to the department for further neuropsychological testing and in depth scanning protocol as part of another research study, which he consented to and undertook in November 2015. GPs imaging and neuropsychological results were compared with 9 age (mean= 73.89; SD= 6.60) and education (mean = 14; SD = 2.79) matched male controls who underwent the same assessment protocol.

## Neuropsychological assessment

The neuropsychological assessment included an extensive battery assessing various aspects of cognitive function, with a particular focus on features mostly targeted by normal and pathological ageing. The battery included the MMSE (Folstein et al., 1975) which was used as a global measure of cognition. Different aspects of language were measured by a variety of tests, including the Token Test (De Renzi and Vignolo, 1962) for language comprehension, Confrontational Naming Task (Snodgrass and Vanderwart, 1980) to test word finding abilities, and two tasks of verbal fluency (Lezak, 2004), Category fluency to test semantic processing and Letter fluency to test for executive abilities. The Pyramids and Palm Trees Test (Howard and Patterson, 1992) also assessed semantic memory and episodic verbal memory was measured using the WMS-III Verbal Paired Associates Test (Wechsler, 1997). The WMS-III Logical Memory Test (Wechsler, 1997) was used to test for immediate and delayed recall of prose memory, the Digit Span (Wechsler, 1997) forward tested verbal short-term memory, while the Digit Span backward tested working memory, Digit Cancellation (Spinnler and Tognoni, 1987) measured visual attention and speed of processing and the Stroop Task (Venneri et al., 1992) measured executive function. Visuoconstruction was assessed using the Visuoconstructive Apraxia Test (Spinnler and Tognoni, 1987) and the Rey Complex Figure Test (Rey, 1941) which also assessed long-term visuographic memory. Finally, abstract reasoning was measured using Ravens Coloured Progressive Matrices (Raven et al., 1977) for nonverbal reasoning, and WAIS-Similarities (Wechsler, 1981) for verbal abstract reasoning.

## Hearing assessment

Pure tone audiometry screening was conducted using a CE70 Handheld Pure Tone Warbler as described in 5.2.2.2. GP also completed the SEAH (Chapter 4 for validation) to assess his subjective hearing disability levels, as described in 5.3.2.1.

## MRI data acquisition, preprocessing and analysis

All participants underwent a MRI scanning protocol using a Philips Ingenia 3.0 T scanner. Structural three dimensional T1-weighted scans were acquired using the following acquisition parameters: voxel size= .94 x .94 x 1.0 mm³, field of view= 256 mm, matrix size= 256 x 256 x 124, repetition time= 8.2 msec, echo time= 3.8 msec, and flip angle= 8°.

A number of voxel based morphometry (VBM) pre-processing steps were carried out before running the analysis, including reorientation, segmentation, normalisation and spatial smoothing (Ashburner and Friston, 2000). All pre-processing and analysis was undertaken using Statistical Parametric Mapping (SPM) 12 software implemented in MATLAB R2017a. In detail, manual reorientation ensured all scans were oriented to overlap with SPM 12 template, which was then segmented to isolate and extract complimentary maps of GM, white matter and cerebrospinal fluid. The GM images were then normalised to ensure all scans were orientated in the same stereotactic space, and smoothed with a 8mm³ full-width at half maximum Gaussian kernel to improve signal to noise ratio and reduce artefacts. Finally, GP’s smoothed GM segments were compared to those of the 9 matched male controls using an independent samples t-test. Control participants were scanned with the same MRI protocol.

Statistical threshold level was set at a set level uncorrected *p*<.005, only clusters surviving a family-wise error corrected *p*<0.05 were considered significant.

Left and right hippocampal volumes were extracted using the ‘ROI online extraction tool’ (<http://cmictig.cs.ucl.ac.uk/niftyweb/program.php?p=BRAIN-STEPS>), an online portal which uses the STEPS algorithm (Cardoso et al., 2013) to segment the hippocampi. The hippocampal volumes reported in this study are the mean of left and right hippocampi, which are then presented as a hippocampal fraction to control for total GM, by dividing by total GM volume. A modified t-test (Crawford and Garthwaite, 2007) was used to compare hippocampal volume and fractions between GP and the group of controls.

# Results

## Neuropsychological assessment

During formal neuropsychological testing, GP scored well within the normal range for most of the tests; his overall cognitive profile is summarised in Table 7.8. Compared to the matched controls, GP scored 2 standard deviations above the mean for the digit span (forward) and 2 standard deviations below the mean on the letter fluency test, visuoconstructive apraxia test and the token test. This suggests that GP could have some impairment in ability to organise and manipulate spatial information; however his score was above average for Rey Complex Figure Test which also includes a component of visuospatial constructional ability.

## Hearing assessment

GP’s hearing thresholds averaged at 58 dB HL for the right ear and 69 dB HL for the left ear, giving an overall PTAv of 64 dB HL for both ears, indicative of a severe HL.

The SEAH score was 64%, which greatly breaches the minimum threshold for hearing disability of 25%, suggesting that there is a moderately severe hearing disability.

## Neuroradiological assessment

In comparison to controls, the independent sample t-test reported no significant difference in the whole brain analysis of GP’s brain. Table 7.9 shows the volumetric analysis of the hippocampus and displays no difference in hippocampal volume (*p* = .853) or hippocampal fraction (*p* =.854) between GP and controls. Figure 7.3 shows GP’s brain, where no significant atrophy of hippocampi can be seen. Figure 7.4 shows a coronal section of all of the 9 control participant’s brains, which are virtually indistinguishable from 7.3.

**Table 7.8.** *GP’s scores on the neuropsychological tests compared with the matched controls*.

|  |  |  |  |
| --- | --- | --- | --- |
| Test | GP’s score | Controls Mean Score (SD) | |
| Mini Mental State Examination | 27 | 27.67 | 1.25 |
| Raven’s Progressive Matrices (PM47) | 34 | 33.78 | 1.55 |
| Digit Cancellation | 51 | 52.00 | 8.34 |
| Confrontational Naming | 20 | 19.22 | 0.79 |
| Verbal Paired Associates | 17 | 18.22 | 1.93 |
| The Pyramids & Palm Trees Test | 52 | 51.11 | 0.87 |
| Rey Complex Figure Test: |  |  | |
| Copying | 35 | 31.11 | 4.09 |
| Delayed (10 minutes) | 15 | 17.50 | 3.04 |
| Category Fluency | 46 | 54.56 | 15.14 |
| Letter Fluency | 35\* | 53.67 | 8.97 |
| Digit Span (Forward) | 9 | 6.11 | 1.10 |
| Digit Span (Backward) | 6 | 5.56 | 1.50 |
| The Stroop Test: |  |  | |
| Time Interference Effect | 17.5 | 24.12 | 11.51 |
| Error Interference Effect | 0 | 0.63 | 3.86 |
| Visuoconstructive Apraxia Test | 10\* | 11.60 | 0.80 |
| Token Test | 32.5\* | 34.67 | 0.94 |
| WAIS- Similarities | 26 | 26.50 | 3.32 |
| Logical Memory: |  |  | |
| Immediate | 14 | 13.89 | 2.69 |
| Delayed (10 minutes) | 20 | 18.78 | 1.93 |

\* Score at least 2 SD lower than those achieved by the sample of matched controls

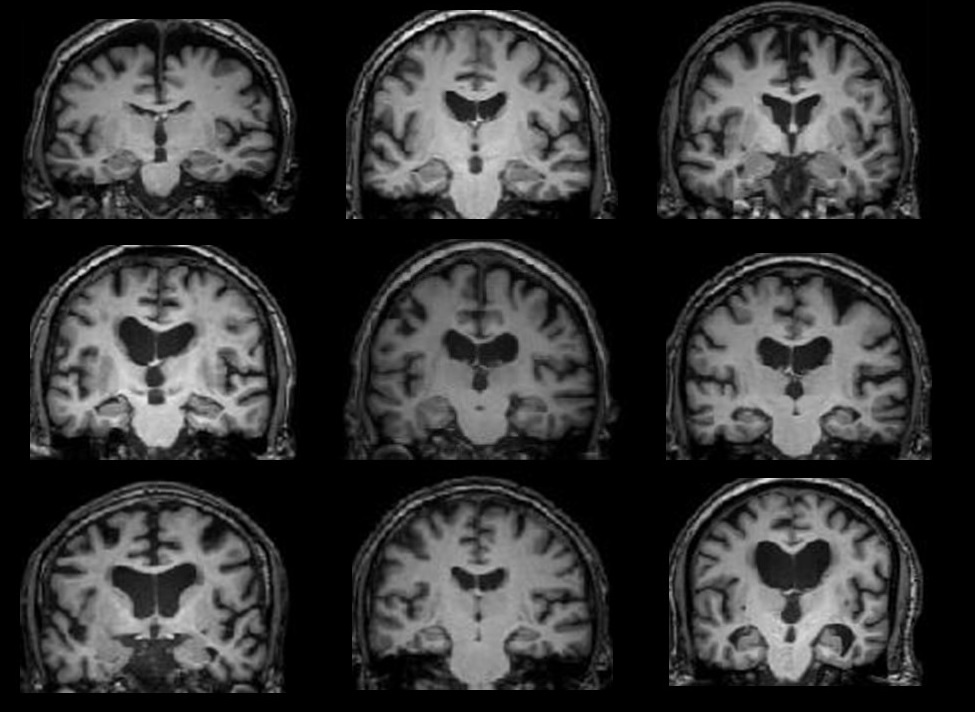
NB. SD = standard deviation

**Table 7.9.** *Hippocampal volumes for GP and controls*.

|  |  |  |  |
| --- | --- | --- | --- |
|  | | **Controls** | |
|  | GP | Mean ± SD | Range | |
| Hippocampal volume (ml) | 2.62 | 2.57 ± 0.249 | 2.14 to 3.03 | |
| Hippocampal fraction | 4.24 x10¯³ | 4.16 x10¯³ ± 0.37 x10¯³ | 3.58 x10¯³ to 4.75 x10¯³ | |



**Figure 7.3**. *Coronal section of GP’s brain showing the hippocampi.*



**Figure 7.4**. *Coronal section of the nine controls brains showing the hippocampi.*

# Discussion

This case study presents a misdiagnosis of AD in a gentleman presenting with subjective memory problems and a severe and debilitating HL. GP’s current neuropsychological profile is not in keeping with early AD, nor someone who has been diagnosed with AD for over two years. This diagnosis was never revised by his consultant, despite lack of evidence for progression of cognitive decline or related symptoms as outlined in the NICE guidelines (2006 (Updated 2016)). Deficits in episodic memory have been termed the clinical hallmark of AD (Weintraub et al., 2012) and GP scored well above normal levels on the Verbal Paired Associates Test of episodic memory. Similarly, it has been reported that semantic disturbance may be the best distinguisher between normal ageing and the early stages of AD (Wakefield et al., 2014, Venneri et al., 2016), and GP scored well within normal limits on tests assessing this. This highlights that the standard diagnostic criteria were not applied in clinical practice and thus reiterates the importance of a diagnostic work up; diagnosis should not rely on screening tests and history alone.

Compared to the matched research controls, GP had poorer performance on the Letter Fluency task, Token Test and Visuoconstructive apraxia test. However, his performance on the Letter Fluency Task and Token Test were well within the normal range of a larger clinical reference sample (Letter Fluency mean=41.44, SD=15.57, Token Test mean=33.87, SD=1.58). The Token Test performance could be confounded by his HL, as this test aims to assess language comprehension, but relies heavily on good auditability as instructions are only given once for each trial. This is supported by another study which documented that there is a significant correlation between HL and performance on the Token Test in a sample of cognitively healthy individuals, where no other associations with HL and cognition were reported (Lodeiro-Fernandez et al., 2015).

The initial report and subsequent two year follow up by GP’s original psychiatrist did not include any mention of HL, or how these could relate to his symptoms. This study highlights the strong connection between HL and psychological symptoms and is consistent with other studies reporting similar findings (Gates and Mills, 2005, Parham et al., 2011). Therefore, the symptoms and psychological associations of GP’s HL could contribute to his subjective memory complaints. Similarly, Lopes et al., (2007) compared MMSE performance between adults with subjective memory complaints and those without, and found there was no significant difference between the groups’ scores. Upon hearing testing, the group with subjective memory complaints had a prevalence of HL of 69% compared to the control group who had a prevalence of 25%, which could suggest that this untreated HL could account for some of the problems associated with subjective memory complaints (Lopes et al., 2007). Therefore a higher percentage of people approaching memory clinics may have cognitive complaints relating to their HL rather than any pathological entity, and thus HL may masquerade as a functional memory disorder.

This problem may be further exacerbated by recent evidence proposing HL as an independent risk factor for cognitive impairment and dementia (Livingston et al., 2017), or suggestions that people with HL may be at a disadvantage whilst undertaking verbally administered cognitive testing (De Silva et al., 2008, Acar et al., 2011). Although this did not happen in GPs original assessment, there is also evidence that individuals with HL may appear to have poorer performance on many tests compared with their normally hearing peers (Acar et al., 2011), but this can be an artefact of the testing procedure and not necessarily a true finding. For example, HL was simulated in a sample of cognitively healthy younger adults, and 16% of participants with a mild to moderately severe simulated HL were ‘misdiagnosed’ as having dementia according to the MMSE, (Jorgensen et al., 2016) which could reflect the number of over diagnosis in the population. Therefore for all of these reasons, it is of upmost importance that the physician is aware of the auditory status of the patient before administration of cognitive tests. However, as GP scored 30/30 on his initial MMSE assessment, the presence of his HL did not bias the clinical performance in this instance, although it may have biased his subjective memory performance, which was subsequently misinterpreted by the memory specialist.

Personally, for GP and his family, the consequences of the AD diagnosis were devastating, where GP reported feeling nervous about telling friends and family, and thus isolating himself so people would not find out. He also reported feelings of anxiousness around driving and cooking, as although he felt competent, he knew these abilities would soon decline along with his cognitive functions. Similar accounts have been reported by patients and health care professionals, who argue that the diagnosis of dementia can affect personal identity, feelings of loss, uncertainty and frustration (Bunn et al., 2012, Le Couteur et al., 2013).

To summarise, HL is a common disorder of the elderly, and symptoms may overlap with those of cognitive decline. Clinicians diagnosing memory problems should assess patients hearing status and the complications associated with HL, such as depression and low self-esteem, before making the diagnosis of dementia. It should be reiterated how important conducting a full psychological profile of a patient before diagnosis, and looking to other possible causes for subjective memory decline in keeping with advances in the research. Treatment of HL with hearing aids and hearing management courses may have a positive effect on the apparent cognitive decline and therefore evade unnecessary over diagnosis of cognitive problems. Failure to make a correct diagnosis led to psychological distress for both GP and his family, which could have been easily avoided.

# **Experiment 7.3 - Central auditory function in persons with neurodegenerative mild cognitve impairment and dementia**

# Introduction

The associations between HL and cognitive impairment may be linked by declines in central auditory processing function. As introduced in Chapter 6, the exact role of cognition on measures of auditory processing is not known, but evidence into the relationship between auditory and cognitive processing has come from studies of patients with cognitive impairment and dementia, where patients with AD have dysregulation in auditory processing (Grady et al., 1989, Gates et al., 1995, Strouse et al., 1995). Therefore this suggests that reduced cognitive capacities may lead to decreased functionality on these tests. However, AD pathology has also been found in the auditory processing pathway (Ohm and Braak, 1989) which may suggest that the pathology is directly responsible for impairment on auditory processing tasks.

For example, Sinha et al., (1993) investigated the features of the auditory system in 9 post mortem AD brains, and reported a specific pattern of distribution of NFT and Aβ plaques throughout the auditory processing pathway nuclei, as well as the primary auditory and auditory association cortices, but not in the cochlear nuclei. Matched controls had no pathology in any of these areas. Some pathological studies have reported none or minimal AD pathology in the primary auditory cortex (Esiri et al., 1986), but increased levels of NFT in the auditory association cortex (Arnold et al., 1991, Esiri et al., 1986), which may further impair these auditory processing abilities, but again, there have been no reports in the peripheral auditory system. As AD doesn’t tend to affect the cochlea, this could be used to support the inconclusive evidence of hearing aid benefit in correcting the consequences of presbycusis. Similarly, it suggests a role linking AD pathology to central auditory dysfunction, which may help to explain higher prevalence rates of hearing difficulties in patients with dementia, and some of the features of diminished language comprehension.

A feature of AD is disruption of language comprehension (Blair et al., 2007) which could also be influenced by diminished auditory processing capacities. Therefore, even though the pattern of cerebral degeneration in AD does not closely link with peripheral HL, the higher processing levels may be dysregulated due to underlying neurodegeneration.

Due to the pathology in the limbic and paralimbic regions (Braak and Braak, 1991), in the early stages of AD, there are impairments in episodic memory formation. Deficiencies of attention and auditory cortical function (auditory attention) can also impair verbal memory registration and encoding (Dhanjal et al., 2013). Dhanjal et al, (2013) investigated whether successful registration and encoding of sentences was reflected in the modulation of activity within the auditory cortex during an fMRI study in patients and controls. In the brains of controls, they reported extensive activity in lateral and midline association cortices of both hemispheres and during successful encoding; there was suppression of activity in the primary and association auditory cortices. However, activation patterns were different in patients, including the suppression of activity in the auditory cortices which was much reduced for MCI and completely abolished in patients with dementia (Dhanjal et al., 2013). This implies that, when listening to speech, there is an altered interaction between the auditory and higher order cortices, together with impairment in auditory attention, which could add to the poorer memory encoding in patients with MCI and AD.

However, another study which measured differences in auditory function between AD patients and elderly and young controls, reported that although there was a difference in the sound localisation, speech discrimination and timbre discrimination abilities between AD and elderly controls, there was no association with age, dementia severity or duration of dementia on any of the peripheral or central auditory tests (Kurylo et al., 1993). The authors concluded that although AD may be accompanied by auditory deficits, these are not reflected in impairment of the auditory functions, especially in auditory association areas which are the most likely to contain pathology. Thus, language disruption seen in AD is not related to deficits in the auditory processing pathway (Kurylo et al., 1993).

Therefore, the mechanisms have not been well defined, but numerous reports have suggested that patients with AD have poorer performance on auditory processing tasks due to temporal lobe atrophy and inhibition of attention processes (Grady et al., 1989). Similarly, a study investigating performance on four central auditory processing tests between 10 individuals with mild to moderate AD and 10 matched controls, reported that AD patients performed significantly worse on three out of the four auditory processing tests (Strouse et al., 1995). Thus suggesting again, that auditory processing tests do not measure the same abilities and thus AD may influence a poorer performance on some due to the overlapping cognitive function required to undertake the test.

The CV dichotic listening paradigm has been suggested as a good measure of central auditory function in AD and neurodegenerative conditions, due to the semantically meaningless CV stimuli (Hugdhal et al., 2009), which therefore will not confound the results in cases where semantic memory is impaired.

The aim of Experiment 7.3 was to investigate whether the central auditory processing abilities, measured by iDichotic, a CV dichotic listening paradigm, vary between patients and controls in this sample, after controlling for the effects of peripheral hearing levels. The second aim was to investigate if there was a difference in baseline laterality between patients with MCI and dementia compared to controls as this would establish whether the disrupted auditory processing were independent of cognitive function, and might be identified on the individual level.

# Methods

## Participants and procedure

The participants included in this sample were the same as Experiment 7.1, described in 7.2.3 with the exception of three participants who could not complete the dichotic listening test of central auditory processing, leaving the sample to consist of 28 patients (17 MCI, 11 dementia). The patients were again compared to 31 age, gender and education matched controls as described in Table 7.1.

The methods are as described in 7.2.2 with the inclusion of the dichotic listening test described in detail in 6.2.2.2. Ethical approval was as described in 7.2.2.1. All participants gave their written informed consent.

## Data analysis

All statistical analysis was undertaken using the same parameters defined in 5.2.2.4.

A series of One Way ANOVAs were conducted to investigate differences between laterality and dichotic performance between the three groups.

Comparisons between neuropsychological testing and iDichotic scores for the whole group were conducted on MMSE, Digit Cancellation and the two measures of verbal fluency, Category Fluency and Letter Fluency, using the non-parametric Spearman’s rho correlation coefficient, with corrected *p* values at *p*=.0125 to control for multiple comparisons between the 4 tests.

Further associations between the extensive battery of cognitive testing and dichotic performance/shift left was undertaken for the patients with MCI and controls with adjusted *p* threshold at *p< 0.01* corrected for multiple comparisons across the 5 tests.

# Results

## Non forced condition

In the whole sample, a right ear advantage was most commonly found, where participants tended to report more correct responses from the right ear compared to the left side (Table 7.10). NF laterality ranged between -35.36 and 51.62. There was a significant difference between NF laterality across the three groups (*F* (2) = 3.720, *p*= .030, ɳ²= 0.12), where controls reported a more positive (right) laterality (mean= 12.34, SD= 12.67) compared to both patients with MCI (mean=0.37, SD=18.24) and dementia (mean=7.52, SD=13.11) (Figure 7.5). Post hoc Bonferroni comparisons showed that this mean difference was only significant between controls and MCI patients (*p*= .026) but not controls and dementia patients (*p*=1.00) or patients with MCI or dementia (*p*=.629). It is clear from Figure 7.5, that although the controls gave more correct answers from the right and left ears, the pattern of right ear advantage was similar for controls and patients with dementia. Conversely, patients with MCI showed no laterality, by reporting on average similar numbers of correct responses from both ears.

**Table 7.10.** *Ear advantage according to patient and control group*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Ear Advantage | Control (31) | MCI (17) | Dementia (11) | Total |
| None | 7 | 3 | 5 | 15 |
| Right | 21 | 8 | 5 | 34 |
| Left | 3 | 6 | 1 | 10 |



**Figure 7.5.** *Correct (mean and SD) responses from right and left ear responses under the non-forced condition for patients and controls*

## Forced conditions

Overall scores on the iDichotic were significantly different between patients and controls (F (2) = 7.53, *p*=.001, ɳ²= 0.2) (Table 7.11). Post hoc Bonferroni comparisons showed that the mean differences were significant between controls and MCI patients (*p*=.044) and controls and dementia patients (*p*=.002), and although the mean performance was lower for dementia patients relative to the MCI group, the difference was not significant (*p*=.619) (Figure 7.6).

**Table 7.11.** *Mean overall performance on iDichotic for patients and controls*

|  |  |  |
| --- | --- | --- |
|  | Mean | SD |
| Control (n=31) | 39.65 | 10.87 |
| MCI (n=17) | 31.71 | 9.89 |
| Dementia (n=11) | 26.55 | 9.90 |



**Figure 7.6.** *Overall performance on concentrate tasks of iDichotic.*

NB. Error bars denote standard deviation. \*p <.05, \*\*p <.01, ns = not significant. Overall score is expressed as a percentage.

### Forced right

Overall, there was a shift in laterality to the right under the FR condition, shown in the middle section of Figures 7.7 A, B and C**.** Controls could on average increase their correct responses from the right ear relative to the NF condition (Figure 7.7A). Similarly, as shown in Figure 7.7B, MCI patients increased their responses from the right ear and decreased the number of correct responses from left ear relative to the NF condition, to achieve a shift towards right laterality. Finally, Figure 7.7C shows that dementia patients could marginally (non-significant mean difference of 0.90%) increase their correct responses to the right ear, but still showed a right laterality similar to the NF condition. Results from the one-way ANOVA showed that there was no significant difference between the ability to shift to the right between the three groups (*F* (2, 56) = 1.59, *p*= .214, ɳ²= 0.05). Similarly, Attend right was not significantly different between the three groups (*p*=.428), as shown in Figure 7.8.

**A**

**B**

**C**



**Figure 7.7.** *Correct right and left ear responses for A)**controls, B)**MCI patients and C)**dementia patients under all conditions.*

NB. R= Right ear, L= Left ear, NF= non-forced, FR= forced right, FL= forced left. Error bars denote standard deviation.



**Figure 7.8.** *Ability to Attend Right under the FR condition for all groups*

### Forced left

Overall, there was a shift in laterality to the left under the FL condition as shown in the final section of Figures 7.7. Figure 7.7A shows that controls were able to overcome their REA by reducing the number of responses from the right ear and increasing the number of correct responses from the left side. MCI patients could not increase their responses to the left ear relative to the NF condition (Figure 7.7B). Figure 7.7C shows that patients with dementia still reported more correct responses from the right ear, although there was a marginal increase in left ear responses relative to the NF condition. Results from the one-way ANOVA showed there was a significant difference between the ability to shift to the left between the three groups (*F* (2, 56) = 4.51, *p*= .015, ɳ²= 0.14) (Figure 7.9). Bonferroni post hoc comparisons demonstrated that this difference in shift left was only significantly different between controls and patients with MCI (*p*=.025) but not controls and dementia patients (*p*=.144) or MCI and dementia patients (*p*=1.00).

The amount of shift left was independent of age (*r* = .072, *p*= .586), education (*rS* = -.200, *p*= .129) or PTAv (*rS* = .084, *p*= .525) for controls and patients.



**Figure 7.9.** *Shift in laterality to the left under FL condition for all participants.*

NB. Error bars denote standard deviation

The ability to Attend to the left varied between patients and controls (Figure 7.10), where a significantly higher proportion of controls could attend to the left compared with both groups of patients (*p* =.013). There was no significant correlation between age, years of education or PTAv with shift left for any of the three groups, as shown in Table 7.12.

Sixty eight percent of controls could attend to the left side, compared with 29% of MCI and 27% of patients with dementia. Adjusted residuals and estimated *p* values suggest that there was a significant difference between controls and the null hypothesis (*p*= .003) but not for patients with MCI (*p*=.057) or dementia (*p*=.110), therefore controls are significantly more likely to attend to the left.

**Table 7.12.** *Correlation coefficient showing no association of demographic factors on shift left*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Controls | | MCI | | Dementia | |
| *r=* | *p=* | *r=* | *p=* | *r=* | *p=* |
| Age | .286, | *.118* | .034 | .897 | -.463 | .151 |
| PTAv | .108 | .562 | .015 | .955 | .019 | .955 |
| Education | -.190 | .306 | -.107 | .681 | -.012 | .971 |



**Figure 7.10.** *Ability to attend to the left under FL condition for all groups*

## Neuropsychology and auditory processing

On the complete patient sample level, there was a significant correlation between Digit Cancellation (*r*S = .443, *p*=.001) and Category Fluency (*r*S = .386, *p*=.004) with Overall iDichotic performance. There was also a significant correlation between the degree of shift to the left (ShiftLeft) and Digit Cancellation (*r*S = -.393, *p*=.004), including the time component (*r*S= .468, *p*=.018), and the Category Fluency Task (*r*S = .408, *p*=.002). There were no significant correlations between ShiftLeft and MMSE or Letter Fluency performance.

Taking just the patients’ neuropsychological performance into account, there was no significant difference in cognitive scores between the patients who could Attend to the left and those who could not (Table 7.13).

**Table 7.13.** *The neuropsychological profiles of patients who could and could not Attend Left*

|  |  |  |  |
| --- | --- | --- | --- |
| Test | Not Attend (SD) | Attend Left (SD) | Significance |
| Mini Mental State Examination | 24.71 (3.48) | 27.33 (2.80) | .132 |
| Raven’s Progressive Matrices (PM47) | 26.18 (6.06) | 29.00 (4.94) | .399 |
| Digit Cancellation | 41.65 (11.39) | 45.67 (5.57) | .819 |
| Confrontational Naming | 17.88 (4.28) | 18.33 (1.63) | .724 |
| Verbal Paired Associates | 8.18 (2.53) | 11.00 (3.41) | .274 |
| The Pyramids & Palm Trees Test | 49.71 (2.47) | 50.83 (1.47) | .301 |
| Rey Complex Figure Test: |  |  | |
| Copying | 28.18 (8.52) | 29.67 (7.45) | .974 |
| Delayed (10 minutes) | 9.32 (5.92) | 12.17 (6.25) | .425 |
| Category Fluency | 32.53 (10.98) | 63.17 (12.54) | .976 |
| Letter Fluency | 30.18 (14.42) | 33.17 (10.61) | .895 |
| Digit Span (Forward) | 5.59 (1.23) | 5.67 (1.37) | .880 |
| Digit Span (Backward) | 3.71 (0.92) | 4.50 (0.55) | .117 |
| The Stroop Test: |  |  | |
| Time Interference Effect | 36.29 (22.05) | 27.17 (8.92) | .192 |
| Error Interference Effect | 5.85 (9.37) | 3.42 (3.47) | .988 |
| Visuoconstructive Apraxia Test | 10.88 (3.16) | 11.00 (2.53) | .737 |
| Token Test | 31.79 (3.23) | 33.25 (1.60) | .701 |
| WAIS- Similarities | 16.35 (7.04) | 19.50 (5.32) | .292 |
| Logical Memory: |  |  | |
| Immediate | 8.35 (2.62) | 12.00 (3.58) | .174 |
| Delayed (10 minutes) | 10.65 (4.61) | 12.67 (6.77) | .843 |

NB. SD = standard deviation

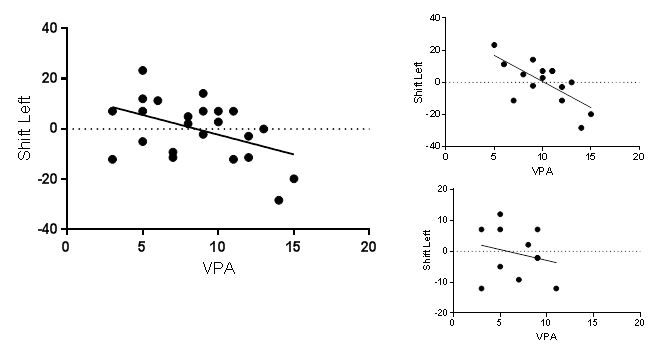
There was a significant relationship between ShiftLeft and performance on the Verbal Paired Associates (VPA), The Rey Complex Figure Delay (ReyDelay), and the time component of the Stroop Test (Stroop) within the whole patient sample (Figures 7.11 to 7.13A). Simple linear repression shows a significant association between ShiftLeft and scores on the VPA test for all patients, regression equation ShiftLeft = 8.67 – 0.13 (VPA), R² = .200, F (1, 24) = 5.99, *p*=.022. Similarly for the Rey Complex Figure Delay, regression equation ShiftLeft = 9.38 - 0.23 (ReyDelay), R² = .184, F (1, 24) = 5.40, *p*=.029, and the Stroop, regression equation ShiftLeft = 34.48 + 0.72 (Stroop), R² = .174, F (1, 23) = 4.84, *p*=.038.

However, Figure 7.11 shows that the strongest association was found for the MCI group (Figure 7.11B), and there was no correlation between ShiftLeft and VPA performance in the dementia group, due to the floor effects of the tests (Figure 7.11C).

The scatterplot (Figure 7.11B) shows a strong linear relationship between the two variables for the MCI patients, confirmed by the Pearson’s correlation coefficient of *r* = .698. Simple linear regression showed a significant relationship between ShiftLeft and scores on the Verbal Paired Associates (*p* = .003). The regression equation was ShiftLeft = 10.10 + -.146 (VPA), the R² value was .483, suggesting that ShiftLeft could explain 48.3% of the variance in VPA within the MCI group.

There was a significant relationship between ShiftLeft and Rey Delay or Stroop Test (Time) for the separate patient groups, suggesting that ShiftLeft can explain 18.4% and 17.4% of the variance in these tests respectively, however not within each sample separately.

**B**



**C**

**A**

**Figure 7.11.** *ShiftLeft and Verbal Paired Associates for A) all patients, B) MCI patients and C) dementia patients*

**C**

**B**

**A**



**Figure 7.12.** *ShiftLeft and Rey Complex Figure (Delay) for A) all patients, B) MCI patients and C)**dementia patients*

**B**

**A**

**C**



**Figure 7.13.** *ShiftLeft and Stroop Test (Time) for A) all patients, B) MCI patients and C) dementia patients*

# Discussion

Under the NF conditions, controls on average reported more correct answers from the right ear, and fewer correct answers from the left ear, resulting in the expected REA. Patients with dementia had a pattern of laterality that followed that of controls; however the number of correct answers from both the right and left side were much reduced. Conversely, MCI patients on average did not have a positive laterality under NF conditions, and on average reported equal numbers of correct answers from the right and left ears, suggesting that they had lost the REA. Table 7.10 shows that a much higher percentage of participants with MCI have a LEA. A recent study investigating the effects of ageing on the NF laterality, administered the same iDichotic listening paradigm to over 3,800 participants, reported that the REA increases with age (Westerhausen et al., 2015). They also reported that this increased REA is not due to more correct responses from the right ear, as these remained relatively constant, but due to a decline in left ear performance (Westerhausen et al., 2015). A different profile to that of ‘normal’ ageing was reported in the dementia condition, where a decline in the number of correct responses from both the right and left ear was found. As the NF condition does not heavily rely on higher order cognitive processes (Westerhausen et al., 2015), poorer performance is potentially indicating reduced central auditory function in people with dementia. The fact then that, in this present study, this pattern of free recall was entirely different in MCI patients, where there were a decreased number of correct responses from the right ear and increased level of correct responses from the left ear, suggest there is a change in the auditory processing abilities, which may reflect a compensatory mechanism.

For example, the right hemisphere might be recruited to compensate for the early stages of pathological changes to the preponderant left hemisphere. As alluded to in Chapter 1, other studies have shown that connectivity and function can go both ways in MCI group, and this bidirectional outcome may suggest that the system is suffering. Thus, the increased numbers of LEA and NEA in MCI could reflect the bilateral processing dominance rather than a left hemispheric dominance for linguistic processing. It has been reported in the later stages of the disease, such as AD, there is a left hemispheric dominance of atrophy, where the left hemisphere appears more susceptible to neurodegeneration as changes in left hemisphere precede the changes in the right (Loewenstein et al., 1989, Janke et al., 2001, Thompson et al., 2003, Donix et al., 2013). Thus, it is possible that during the MCI phase auditory processing may be more right lateralised to maintain the function of auditory processing disrupted by a failing left hemisphere.

As there was no difference in age or education levels between the 6 MCI patients with a left ear advantage and the rest of the MCI group, it is not easy to explain why adaptive processes may be more active for these individuals, but it may signify a differing aetiology or stage of neuropathological disease progression. A major limitation is the small sample size of the MCI group, and investigating central auditory function in a larger group of patients with MCI over time would be interesting to investigate whether they would report REA when they will reach the dementia phase.

Under the forced conditions, there was a step wise reduction in the Overall iDichotic performance, relating to the severity of cognitive impairment. On average, controls performed better than MCI patients, who performed better than dementia patients (Figure 7.6). Comparable findings have been described by Gates et al., (2008a) and Grimes et al., (1987) who reported performance on the staggered spondaic word test, another dichotic speech paradigm, related to the degree of temporal lobe impairment in patients with AD (Grimes et al., 1987). A more recent study reported a gradient of CAP dysfunction where AD patients performed significantly worse than controls and MCI, and MCI patients significantly worse than controls (Idrizbegovic et al., 2011). Idrizbegovic et al., (2011) also reported a stronger REA for AD than MCI and controls, where differences were most strongly found under the FL conditions. These findings closely mirror ours; suggesting that patients with AD or a neurodegenerative dementia, have a bottom up right ear advantage which cannot be modified by top down processing.

The ability to ‘Attend’ to the right did not differ between the three groups, which has been reported in the literature (Claus and Mohr, 1996, Bouma and Gootjes, 2011), but there was a significant difference between Attend left, where controls were more likely to be able to Attend than the other two groups. Due to this situation involving cognitive conflict (Hugdahl et al., 2009), it is hypothesised that this was due to a top down failure to modulate attention rather than a failure of bottom up lateralised perception. This is supported by the fact there were no reported differences in left ear hearing acuity and it symmetrical hearing thresholds across all participants were assured.

The forced conditions enabled further investigation into the function of the MCI group. It was reported that the LEA was found in patients with a more severe MCI, as demonstrated by the association with the cognitive tests, namely the VPA test which measures explicit episodic memory performance. Therefore, supported by the findings of an fMRI study reported in section 7.4.1 (Dhanjal et al., 2013); the ability to encode memories may be closely linked with the integrity of the central auditory processing pathway. Figure 7.11B demonstrates that ShiftLeft could significantly predict the variance in cognitive performance on this test, and thus this reduction in hemispheric asymmetry might be due to increased levels of pathology driving the adaptive process. As auditory processing becomes dysregulated during the MCI phase, it could be suggested that disruption of auditory processing under the NF condition may be a marker of disease severity. There was no association between ShiftLeft and cognitive performance for dementia patients alone, due to low group performance with little variance between the scores, reflecting the floor effects on the tests. These are clearly demonstrated in Figures 7.11 and 7.12C, which show much lower scores for the dementia patients with little variance.

Our results closely support findings from a recent fMRI study investigating auditory laterality in premanifest and manifest Huntington’s disease, using an auditory stimulation programme. The authors reported controls had a mainly left hemispheric activation, which was unexpectedly reversed in people with premanifest Huntington’s disease to an increased right activation. The premanifest Huntington’s disease groups were further split by time to conversion, into close and far, which then led to the finding that the ‘far’ patients had higher left hemispheric activation, but the ‘close’ premanifest Huntington’s disease group showed no difference in activation between the right and left hemisphere (Saft et al., 2008). This mirrors the behavioural results in our MCI group which showed no lateralisation under the NF condition, and could suggest compensatory changes via recruitment of additional brain areas and correlates with cognitive performance suggesting these patients may be close to conversion to dementia.

The results are not in accordance to those reported by Krishnamurti et al., (2011), who found that there was no clear difference in auditory processing function between individuals with AD and controls, and concluded that central auditory function declines naturally with age rather than as a result of pathology. Also, Duchek and Balota (2005) reported no evidence of recruitment of the right hemisphere in patients in the ‘very mild’ mild AD group. However, as previously alluded to, different measures of auditory processing all measure slightly different auditory aspects, which could explain the disparity in findings.

Different cholinergic pathways play an important role in attention (Oros et al., 2014), which could also have an influence on the dichotic listening task for some patients, with AD for example. A limitation of this experiment was that patient medication was not reported. Donepezil, a medication prescribed to patients with AD, has been shown to restore the normal response of the auditory cortex to that of controls during tasks of auditory verbal memory encoding (Dhanjal et al., 2013). Similarly, it has been suggested that the auditory cortex may directly receive cholinergic innervation (Hutsler and Gazzaniga, 1996, Metherate, 2011). Therefore, some of the beneficial effects of Cholinesterase inhibitors may operate through modulation of the function of the auditory cortex, which could help to explain why some participants with dementia could Attend to the left and some could not. Also, not all of the dementia group were AD patients and thus would not have received any anticholinesterase medication. Another study has reported that patients with Parkinson’s disease could selectively Attend to the left whereas individuals with AD and Huntington’s disease dementia could not (Claus and Mohr, 1996), suggesting that this ability may be linked to disease specific or cognitive specific degeneration.

Although the majority of poorer results was found in the patient groups, some control individuals also obtained poor performance on the iDichotic which indicates that tests may have less than perfect specificity for identifying cognitive impairment or neurodegeneration, which has also been reported by Gates et al., 2008. Therefore, without longitudinal data it cannot be concluded whether dichotic listening performance could be a marker for underlying neurodegenerative pathology, but as there appears to be a close link with disease progression it is likely that this method may be a way to assess disruptions in inter- and intrahemispheric connectivity in the early stages of disease.

# **Experiment 7.4 - Structural brain changes in ageing, presbycusis and cognitive impairment**

# Introduction

It has been well documented that cognitive decline in ageing is associated with structural and functional changes to the brain. As introduced in 1.2.1, imaging studies have shown that older adults have regional and global grey matter (GM) reduction, reduction in white matter, and disrupted connectivity between different neuronal networks (Jernigan et al., 2001, Good et al., 2001, Cabeza et al., 1997, Cabeza, 2001, Raz et al., 2005). These changes can be domain specific and the association cortices, cerebellum, caudate and hippocampus are postulated to be the most affected by ageing, with relative sparing of sensory areas (Raz et al., 2005). For example, in a study by Hafkemeijer et al., (2014), GM regions were organised into anatomical networks so that the effects of ageing on the separate networks could be evaluated. The authors reported no association between ageing and declines in GM of the auditory network (the exact regions of which were undefined), although the network which showed the greatest age related decline included the thalamus, nucleus accumbens, caudate nucleus, hippocampus and Heschl’s gyrus (Hafkemeijer et al., 2014). As the primary auditory cortex is located within Heschl’s gyrus (Morosan et al., 2001), it is plausible that this area is also degenerated with ageing. In the same way, age related declines in the auditory system are inconsistent and highly confounded by the prevalence of HL. Some studies have reported changes in GM volume of the auditory cortex in people with HL (Eckert et al., 2012, Boyen et al., 2013, Qian et al., 2017) and others have found no association (Profant et al., 2014, Rigters et al., 2017).

## Structural changes to the auditory cortex and other brain regions as a result of hearing loss

The human auditory cortex is located in the superior temporal gyrus although the exact location and functional boundaries have not been fully described (Hackett, 2015). Therefore, inconclusive and conflicting evidence may result from differences in the regions used to define auditory areas throughout the studies (Cardin, 2016). Table 7.14 outlines the main methods and findings of previous VBM studies investigating GM changes, which reflects the overlapping and inconsistent evidence, for not only the direct effects on auditory areas, but wide-spread neuroanatomical GM differences amongst people with different hearing abilities.

Table 7.14 shows there is evidence that HL is associated with reduction in GM volume in the auditory cortices, (Husain et al., 2011, Peelle et al., 2011, Eckert et al., 2012) where Hussain et al., (2011) and Peelle et al., (2011) reported bilateral decreased GM in the primary auditory cortices, while Eckert et al., (2012) reported this reduction was stronger in the left auditory cortex. The GM atrophy was most pronounced in the Tel.0 region, which was believed to include the primary auditory cortex, which receives the greatest thalamic input; the authors proposed that peripheral presbycusis has a direct effect on the integrity of thalamic inputs to the auditory cortex, mediating changes which lead to cortical atrophy independently of age (Eckert et al., 2012). These finding are strengthened by a recent study which, using a software algorithm to calculate atrophy based on the ratio of CSF to parenchyma, has reported that high frequency HL correlates with temporal lobe atrophy, independently of the effects of age (Qian et al., 2017).

However, Boyen et al., (2013) reported that participants with HL actually had increased volumes of GM in the right superior temporal gyrus, specifically in Brodmann area (BA) 22, the auditory association cortex. Other studies have reported no differences in GM volumes in auditory areas, including Heschl’s gyrus, planum temporale and inferior frontal gyrus, between individuals with and without HL (Profant et al., 2014), which has been corroborated by the findings at baseline from a longitudinal study, which reported no GM differences relating to hearing acuity (Lin et al., 2014).

Inconsistent evidence may be due to the fact that many of these studies have been carried out on relatively small samples. A recent study investigated the effects of HL on cortical integrity in a large population cohort of almost 3,000 participants (Rigters et al., 2017). The authors reported that higher hearing thresholds were significantly associated with smaller total brain volumes, which were primarily driven by decreases in the white matter, but there were no significant changes in GM volume in any areas. A longitudinal study investigating the association of HL on rates of brain atrophy followed 126 participants for an average of 6.5 years, and reported that the presence of HL was associated with increased rates of atrophy of total GM and specifically in the right temporal lobe, which was not related to severity of HL (Lin et al., 2014).

This longitudinal study has provided evidence that HL is associated with accelerated whole brain and right temporal lobe atrophy, which may have an effect on cognitive function. The authors reported that 13 participants were excluded from the follow up part way through the experiment, due to the development of incident dementia (Lin et al., 2014). However, their scans were included in the analysis up until their diagnosis, which could potentially influence the results, as higher rates of atrophy would be expected in individuals in the early or preclinical stages of dementia (Lehmann et al., 2013, Zahodne et al., 2015b). The authors did not report whether these individuals had HL, as this would have been interesting to investigate whether the accelerated rates reported were due to impending cognitive impairment. This, together with the inconsistent evidence provided in Table 7.14, highlights the fact that some other factor to peripheral hearing levels may be driving the reductions in GM, which could include underlying cognitive impairment.

Previous studies have not investigated the role of HL in patients with cognitive impairment, or the effects of both HL and underlying neuropathology. Therefore, it is not known whether people with HL who have GM atrophy are at risk of cognitive impairment, or whether the reductions in GM are due to a common cause mechanism. Therefore, the aim of this study was to investigate whether HL is associated with structural GM changes in a VBM correlation study, including individuals with cognitive impairment. The secondary aim was to identify whether this association were different in cognitively healthy adults and patients with a neurodegenerative cognitive decline. The hypothesis was that HL may be associated with reductions in GM volume in auditory areas, that might be more pronounced and extend to extra-auditory regions in patients.

**Table 7.14.** *An overview of previous VBM studies investigating grey matter changes with hearing loss*

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| Authors | Participants (n) | Mean age (SD) | Methods | Findings |
| --- | --- | --- | --- | --- |
| Husain et al., (2011) | HL = 7  NH = 11  (TIN + HL= 8) | HL = 51.38 (11.45)  NH = 48.09 (10.42)  (TIN + HL = 56.13 (7.04)) | Cross sectional  HL: classified by threshold >25 dB between 250 Hz to 8 kHz  MRI: ANOVA followed by t-test between HL and NH, whole brain and ROI  Covariates: TIV  ROI mask x2 (1 x subcortical auditory nuclei, 1 x cortical auditory regions)  (\*)ANOVA+cortical auditory mask with PTAv as regressor | Whole brain:  HL ↓ right anterior cingulate  HL ↓ bilateral MFG  ROI:  ↓ bilateral STG  (\*)  ↓ bilateral MFG  ↓ left anterior cingulate  ↓ left SFG |
| Eckert et al., (2012) | 49 (varying levels of hearing acuity) | 69.58 (8.22) | Cross sectional  HL: factor analysis to classify high (HFHL) and low (LFHL) frequency metrics, based on frequencies between 250 Hz and 8 kHz  MRI: multiple linear regression analysis, whole brain and ROI  Covariates: TGM  ROI PAC masks x3 including Tel.0, Tel.1 and Tel.2 | Whole brain:  HFHL ↓ bilateral PAC (stronger in left side) most prominently in Tel.0 and Tel.2  HFHL ↓ left primary somatosensory cortex  ROI:  HFHL ↓ bilateral PAC (specifically Tel.0)  LFHL ↓ left Tel.2 in females only |
| Boyen et al., (2013) | HL = 16  NH = 24  (TIN + HL= 31) | HL = 63.00 (10.00)  NH = 58.00 (6.00)  (TIN + HL= 56 (9.00)) | Cross sectional  HL: PTAv at frequencies 1, 2 and 4 kHz of between 30 to 60 dB in both ears  MRI: ANCOVA, followed by t-test between HL and NH, whole brain and ROI  ROI based on 78 BA, 8 subcortical auditory nuclei and 2 cerebellum | Whole brain:  HL ↑ right STG  HL ↓ right occipital lobe  HL ↓ right hypothalamus  ROI:  HL ↑ right BA 22  HL ↑ bilateral BA 35  HL ↑ right BA 36  HL ↓ bilateral BA 8  HL ↓ bilateral BA 9  HL ↓ left BA 11 |
| Lin et al., (2014) | HL = 51  NH = 75 | HL = 73.80 (7.3)  NH = 67.00 (6.9) | Longitudinal (mean 6.4 years)  HL: PTAv >25 dB in the better hearing ear at frequencies 0.5, 1, 2 and 4 kHz  MRI: TIV at baseline, ROI= STG, MTG, ITG, Hippocampus, PHG, Entorhinal Cortex, Perirhinal Cortex, Frontal lobe, parietal lobe, occipital lobe  For each volume a linear mixed effect model association of HL as a time invariant predictor in brain volume over time  Covariates: TIV, age, gender, hypertension, years of follow up from baseline  (\*\*)analysis with only age and gender as covariates  NB, did not perform adjustment for multiple comparisons | Baseline: no differences GM volume  FU: significant rate of atrophy across all ROI for all participants  HL accelerated rate of ↓ in right STG, MTG, ITG and PHG and whole brain independent of right temporal lobe ↓  No association with severity of HL and rate of decline  (\*\*)HL ↓ right:  precentral gyrus (BA 44), STG (BA 22), hippocampus (BA 28), Insula (BA 47 & 48), MTG (BA 20)  HL ↓ left middle cingulum (BA 23) |
| Profant et al., (2014) | Older, Mild HL = 17  Older, Severe HL = 17  Young, NH = 20 | Mild HL = 67.9 [0.45]  Severe HL = 70.38 [1.18]  NH = 24.34 [0.51] | Cross sectional  HL: measured frequencies between 125 Hz to 8 kHz, and then 10, 12.5 and 16 kHz  MRI: Multiple linear regression with ROI  ROI mask x 4 (HG, planum temporale, SFG and visual cortex)  Age associations = young NH \* Mild HL  HL association = Mild HL \* Severe HL | No associations with HL after controlling for age  Age ↓ bilateral HG and planum temporale (stronger for right)  Age ↓ bilateral visual cortex |
| Rigters et al., (2017)  210  Rigters et al., (2017) continued | 2908 (varying levels of hearing acuity) | 64.90 (7.3) | Cross sectional  HL: PTAv of frequencies between 125 Hz to 8 kHz  MRI: 2 x Multiple linear regression models  Model 1: adjusted for age, gender, time between MRI and hearing test, TIV  Model 2: adjusted for MMSE, education, blood pressure, diabetes, cholesterol, BMI, alcohol intake and smoking | HL ↓ brain volumes  When measured GM and WM independently, no statistical association between PTAv and GM (did not survive threshold for multiple comparisons) but trend towards:  HL ↑ bilateral SFG  HL ↑ left SPG  HL ↓ right MOG  (changes in WM driving smaller brain volumes) |
| Qian et al., (2017) | 34 (all with HL) | 85.50 (4.6) at hearing test  83.20 (4.5) at MRI | Cross sectional  HL: factor analysis to classify high (HFHL) and low (LFHL) frequency metrics, based on frequencies between 250 Hz and 8 kHz in the better hearing ear  MRI: Software algorithm to quantify ‘atrophy’ rather than GM/WM volumes using ratio of CSF to parenchyma based on FLAIR templates. Generated whole brain and lobar specific atrophy estimates for each hemisphere. Linear regression of HL and atrophy | HFHL correlated with temporal lobe atrophy, independently of age  LFHL = no associations with any measure of atrophy |

Abbreviations: HL= hearing loss, NH= normal hearing, TIN+HL= tinnitus with hearing loss, ROI= region of interest, MFG= medial frontal gyrus, STG= superior temporal gyrus, SFG= superior frontal gyrus, PAC= primary auditory cortex, TGM=total grey matter, BA=Brodmann area, MTG=medial temporal gyrus, ITG=inferior temporal gyrus, PHG=parahippocampal gyrus, TIV=total intracranial volume, HG= Heschl’s gyrus, BMI= body mass index, SPG= superior parietal gyrus, MOG= medial orbital gyrus.

NB, studies by Hussain et al., (2011) and Boyen et al., (2013) included associations between tinnitus (HL+TIN) which results have not been reported for. WM was also investigated by Hussain et al., (2011) and Rigters et al., (2017) which has not been reported.

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# Methods

## Participants and procedure

Ten patients with neurodegenerative cognitive impairments (9 MCI, 1 AD) from the memory clinics at the Royal Hallamshire Hospital, Sheffield, and 25 cognitively healthy controls were included in this study. Participants were originally recruited as part of another large European study, VPH-DARE@IT.

Exclusion criteria consisted of any other major medical conditions including presence of cardiovascular disease, psychiatric disorders, history of stroke and ineligibility to qualify for MRI scanning, such as presence of ferromagnetic implants or pacemakers. Patients with MRI abnormalities on structural scans were excluded from the study.

All participants underwent in-depth neuropsychological examination by a Clinical Psychologist to classify them as healthy or with cognitive impairment. Participants were then recruited to this study on a follow up visit to the department, and consented to the retrospective analysis of their MRI scans.

## Hearing assessment

All participants underwent peripheral hearing testing as described in 5.2.2.2.

## MRI data acquisition, preprocessing and analysis

All participants underwent the same MRI scanning protocol, and pre-processing steps as described in 7.3.2.4. In addition to this, multiple regression was performed to characterise the extent to which GM volume was associated with peripheral hearing thresholds using a whole brain approach. Voxel-based analysis included the following covariates: age and GM fraction as a proxy of GM volume, to examine specific associations of hearing thresholds independently of the global variance in GM volume. Separate regressions using the same parameters were run then for patients and controls.

In all models, the statistical threshold level was set at a set level uncorrected *p* <.001, only clusters surviving a family-wise error *p* <0.05 were considered significant. Peak MNI coordinates were converted to Talairach space to facilitate the interpretation of results, using the Talairach Daemon (Lancaster et al., 2000).

Data analysis between groups was undertaken using IBM-SPSS statistics software, v22. Two-tailed hypotheses were tested, and a significant *p* value was set at .05. To explore the demographic differences between the patients and controls, independent samples t-test was used. Where the assumption of homogeneity of variance was violated, the degrees of freedom were adjusted to reflect this. Differences between the categorical variable gender were explored using Fisher’s Exact Test, as the assumptions of Pearson’s χ² were violated.

# Results

## Participants

The complete sample included 35 participants, ranging between 49 to 88 years. There were 18 males and 17 females, with between 10 and 20 years of education. The demographic characteristics of the sample and groups respectively are included in Table 7.15. Although on average controls were older than the patient group, there was no significant difference between the ages of patients and controls (*t* (33) = 1.19, *p* =.242, *d* =.45). The proportion of males to females was different between patients and controls, where 80% of patients were males and only 40% of controls were males, although this was not significantly different (*p* =.06). As expected, there was a significant difference between years of education for patients and controls, where patients had less education (*t* (33) = 2.57, *p* =.015, *d* =.94), reflecting a well reported risk factor. Similarly MMSE scores were different between the two groups, reflecting the differing cognitive profiles, *t* (10.15) = 2.00, *p* =.008, *d* =.86. There was, however no difference between the average hearing thresholds of patients and controls (*t* (33) = .268, *p* =.790, *d* =.10) or the ratio of GM (*t* (33) = .506, *p* =.616, *d* =.18).

**Table 7.15.** *Demographic characteristics of the sample, separated for patients and controls*

|  |  |  |  |
| --- | --- | --- | --- |
|  | Patients (n=10) | Controls (n=25) | Sample (n=35) |
| Age | 65.20 (11.13) | 70.16 (11.13) | 68.74 (11.18) |
| Gender M/F | 8/2 | 10/15 | 18/17 |
| Education | 12.30 (2.71) | 14.76 (2.51) | 14.06 (2.77) |
| MMSE | 25.80 (3.50) | 28.08 (1.38) | 27.43 (2.38) |
| PTAv | 31.08 (12.72) | 29.80 (12.92) | 30.71 (12.60) |
| GM fraction | 0.413 (0.053) | 0.423 (0.049) | 0.420 (0.049) |

NB. The age, education, Mini Mental State Examination (MMSE), PTAv (dB) and grey matter (GM) fraction reported as the mean with standard deviation in brackets.

## Correlation with hearing loss and grey matter volume

On the whole group level, the analysis reported a significant positive correlation between hearing levels and GM in various regions. These included bilaterally in the prefrontal cortex and orbitofrontal areas, anterior and posterior cingulate gyrus and left caudate (Table 7.16), where higher hearing thresholds (more HL) were significantly associated with increased volume of GM in these areas. These are shown in Figure 7.14.

There was no association between HL and GM volumes in control participants suggesting that the associations are driven by the patient sample. When taking just the patients into account, HL was associated with significant increased GM volume again bilaterally in the prefrontal cortex and anterior and posterior cingulate gyrus, but also including the parahippocampal gyrus and superior temporal gyrus (Table 7.17, Figures 7.15).

**Table 7.16.** *Regions with increased grey matter volume in the complete sample*

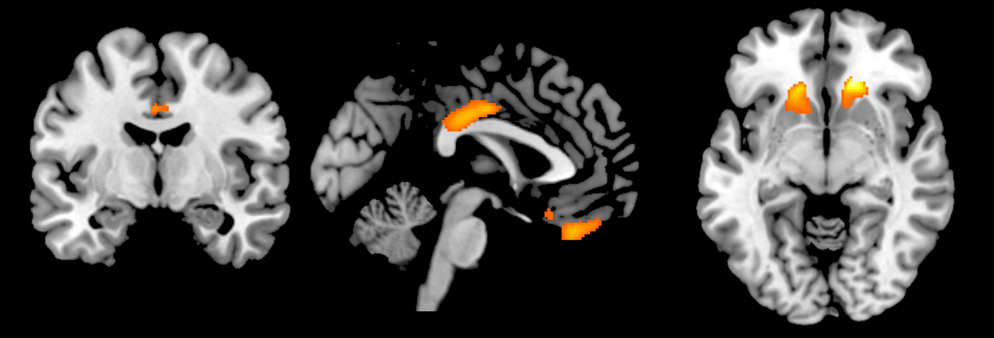
|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Cluster | pFWE | Extent | Talairach | | | z score | Hem | Region | BA |
| X | Y | Z |
| 1 | 0.025 | 604 | 15 | 31 | -4 | 5.22 | R | Anterior Cingulate | 32 |
|  |  |  | 8 | 14 | -9 | 3.73 | R | Anterior Cingulate | 25 |
|  |  |  | 3 | 20 | -18 | 3.67 | R | Medial Frontal Gyrus | 25 |
|  |  |  | -4 | 25 | -14 | 3.16 | L | Medial Frontal Gyrus | 11 |
|  |  |  |  |  |  |  |  |  |  |
| 2 | 0.015 | 685 | -21 | 25 | 1 | 4.05 | L | Sub-lobar, Caudate Head |  |
|  |  |  | -15 | 26 | -6 | 4.01 | L | Sub-lobar, Caudate Head |  |
|  |  |  | -22 | 21 | 12 | 3.59 | L | Sub-lobar, Claustrum, |  |
|  |  |  | -8 | 11 | -8 | 3.40 | L | Sub-lobar |  |
|  |  |  |  |  |  |  |  |  |  |
| 3 | 0.019 | 646 | 2 | -18 | 32 | 3.98 | R | Cingulate Gyrus | 23 |
|  |  |  | 0 | 8 | 35 | 3.83 | L | Cingulate Gyrus | 24 |
|  |  |  |  |  |  |  |  |  |  |
| 4 | 0.017 | 663 | -2 | 32 | -25 | 3.80 | L | Frontal Lobe, Rectal Gyrus | 11 |
|  |  |  | -16 | 26 | -24 | 3.70 | L | Frontal Lobe, Orbital Gyrus | 47 |
|  |  |  | -3 | 43 | -24 | 3.66 | L | Frontal Lobe, Rectal Gyrus | 11 |
|  |  |  | -6 | 54 | -25 | 3.23 | L | Superior Frontal Gyrus | 11 |

NB. pFWE= Family wise error correction, Extent= cluster size, Hem=hemisphere, R= right, L= left

**Table 7.17.** *Regions with increased grey matter volume in the patient sample*

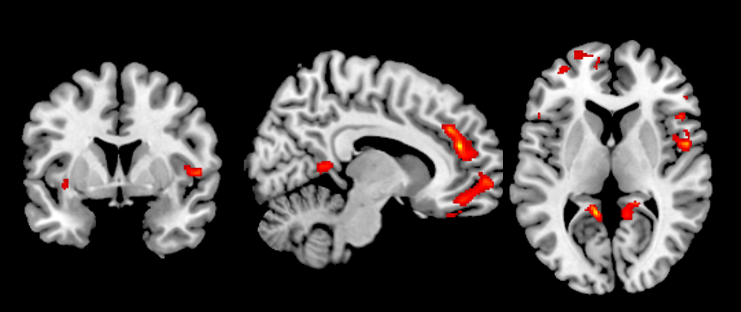
| Cluster | pFWE | Extent | Talairach | | | z score | Hem | Lobe & region | BA |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| X | Y | Z |
| 1 | 0.015 | 325 | -3 | 34 | 52 | 5.01 | L | Superior Frontal Gyrus | 11 |
|  |  |  | -8 | 46 | 38 | 4.15 | L | Superior Frontal Gyrus | 8 |
|  |  |  | -18 | 45 | 33 | 3.8 | L | Superior Frontal Gyrus | 9 |
|  |  |  | -14 | 51 | 28 | 3.73 | L | Superior Frontal Gyrus | 9 |
|  |  |  | -8 | 39 | 45 | 3.62 | L | Superior Frontal Gyrus | 8 |
|  |  |  |  |  |  |  |  |  |  |
| 2 | <.001 | 1517 | -22 | 62 | 6 | 4.80 | L | Middle Frontal Gyrus | 10 |
|  |  |  | 9 | 42 | 17 | 4.70 | R | Medial Frontal Gyrus | 9 |
|  |  |  | -4 | 51 | 25 | 4.54 | L | Medial Frontal Gyrus | 9 |
|  |  |  | 9 | 36 | 28 | 4.32 | R | Medial Frontal Gyrus | 9 |
|  |  |  | -4 | 44 | 22 | 4.24 | L | Medial Frontal Gyrus | 9 |
|  |  |  | -9 | 57 | 21 | 3.95 | L | Superior Frontal Gyrus | 9 |
|  |  |  | -10 | 56 | 6 | 3.74 | L | Medial Frontal Gyrus | 10 |
|  |  |  | -18 | 61 | -1 | 3.67 | L | Superior Frontal Gyrus | 10 |
|  |  |  | -18 | 57 | 12 | 3.66 | L | Superior Frontal Gyrus | 10 |
|  |  |  | -6 | 50 | 9 | 3.62 | L | Medial Frontal Gyrus | 10 |
|  |  |  | -3 | 38 | 26 | 3.59 | L | Medial Frontal Gyrus | 9 |
|  |  |  | -6 | 57 | 14 | 3.57 | L | Medial Frontal Gyrus | 10 |
|  |  |  | -2 | 50 | 11 | 3.55 | L | Medial Frontal Gyrus | 10 |
|  |  |  | -4 | 53 | 12 | 3.50 | L | Medial Frontal Gyrus | 10 |
|  |  |  | 6 | 50 | 21 | 3.49 | R | Medial Frontal Gyrus | 9 |
|  |  |  | 16 | 49 | 16 | 3.25 | R | Medial Frontal Gyrus | 10 |
|  |  |  |  |  |  |  |  |  |  |
| 3 | <.001 | 2885 | -38 | 39 | 23 | 4.70 | L | Middle Frontal Gyrus | 10 |
|  |  |  | 12 | 61 | -3 | 4.46 | R | Medial Frontal Gyrus | 10 |
|  |  |  | -7 | 48 | -20 | 4.17 | L | Orbital Gyrus | 11 |
|  |  |  | -6 | 55 | -5 | 4.15 | L | Medial Frontal Gyrus | 10 |
|  |  |  | -24 | 54 | -11 | 4.11 | L | Middle Frontal Gyrus | 10 |
|  |  |  | 6 | 43 | -16 | 4.01 | R | Medial Frontal Gyrus | 11 |
|  |  |  | -48 | 25 | -1 | 3.90 | L | Inferior Frontal Gyrus | 47 |
|  |  |  | 4 | 20 | -14 | 3.89 | R | Subcallosal Gyrus | 25 |
|  |  |  | 2 | 58 | -6 | 3.84 | R | Medial Frontal Gyrus | 10 |
|  |  |  | -46 | 33 | -4 | 3.83 | L | Middle Frontal Gyrus | 47 |
|  |  |  | -32 | 48 | -11 | 3.76 | L | Middle Frontal Gyrus | 11 |
|  |  |  | 6 | 25 | -18 | 3.75 | R | Medial Frontal Gyrus | 25 |
|  |  |  | 6 | 34 | -24 | 3.71 | R | Rectal Gyrus | 11 |
|  |  |  | -38 | 49 | -4 | 3.71 | L | Middle Frontal Gyrus | 10 |
|  |  |  | -33 | 53 | 6 | 3.70 | L | Middle Frontal Gyrus | 10 |
|  |  |  | 4 | 31 | -2 | 3.69 | R | Anterior Cingulate | 24 |
|  |  |  |  |  |  |  |  |  |  |
| 4 | 0.009 | 357 | -10 | -44 | 40 | 4.60 | L | Posterior Cingulate | 29 |
|  |  |  | -9 | -43 | 13 | 4.55 | L | Posterior Cingulate | 29 |
|  |  |  | -22 | -44 | 0 | 4.28 | L | Parahippocampal Gyrus | 19 |
|  |  |  | -16 | -43 | -1 | 3.89 | L | Occipital Lobe, Lingual Gyrus | 19 |
|  |  |  | -18 | -39 | 0 | 3.74 | L | Parahippocampal Gyrus |  |
|  |  |  | -8 | -54 | 12 | 3.47 | L | Posterior Cingulate | 23 |
|  |  |  |  |  |  |  |  |  |  |
| 5 | <.001 | 681 | 20 | 20 | -20 | 4.33 | R | Inferior Frontal Gyrus | 47 |
|  |  |  | 34 | 13 | -12 | 4.16 | R | Inferior Frontal Gyrus | 13 |
|  |  |  | 33 | 31 | -7 | 3.72 | R | Inferior Frontal Gyrus | 47 |
|  |  |  | 45 | 26 | -4 | 3.68 | R | Inferior Frontal Gyrus | 47 |
|  |  |  | 26 | 19 | -16 | 3.62 | R | Inferior Frontal Gyrus | 47 |
|  |  |  | 28 | 14 | -14 | 3.52 | R | Inferior Frontal Gyrus | 13 |
|  |  |  | 38 | 27 | -8 | 3.52 | R | Inferior Frontal Gyrus | 47 |
|  |  |  | 33 | 20 | -6 | 3.46 | R | Inferior Frontal Gyrus | 47 |
|  |  |  | 50 | 29 | -1 | 3.46 | R | Inferior Frontal Gyrus | 47 |
|  |  |  | 30 | 19 | -9 | 3.45 | R | Frontal Lobe, Extra-Nuclear | 47 |
|  |  |  |  |  |  |  |  |  |  |
| 6 | 0.022 | 300 | 51 | 2 | 5 | 4.31 | R | Superior Temporal Gyrus | 22 |
|  |  |  | 50 | 8 | 2 | 4.08 | R | Superior Temporal Gyrus | 22 |
|  |  |  | 53 | -9 | 2 | 3.19 | R | Superior Temporal Gyrus | 22 |
|  |  |  |  |  |  |  |  |  |  |
| 7 | 0.003 | 426 | 16 | -41 | 4 | 4.30 | R | Parahippocampal Gyrus |  |
|  |  |  | 26 | -39 | -5 | 4.25 | R | Parahippocampal Gyrus | 36 |
|  |  |  | 10 | -48 | 10 | 3.81 | R | Posterior Cingulate | 29 |
|  |  |  | 9 | -43 | 10 | 3.69 | R | Posterior Cingulate | 29 |
|  |  |  | 22 | -38 | -6 | 3.69 | R | Parahippocampal Gyrus | 36 |
|  |  |  |  |  |  |  |  |  |  |
| 8 | 0.005 | 395 | 55 | 30 | 11 | 4.13 | R | Inferior Frontal Gyrus | 46 |
|  |  |  | 55 | 26 | 13 | 4.02 | R | Inferior Frontal Gyrus | 45 |
|  |  |  | 51 | 21 | 13 | 3.95 | R | Inferior Frontal Gyrus | 45 |
|  |  |  | 50 | 21 | 6 | 3.85 | R | Inferior Frontal Gyrus | 45 |
|  |  |  | 51 | 33 | 7 | 3.68 | R | Inferior Frontal Gyrus | 45 |
|  |  |  |  |  |  |  |  |  |  |
| 9 | 0.006 | 387 | -21 | 32 | -13 | 4.10 | L | Middle Frontal Gyrus | 11 |
|  |  |  | -30 | 26 | -16 | 3.74 | L | Inferior Frontal Gyrus | 47 |
|  |  |  | -20 | 25 | -18 | 3.73 | L | Middle Frontal Gyrus | 11 |
|  |  |  | -39 | 35 | -8 | 3.58 | L | Middle Frontal Gyrus | 47 |
|  |  |  | -34 | 2 | -17 | 3.48 | L | Inferior Frontal Gyrus | 47 |
|  |  |  | -18 | 19 | -19 | 3.47 | L | Inferior Frontal Gyrus | 47 |
|  |  |  | -39 | 34 | -12 | 3.31 | L | Middle Frontal Gyrus | 11 |
|  |  |  |  |  |  |  |  |  |  |
| 10 | 0.017 | 316 | -30 | 26 | -16 |  | L | Inferior Frontal Gyrus | 47 |
|  |  |  | -20 | 25 | -18 |  | L | Middle Frontal Gyrus | 11 |
|  |  |  | -32 | 21 | -8 |  | L | Inferior Frontal Gyrus | 47 |

NB. pFWE= Family wise error correction, Extent= cluster size, Hem=hemisphere, R= right, L= left



**Figure 7.14.** *Effects of hearing loss on grey matter for the whole sample.*

NB. Statistical parametric maps of multiple regression analysis with HL as the variable of interest. Clusters indicate areas with increased GM in association with increased levels of hearing loss, shown in coronal slice (left), sagittal slice, (middle) and axial slice (right). The differences are overlaid on a standard template and findings are presented in neurological convention.

**

**Figure 7.15.** *Effects of hearing loss on grey matter for patients with cognitive impairment.*

Statistical parametric maps of multiple regression analysis with HL as the variable of interest. Clusters indicate areas with increased GM in association with increased levels of hearing loss, shown in coronal slice (left), sagittal slice, (middle) and axial slice (right). The differences are overlaid on a standard template and findings are presented in neurological convention.

# Discussion

The study is first pilot study looking into the effects of HL in a sample of participants with cognitive impairment. In this sample, increased hearing thresholds, indicative of a more severe HL, were associated with increased volumes of GM in prefrontal areas, the anterior and posterior cingulate gyrus and the superior temporal gyrus, areas which may be all involved in auditory processing or language related functions (Ingvar, 1983, Dhanjal et al., 2013, Reverberi et al., 2015).

The hypothesis was that if HL drives atrophy in normal ageing, patients in the early stages of neurodegeneration may be more affected by their HL; our findings were the contrary to this prediction. When cognitively healthy participants alone were included in the regression, there was no association with HL and GM changes, supporting the findings previously reported by Profant et al., (2014) and Rigters et al., (2017). In the complete sample, however, a positive association with HL and GM volume was found, namely in the prefrontal cortex, orbitofrontal areas and cingulate gyrus. Again, similar results have also been found in the literature, which reported increased GM in the superior frontal gyrus and superior parietal gyrus in cognitively healthy people with HL, although these did not reach significance at the threshold corrected for multiple comparisons (Rigters et al., 2017). When patients were included alone in the regression model, there was again increased GM in association with higher hearing thresholds which suggests there may be a compensatory mechanism occurring during the early stages of neurodegeneration which is further affected by HL. This may help to explain the inconsistent prior findings in the literature.

Areas associated with more GM in patients included larger clusters in the prefrontal cortex, specifically the left superior frontal gyrus, middle frontal gyrus and orbital gyrus; the right subcallosal gyrus, and bilaterally the medial and inferior frontal gyri. Prefrontal cortical areas are mainly involved in higher cognitive processing (Frith and Dolan, 1996) but research has reported that they may be required for successful linguistic and acoustic processing (Price, 2010). In the same way, people with HL have shown a recruitment of frontal cortices to help compensate for diminished speech perception during fMRI tasks (Cardin, 2016). Also, an EEG study which recorded auditory evoked potentials in response to differing speech stimuli, reported that participants with HL had additional recruitment of frontal areas for all recorded auditory evoked potentials (Campbell and Sharma, 2014).

Therefore the increased GM volumes reported in our study may be due to an increased use or reliance on these processes due to a long-term HL. For example, the superior frontal gyrus has been implicated in language organisation and non-speech auditory processing, where a direct connection by association fibres between the left Broca’s area and superior frontal gyrus has been reported (Kinoshita et al., 2012). The inferior frontal gyrus is involved in grammatical and syntactic language processing (Tyler et al., 2011, Udden and Bahlmann, 2012). Other studies have reported decreased GM volumes in prefrontal regions in people with HL (Husain et al., 2011, Boyen et al., 2013); the authors of these studies attributed the atrophy to a direct consequence of impoverished peripheral input. However, although these areas may be associated with language processing or speech comprehension as reported above, their main function is not sensory processing and thus it is difficult to comprehend how HL alone could drive increased atrophy leading to diminished GM in these areas. As both studies were investigating between group differences of small sample sizes, GM volumetric variations could reflect the neuroanatomical differences between participants.

Other clusters were reported, namely in the anterior (right) and posterior (bilateral) cingulate gyrus, the left parahippocampal gyrus and lingual gyrus, and the right superior temporal gyrus, specifically in the auditory association areas, BA 22. The anterior cingulate and caudate have too been implicated in information processing and the cognitive control of language, including selective attention to speech and listening effort (Mulert et al., 2005, Botvinick, 2007, Reverberi et al., 2015) amongst many other functions. The posterior cingulate has been associated with comprehension of sentences (Whitney et al., 2009). BA 19 is part of the lingual gyrus of the occipital lobe, which may have increased GM in our sample due to the reliance on lip reading and visual cues in people with HL to aid auditory perception (Plass et al., 2014, Hallam and Corney, 2014). Lastly, increased GM volume in BA 22 has also been reported in people with HL in the study by Boyen et al., (2013), and the authors have postulated that this could be due to the role of BA 22 in semantic memory processing, where participants with HL rely more heavily on semantic memory to give context to the impoverished signals coming in. Therefore again, these areas may have increased GM volume in people with HL due to the increased use.

It is not clear why there was no association with GM volume and HL in our sample of cognitively healthy controls, but only for patients with cognitive impairment. As the within group variability of HL was the same for controls and patients, a difference in GM volumes associated with HL is therefore likely to be due to the variability in the brains of patients thus indexing the disease (Roalf et al., 2016). Therefore, increased levels of GM in people with HL and cognitive impairment may propose the occurrence of compensatory processes. This is not the first time compensation has been reported in MCI or the early stages of neurodegeneration. For example, fMRI studies have shown patients with MCI show increased activity in various brain areas during different tasks (Gardini et al., 2015, Liang et al., 2011), suggesting a reorganisation of brain functions. Patients in the early stages of neurodegeneration recruit prefrontal areas to undertake tasks (Grady et al., 2003), which could thus lead to increased GM or relative sparing of GM volumes in these areas. Grady et al., (2003) reported that patients with cognitive impairment recruit additional prefrontal areas across a variety of different cognitive tasks indicating that this enhancement is not task specific but rather a general adaptation to a loss of cognitive resources. Therefore, people with neurodegeneration and HL may have a ‘double hit’ where they more heavily rely on prefrontal areas which could lead to the larger GM volumes.

This evidence supports the cognitive load on perception hypothesis, as it could reflect the differences in cognitive and auditory processing between healthy individuals and those with cognitive impairment. For example, cognitively healthy individuals may rely minimally on other cortical areas for assistance with auditory perception, whereas people with neurodegeneration already have a stress on their brains, and thus are relying more heavily on these extra areas for speech processing and understanding, resulting in increased use and consequently increased GM volume. This could also support the notion of increased central auditory dysfunction in persons with neurodegeneration (as reported in Experiment 7.3), again leading to further changes in cognitive cortical resource allocation, and could explain the larger GM in the right superior temporal gyrus.

Limitations in this study include the small number of subjects in both groups, which could lead to underpowered analysis and thus larger samples are required to investigate the influence of HL on cognitive impairment further. Our patient sample included only 9 participants with MCI and 1 participant with AD, and due to the compensatory processes involved in MCI, it would be interesting to investigate how this association with increased GM may change over time. This increased prefrontal cortical activation in MCI declines with disease severity (Clement and Belleville, 2010), and thus it cannot be concluded whether HL has any further influence or protective role on GM in the frontal areas throughout the neurodegenerative trajectory or the MCI phase only. Therefore a longitudinal study would be needed to investigate the role of HL on GM changes including more severe cases of MCI and the early and later stages of dementia. Another limitation of our pilot study was that the investigations was limited to GM only, and as HL has been proposed to influence the white matter integrity (Husain et al., 2011, Rigters et al., 2017), further investigation into the effects of HL on white matter in cognitive impairment is needed. Also, due to the small sample size the effects of hearing aid use on GM volumes were not investigated. As 20 participants had HL and 12 of these wore hearing aids, comparisons between 8 and 12 would have been underpowered and further underpowered in the patient sample alone.

To conclude, from our pilot study there is no evidence that HL alone leads to structural GM changes in cognitively healthy adults. However, increased hearing thresholds were positively associated with GM volume in patients with cognitive impairment. The areas where increased peripheral hearing thresholds were positively associated with GM volume included areas that are involved or may aid auditory processing, suggesting that increased GM was found due to a compensatory mechanism. This association appeared to be stronger in people MCI and HL, as they not only have underlying neurodegeneration, but they have also had a (long-term) HL and therefore may have over relied on prefrontal areas for some length of time.

# General Discussion

Our findings suggest that peripheral and central auditory changes occur in the early stages of neurodegeneration, but there was no evidence to suggest that it was HL that was driving these changes in cognition.

A non-significant higher prevalence of HL was reported in the patient sample supporting the role of shared risk factors or the common cause hypothesis. Experiment 7.1 outlined that peripheral HL did not lead to exacerbated cognitive function as there was no association between the severity of HL and the severity of cognitive impairment. Therefore, as both HL and cognitive decline are progressive, and more severe HL were reported for MCI cases compared to controls and dementia patients, it is unlikely that HL may be driving the risk of cognitive impairment. A prospective longitudinal study is thus needed to investigate the role of HL and cognitive function further in people with neurodegenerative MCI or dementia.

Studies have reported subjective HL is more likely to lead to incident dementia (Davies et al., 2017, Golub et al., 2017), however our results from Experiment 7.1 may suggest subjective accounts may be confounded by the pre-morbid stages of the disease. A weaker association between hearing disability and measured hearing levels was observed in patients compared to controls (7.2.3.3), which may suggest that people with cognitive impairment and normal hearing may overestimate or misattribute their memory problems to hearing difficulties. Experiment 7.2 also reported the contrary, where a case study showed that severe HL and heavy hearing disability may be misattributed to cognitive decline, even by memory specialists. Therefore, this indicates the overlapping nature of the symptoms of HL and cognitive impairment and highlights the importance of recognising the psychosocial association and features of HL which may complicate the cognitive evaluation. Again, a proper diagnostic work up and special considerations for sensory loss during cognitive examinations must be taken into account.

A secondary aim included investigating the role of hearing aids on the relationship between these factors to identify whether the use of hearing aids may reduce the risk or severity of cognitive impairment in people with HL. However, as the role of aids is to amplify signals and participants with cognitive impairment have higher levels of auditory processing deficits (Gates et al., 1995, Strouse et al., 1995), they may not find the same benefit from hearing aids. For example, the auditory signal is able to stimulate the cochlea but cannot be processed further in the ascending auditory pathways leading to little hearing aid benefit. However, in this sample, patients reported higher rates of hearing aid use and a higher satisfaction with their hearing aids. Although a cross sectional design was used and thus have no longitudinal evidence, the fact that patients reported benefit from their hearing aids and a higher proportion in the patient sample wore hearing aids may suggest that their use does not reduce all (if any) of the risk. Again, this evidence supports the common cause hypothesis where another factor is leading to both HL and cognitive impairment, and thus treating HL has no impact on cognitive decline.

Experiment 7.3 found evidence to support the literature of disrupted auditory processing in cognitive impairment independently of peripheral hearing levels. Under the forced listening conditions there was a step down reduction in performance in patients with MCI and dementia, reflecting the decreased attentional and cognitive control with impending disease severity. This has been reported elsewhere in the literature and for other neurodegenerative conditions (Bouma and Gootjes, 2011, Profant et al., 2017). For example, auditory testing of a group of patients with another neurodegenerative condition, Huntington’s disease, has reported that although PTAv levels are slightly higher for patients than controls, this was not significant, and there was no difference in speech understanding in quiet, reflecting similar findings to ours in Experiment 7.1. However the test of speech understanding in babble (measuring central auditory function) was significantly worse for the Huntington’s disease group compared to the controls, suggesting a deterioration in speech processing in people with Huntington’s disease, which was not confounded by PTAv but correlated with disease severity (both cognitive and motor) (Profant et al., 2017). Similarly, longitudinal studies of multiple sclerosis patients have shown that the dichotic listening performance is reduced due to the breakdown of white matter in the corpus callosum, leading to an increased right ear advantage (REA) (Gadea et al., 2009, Bergendal et al., 2013), as reported for dementia patients. There is involvement of corpus callosum degeneration during AD (Anandh et al., 2014) where the rate of atrophy is associated with cognitive decline (Zhu et al., 2014), which together with the changing shape may be an indicator of prodromal AD in MCI subjects (Ardekani et al., 2014, Elahi et al., 2015). Therefore, neurodegeneration affecting the corpus callosum may have an indirect effect on central auditory processing abilities, including recall and inhibition between the two hemispheres during linguistic processing which may lead to the deficits reported for dementia patients. Thus providing evidence once more that impending neurodegeneration may affect auditory abilities and not the other way round.

Interestingly, in our sample, under NF conditions which have limited cognitive involvement (Westerhausen et al., 2015), patients with dementia had the same pattern of response as the controls, but to a much reduced ability. Patients with MCI reported a ‘reversal’ of the prevalent REA to a more left sided dominance which may be reflective of dysregulation of auditory function and compensatory cognitive mechanisms. The findings from Experiment 7.4 help to support this notion of compensatory mechanisms occurring during the MCI phase, as there is recruitment of the other hemisphere for auditory processing.

A positive association between HL and GM volume was found in the right superior temporal gyrus of patients, 90% of whom had MCI. This is potentially reflecting these compensatory mechanisms due to diminished auditory processing, where there is recruitment of the right auditory cortex, which would result in the left ear advantage (LEA) reported in Experiment 7.3 for patients with MCI. Taking into account the auditory processing performance of the 35 participants included in Experiment 7.4, it was found that 50% of the patients with HL had a LEA compared to 8% of controls with HL (results not shown). Together, this could suggest that HL could further influence the compensatory mechanisms present in MCI and the early stages of dementia. This would support the increased GM in the prefrontal areas which has been reported in both HL (Cardin, 2016) and MCI (Grady et al., 2003) and why there is increased involvement of the right auditory association area in patients with HL.

In Experiment 7.3, a LEA was indirectly recorded in patients with a more severe cognitive phenotype (7.4.3.3.), which does not support the adaptive processes and recruitment of prefrontal areas early in the degenerative trajectory (Clement and Belleville, 2010). However, this could explain why HL was also associated with higher volumes in the right auditory association areas in MCI phase (Table 7.17), as the system could be suffering more and thus having to recruit extra areas. However, in the small sample of 10 patients included in the pilot study in Experiment 7.4, the function of auditory processing (ShiftLeft) was not associated with cognitive performance (data not shown) which may be underpowered due to the small numbers and limited variability within the sample. However, evidence to support this notion comes from another fMRI study of auditory laterality in Huntington’s disease patients and near and far pre-Huntington’s disease patients. Near pre-Huntington’s disease patients recruit additional brain areas as they are closer to conversion compared to Huntington’s disease patients or the far pre-Huntington’s disease group (Saft et al., 2008), and thus adaptive processes are not necessarily only involved in the earliest of stages.

Limitations to these Experiments include the cross sectional design, in that cannot discount the fact that auditory dysfunction may be impacting on cognitive function during cognitive tasks (7.4.3.3) due to the strong connections between auditory, language and higher order processing which have been described above, rather than the other way round. Therefore, it would be interesting to investigate whether cognitive stimulation therapy, shown to increase cognitive performance and quality of life in MCI and dementia (Aguirre et al., 2013), would have an impact on the auditory processing abilities in people with cognitive impairment. Therefore, cognitive stimulation therapy may be able to access or take advantage of the adaptive processes occurring during MCI, and including auditory processing tasks into individualised cognitive stimulation therapy for dementia (Yates et al., 2015) may help to maintain cognitive and auditory abilities for longer. Multisensory cognitive stimulation has been shown to benefit cognitive performance in institutionalised cognitively healthy individuals (De Oliveira et al., 2014) and auditory attention training using dichotic listening in individuals with attentional deficits has the ability to generalise increased attention onto untrained attentional tasks (Soveri et al., 2013, Tallus et al., 2015). Therefore, it would be interesting to investigate whether participants with cognitive impairment are able to improve performance on iDichotic after training, and how this impacts on other cognitive functions.

Another limitation is that the effects of medication were not investigated for patients or controls, which may have an influence on hearing participation, auditory processing abilities and GM volumes (Dhanjal et al., 2013).

Chapter 7 is concluded by reporting that hearing problems may be exacerbated in people with cognitive impairment, but these may reflect auditory processing abilities which are due to cognitive dysfunction or a common cause mechanism rather than peripheral HL exacerbating the effects of cognitive impairment. Longitudinal studies monitoring peripheral and central hearing functions with imaging data are needed to help the understanding of this relationship further.

# Chapter 8: General Discussion

Dementia is a world public health priority due to the symptoms and impacts on the individuals, which has a knock on effect to friends, family and the wider society. Families and carers are at a greater risk of anxiety and depression (Mahoney et al., 2005), and due to increasing dependence and high demands on health and social care, there are vast cost implications to society (Department of Health, 2009). Therefore as the ageing population is on the rise, so is the prevalence of cognitive impairment and dementia, which is expected to increase to 66 million by 2030 (Prince et al., 2015), thus increasing the burdens associated with dementia. Despite the knowledge of the pathogenesis of AD and other less common causes of dementia, there is still lack of disease modifying treatments. Research efforts have shifted to include an emphasis towards risk reduction, which has identified modifiable risk factors which may reduce the onset of dementia. Current statistics have reported the projected incidence rate of dementia has actually reduced due to the improvements in controlling well acknowledged risk factors such as hypertension and diabetes (Matthews et al., 2013). Therefore, delaying the onset of dementia by even a few years has great implications for individuals’ quality of life and wellbeing which extends to the society (Tom et al., 2015).

The most recently established modifiable risk factor for incident dementia is midlife HL (Livingston et al., 2017). The results from the metanalysis look promising; however this was based on evidence from three longitudinal studies alone (Lin et al., 2011b, Gallacher et al., 2012, Deal et al., 2016) which include some confounding factors that have already been discussed throughout this thesis. Another issue with the conclusion reported in this paper is that it is not known whether ‘treating’ HL, again the treatment is symptomatic with no current cures (Muller and Barr-Gillespie, 2015), would lead to a reduction in cognitive decline and thus, as such naming HL as a modifiable risk factor may be leading to conclusions which have not been established yet.

In this thesis, further investigation into the relationship between HL and cognitive decline was conducted, focusing on three characteristics associated with an ARHL; peripheral HL, central HL and the social and emotional consequences of acquired HL in older age. This would allow separation of these factors to investigate how each one may interact specifically with cognitive changes during ageing, both normal and pathological.

# 8.1. Peripheral hearing levels

The influence of peripheral hearing levels on cognition were first explored during Chapter 5, in a group of cognitively healthy participants. The main aim was to identify whether the inconsistent evidence of poorer cognitive performance for people with HL was due to the fact that these individuals were being disadvantaged by the testing procedure. No difference in cognitive performance at baseline was reported, when using a battery of tests which do not heavily rely on auditory perceptual processing. Thus suggesting in this sample, HL does not lead to lower performance. This is supported by our finding that hearing aids did not have any effect on cognitive performance, which was suggested to be due to a lack of increased perceptual effort during the tests and thus the use of hearing aids is not superior. A more severe HL was associated with an increased likelihood of wearing hearing aids each day, but the use of hearing aids did not reduce the associated perceived disability. Therefore this suggests that the literature which reports lower performance in healthy subjects with HL (Lin et al., 2013, Gurgel, 2014) may be heavily confounded by the effects of age and peripheral hearing levels on the testing, leading to artificially induced lower scores. Therefore when using this same battery of cognitive tests, any decline in performance would not be due to an artefact of the testing procedure.

To investigate whether HL was associated with decline in cognitive performance over time, the assessment was repeated at 12 months, and as reported in Experiment 5.3, a significant interaction between high performers with HL at baseline and decline on the Letter Fluency test at T2 was found, with a similar (non-significant) trend for many of the other cognitive tests. These results are interesting and due to the stable performance of people with lower cognitive profiles and HL suggest a case for the common cause mechanism. An unidentified common factor may have induced HL and impending cognitive decline in these people; however, this was not related to a decline in hearing thresholds which would have substantiated the assumption. It was therefore determined that a longer follow up was needed to ensure a conclusion could be drawn between HL and change in performance over time, as this minimal ‘decline’ was not necessarily indicative of any underlying pathology.

In Experiment 7.2, the case of a gentleman, GP, diagnosed with the early stages of AD was discussed. After thorough cognitive testing and imaging analysis, no evidence of cognitive impairment or AD was found. Subjective HL and subjective memory problems often lead to similar and overlapping symptoms, which could help to explain some of the conflicting evidence in the literature. Overlapping symptoms of working memory problems, difficulty following conversations and repetition are common during HL (Salthouse, 1996, Dalton et al., 2003) and in the early stages of memory disorders (Nyatsanza et al., 2003, Bozeat et al., 2000). Due to the increased awareness of cognitive impairment as a public health priority, individuals experiencing these symptoms may be inclined to visit the memory clinics, as reported in GP’s case. This study also helps to highlight the importance of a diagnostic work up, as even though GP scored 100% on the MMSE at his initial assessment, he was still diagnosed with the early stages of dementia. Interestingly, although GP’s neuropsychological assessment was in keeping with the clinical norms for his age range, when compared with 9 age and education matched male volunteers, Experiment 7.2 found his performance on the Letter Fluency Task to be 2 standard deviations below the group mean. This could possibly indicate a reduction in language fluency or executive control in people with HL, but it also indicates the high cognitive performance reported in volunteer samples, which could lead to the overestimation of any real associations. Therefore, this also brings to light the fact that lower performance over time on the Letter Fluency task (Experiment 5.3) may in fact not be indicative of impending cognitive decline, as after approximately four years from initial assessment, GP remained cognitively healthy and retained functional skills. These results are supported by an older study which found no association between peripheral hearing abilities and cognitive performance at 5 years follow up, suggesting that in cognitively healthy sample, there is no association between HL and cognitive decline (Gennis et al., 1991) but this may be different in pathological ageing.

The main limitations to these studies are the exclusive use of a cognitively healthy sample, which were followed up over a short time period, leading to a lack of variation on cognitive tests throughout the sample. Research has suggested that people with subjective memory problems may be at greater risk of cognitive impairment (Mitchell et al., 2014), and thus it would have been interesting to measure the differences in hearing acuity and disability between participants with healthy controls, subjective memory problems and clinically diagnosed cognitive impairment.

In Experiment 7.1 a non-significantly higher prevalence of peripheral HL was reported in the sample of patients with neurodegenerative cognitive impairment compared to age, education and gender matched controls. Hearing severity did not correlate with cognitive severity, and as both factors are progressive, it is unlikely that HL is ‘the’ factor which has led to the clinical onset of pathological cognitive impairment. However, in Experiment 7.4, where the influence of HL on GM volume in a sample of 35 participants, including a subsample of patients with cognitive impairment was explored; no association between GM volumes and HL were reported in the control sample, but when taking just patients into account, there was a positive association where higher hearing thresholds were associated with more GM bilaterally in the prefrontal areas, cingulate gyrus and right superior temporal gyrus. As most of the patients had MCI, it was suggested that this was due to a recruitment of additional brain areas during the MCI phase, as previous research has reported additional recruitment of frontal areas during fMRI tasks during the early stages of neurodegeneration (Grady et al., 2003). Therefore, this increased volume of the contralateral auditory association area (right hemisphere), could perhaps suggest that HL feeds into this compensatory process or is part of the same disease spectrum in these individuals. For example, a severe HL is adding to the burden or increased stress on the brain and as a consequence, compensatory processes are upregulated more, whereas cognitively healthy individuals with HL had no association with GM volume. This idea is also unsupportive of the cognitive load on perception model as it suggests that HL may be part of the same disease process in these people or it may act as an additional burden rather than a consequence of reduced cognitive capacity.

Taking this evidence together, a theory suggests that subjective memory problems which occur as a consequence of untreated HL, may bias the assumption of hearing problems and cognitive impairment. This coupled with tests which rely on verbal administration and auditory comprehension, thus leading to increased perceptual effort, may further disadvantage people with HL. However poorer cognitive performance is not indicative of a clinical cognitive impairment nor is it necessarily reflective of underlying pathology. These factors reiterate the importance of a comprehensive diagnostic work up in the assessment of dementia, and the special consideration needed when evaluating the cognitive status of individuals with sensory impairments. With increased awareness around the treatment of HL with hearing aids there may be a double benefit of reducing over diagnosis and possible risk reduction of cognitive impairment if HL is a factor influencing this relationship. However, considering all of the evidence has suggested that it is unlikely that HL is an independent risk factor or the driving force behind cognitive impairment, due to the fact that increased hearing thresholds in patients were not associated with more severe cognitive deficits. Therefore there may be a separate mechanism which leads to both hearing impairment and cognitive impairment in people with underlying pathology. For example, oxidative stress and excitotoxicity are two factors which lead to neuronal damage during neurodegeneration (Mehta et al., 2013, Kim et al., 2015), and similarly the cochlea is vulnerable to oxidative stress and excitotoxicity compared to other organs due to the high metabolic demands of the hair cells (Lin et al., 2011f, Mehta et al., 2013).

# 8.2. Central auditory processing

The role of central auditory processing and the links with cognition in a cognitively healthy sample were investigated in Chapter 6. It was noted that cognitive processes are involved in tasks of central auditory function, and thus the iDichotic, an app version of the C-V dichotic listening paradigm (Bless et al., 2013) was utilised, as this measures both the structural language laterality as well as the influence of attention, inhibition and cognitive control on the auditory pathways (Hugdahl and Andersson, 1986). The main aim of Experiment 6.1 was to identify whether structural laterality had an impact on the forced listening conditions, and which aspects may be related to cognition. It was observed that in the cognitively healthy sample there is a high prevalence of REA, reflecting the left dominant hemisphere for linguistic processing. The literature has reported an increased REA in older people, under the NF and forced listening situations (Hugdahl and Andersson, 1986, Hugdahl et al., 2001, Takio et al., 2009), which may suggest that with ageing there are natural deficits in abilities to attend. However, in our cognitively healthy sample, older adults were still able to maintain top down manipulation of the bottom up processing, although the amount to which they could do so successfully was slightly reduced compared with younger adults. Although there were associations between iDichotic and cognitive performance, after adjusting the statistical threshold for multiple comparisons, the ability to Attend Left (cognitive conflict situation) was significantly associated with visual memory recall (Experiment 1) after controlling for the effects of ageing and peripheral hearing levels. It was discussed that this may indicate a difficulty in attention, which is not readily detected using the neuropsychological battery due to the ceiling effects of the test in a healthy sample, but it may suggest that the iDichotic is a more sensitive measure of neuronal change. There was also a difference in the ability to perform under the forced listening conditions in people who reported NEA. It was therefore proposed that under the NF condition, NEA may be indicative of disrupted auditory processing, regardless of age and peripheral hearing levels, which then impacts on the ability to modulate attention under the forced listening conditions. To investigate this further, participants were followed up over a 12 month period (Experiment 6.2), where a significant association was observed between consistent performance to Attend Left and performance on the SCEB, a short cognitive evaluation battery designed to identify changes between AD dementia, normal ageing and depression (Robert et al., 2003, Girtler et al., 2012). Consequently, auditory processing abilities may be a more sensitive marker of neuronal changes, which could help to explain the associations with reduced auditory processing in people with cognitive decline (Gates et al., 1995).

In Experiment 7.3, differences were reported in the auditory processing abilities of controls, MCI patients and patients with dementia. Patients with dementia maintained a REA but had reduced auditory processing abilities and lack of cognitive control, as they could not readily modulate attention to the non-dominant auditory pathway. The patients with MCI showed decreased correct responses from the right ear and higher number of responses from the left ear, indicating cases of LEA. It was suggested that in MCI patients, a compensatory mechanism may be occurring to counteract the underlying changes in auditory processing, to try to maintain behavioural function and cognitive performance. Therefore, there may be recruitment of the right hemisphere for auditory processing which leads to a rearrangement in language laterality under the NF conditions. The step down behavioural performance between controls, MCI and dementia patients help to corroborate this idea. Associations between iDichotic performance and neuropsychological testing in patients suggests the ability to undertake the forced listening conditions correlates with disease progression, thus signifying that this may be a marker of disease severity.

As it was suggested that MCI patients have an increased LEA due to the recruitment of the contralateral hemisphere, it is possible that the individuals in the control group who reported NEA (Experiment 7.1) may be in an earlier or pre-MCI phase where the equal responses from the right and left ears reflects the beginnings of the reduction in hemispheric asymmetry. Therefore, these individuals may be at risk of future pathological cognitive impairment.

To corroborate the behavioural findings, in Experiment 7.4, the influence of HL on GM volume in the subsample of patients who predominantly had MCI was investigated. Results showed a more severe HL was indicative of increased GM volumes, including the right superior temporal gyrus. When investigating the central auditory function, 50% of the participants had a LEA. Although the correlation was with PTAv hearing thresholds, due to the influence of HL on auditory processing, it was suspected that the LEA in these people is driven by the increased volumes of GM in the right auditory association area.

Due to the high and inconsistent prevalence of auditory processing dysfunction reported in cross sectional samples (Stach et al., 1990, Cooper and Gates, 1991, Golding et al., 2004), the usefulness of auditory processing abilities in predicting cognitive function may be diminished. Similarly, the iDichotic may not be specific enough to predict any differences in neuronal integrity of pre-clinically underlying pathology at the individual level, as 40% of the sample had a change in NF laterality between T1 and T2, which may have been influenced by attention with subsequent testing. Therefore a limitation in our studies was the lack of practice trials, which might have increased the validity of the scores, and helped to support our conclusions. The dichotic listening CV paradigm was chosen for its limited ceiling effects; however this problem was reported with the neuropsychological tests, which again makes the inference hard in a healthy population. Therefore a larger sample is needed to establish normality data on this test for each age range to make it suitable for clinical use to predict impending cognitive decline. This would also need to include an increased sample size for the patient cohort, which can then be followed longitudinally, to identify whether any changes in the NF and forced conditions may be suggestive of underlying neurodegeneration.

# 8.3. The social and emotional associations of hearing loss

A new tool to measure hearing disability in the general population, the SEAH, was developed in Experiment 4.1 and subsequently validated in Experiment 4.2. It was concluded to be a specific, valid and reliable questionnaire to measure the social and emotional associations of HL. As such it was then used in subsequent chapters and experiments (Experiment 5.2, Experiment 6.1 and Experiment 7.1) to quantify specifically whether the effects of subjective hearing related disability contribute to current cognitive profiles, the risk of decline in performance over time or the impact of HL in MCI and dementia. As a secondary aim, any difference in disability scores or an influence on the factors described above by the use of hearing aids was also explored.

During Experiment 5.2, it was reported that SEAH scores were significantly correlated with the severity of HL, but there was no independent association between SEAH scores and cognitive performance. Similarly, the use of hearing aids was not associated with fewer hearing associated disabilities, although in this study comparisons were made between individuals with and without hearing aids, rather than benefit pre and post- hearing aid fitting and as such results are partially confounded by the more severe HL leading to the use of hearing aids.

A study investigating the effects of loneliness on auditory processing abilities suggested that people who were lonely failed to shift their attention to the left under the FL condition, which the authors suggested was due to a loss of cognitive control over attention and increased distractibility (Cacioppo et al., 2000). However, although in our sample SEAH scores were related with poorer auditory processing scores (Experiment 6.2), this association was confounded by the influence of peripheral HL. This again proposes the specific nature for hearing disability rather than general loneliness, and suggests that the limitations associated with HL do not influence cognitive performance.

Furthermore, subjective hearing disability levels did not interact with a change in cognition over time (Experiment 5.3) after taking age and peripheral hearing levels into account. Therefore, it was concluded that hearing disability did not influence cognitive performance in any way in the volunteer sample, although as already suggested, the variability in cognitive scores were low and thus a longer follow up period would help to justify the conclusion. Similarly, it would be interesting to investigate the effects of subjective hearing disability on subjective memory problems to identify whether there is any difference in perceived hearing disability in these people, or the risk of conversion to cognitive decline.

Subjective hearing disability levels did not vary between patients and controls, although the association between level of disability and measured hearing thresholds was stronger for controls, which may suggest that some patients without HL feel disadvantaged by their hearing in some situations. This may once again highlight the overlapping symptoms between cognitive impairment and HL. There was also no difference in reported hearing aid use, duration or benefit between patients and controls, thus suggesting that the use of hearing aids does not contribute to perceived disability or influence of HL on cognitive decline. However, this does highlight that a high percentage of our patient population wore hearing aids, despite evidence in the literature that hearing aids are underused in patients with dementia (Cohen-Mansfield and Infeld, 2006).

Although the evidence presented here cannot be used to comment on whether the social and emotional associations of HL may exacerbate the declines in cognitive function over time, our evidence suggests that any increased risk or associations between HL and cognitive decline are not due to this psychosocial pathway. Due to the lack of longitudinal data from the patient sample, the role of hearing aids could not be fully explored in this population, although it was identified that hearing aids do not necessarily mitigate the disability associated with HL; this finding may be cofounded by hearing aid uptake with more severe HL.

# 8.4. Summary and conclusions

To summarise, consistent results with the different aspects of HL and cognition were not reported in this thesis, however our findings have led to the proposition that peripheral HL is in fact not an independent risk factor for cognitive impairment, but rather supports the role of hearing abilities and cognitive decline being affected by a common process in pathological ageing. Thus the relationship between these factors may be different in normal ageing and in neurodegeneration, where HL may have diverse effects on cognition depending on the trajectory of cognitive impairment. For example HL may lead to subjective memory problems or diminished cognitive functions in healthy ageing, as untreated HL may lead to the symptoms of memory impairment which can have an effect on quality of life. The results gave no evidence that HL leads to exacerbated pathological cognitive decline, or that hearing aids would mitigate this decline, although longer follow up periods are needed to confirm these assumptions.

Evidence from the literature to support this comes from a large epidemiological study which evaluated medical records of over 150,000 individuals. The authors reported an increased risk (HR = 1.43, P<.001) of dementia in people with a bilateral HL, but the risk was actually reduced for participants with a unilateral HL or a disorder of the ear which did not affect hearing (Fritze et al., 2016). As unilateral HL would also be debilitating, this suggests that it is not the random presence of HL that leads to cognitive decline, but rather supports this idea of a central degenerative process driving neurodegeneration of the central nervous system, central auditory system and affecting the peripheral senses.

Due to the variability in normal ageing and the effects on cognitive function, this hypothesis of a common causal factor in pathological but not normal ageing is difficult to study. ‘Ageing’ samples will include subjects from both normal and pathological ageing trajectories. However, this hypothesis may help to explain the inconsistent evidence in the literature regarding the associations between HL and cognition, cognitive decline and risk for incident dementia. It could also be used to explain the association between severity of HL and subsequent risk of cognitive impairment (Lin et al., 2011b, Deal et al., 2016). For example, within the longitudinal ageing studies some participants may have pre-manifest underlying neuropathology. This pathology, which accelerates the rates of ageing, could also affect the auditory system, resulting in a decline in peripheral auditory function, due to for example, excitotoxicity (Mehta et al., 2013). Therefore, hearing deficits may manifest earlier than deficits in cognitive symptoms. HL in these people could be an early sign of incipient cognitive impairment, but due to the vulnerability of the hearing system in normal ageing, for most people with HL, this will be completely unrelated to cognitive impairment.

The results from this thesis may suggest that HL may be one phenotype or a symptom of neurodegeneration. As AD and other dementias are variable syndromes with high heterogeneity of clinical manifestations, auditory dysfunction may be one phenotype of the disease, which again could explain the lack of consistency in hearing abilities in both healthy and patient populations, as it is not expected that all patients conform to the same symptoms (Spalletta et al., 2010).

Therefore, the challenge remains to distinguish who with HL is at risk of cognitive impairment, and detailed assessment of auditory processing function may help to identify this. The different studies have shown a variability in auditory processing abilities throughout healthy ageing, but over time it is associated with cognitive performance, and correlates with disease severity in the patient population. Therefore monitoring central auditory function may help gain insight into the physiological integrity of the brain as it may be predictor of underlying neuronal function in disease but not in healthy ageing.

The findings of this thesis suggest that, although each aspect of hearing abilities was separated out for the purpose of identifying possible mechanisms, in future studies it might be better to investigate the contribution of HL, perceived hearing disability and central dysfunction as one factor. These factors may all contribute to an increased understanding and thus aid the diagnosis of pathological cognitive impairment in people with hearing dysfunction. Due to the inconsistent evidence regarding the use of the iDichotic, no definite evidence has been provided that this procedure can be used to predict underlying neuronal integrity and thus cognitive performance over time. The overall evidence, however, suggests that a measure of central auditory processing skills (although needing more research and further refinement prior to routine implementation), might unveil a possible mechanism to gleam insight into an early manifestation of cognitive impairment and aid detection of a phenotype of neurodegeneration.

# Appendices

## Appendix 1 - Quality assessment criteria

|  |  |
| --- | --- |
| Questions | Values |
| 1. Were the aims of the study clearly described? | no = 0; yes = 1 |
| 1. Was the study design evident and appropriate? | no = 0; yes = 1 |
| 1. Were demographic details clearly provided? | no = 0; yes = 1 |
| 1. Did all members of the dementia\* group have a clinically definite/relevant diagnosis? | no = 0; yes = 1 |
| 1. Was hearing loss diagnosed according to hearing thresholds? | no = 0; yes = 1 |
| 1. Was auditory processing evaluated? | no = 0; yes = 1 |
| 1. How large was the sample size? | <25 = 0; ≥ 25 = 1 |
| 1. Were the analytic methods adequately described, justified and appropriate? | no = 0; yes = 1 |
| 1. Were the results reported in sufficient detail? | no = 0; yes = 1 |
| 1. Was the sample followed longitudinally? | no = 0; yes = 1 |
| 1. Was there a difference in baseline demographics for people with and without hearing loss- were these controlled for? | no = 0; yes = 1 |
| 1. Were the conclusions supported by the results? | no = 0; yes = 1 |
|  |  |

\*or other form of cognitive decline

## Appendix 2 – The social and emotional Associations of hearing loss

**Social & Emotional Associations of Hearing loss (SEAH)**

The purpose of this questionnaire is to identify any difficulties you are currently experiencing as a result of hearing loss. **Select a number from 1-5 next which corresponds to each statement, (please only pick one answer for each question)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 1. **How often do you have communication difficulties when speaking with one other person?** | 1 | 2 | 3 | 4 | 5 |
| 1. **How often do you have communication difficulties when speaking in a small group of people?** | 1 | 2 | 3 | 4 | 5 |
| 1. **How often do you have difficulty hearing or communicating in a noisy environment?** | 1 | 2 | 3 | 4 | 5 |
| 1. **Do you lose track of conversations and become embarrassed by the outcome?** | 1 | 2 | 3 | 4 | 5 |
| 1. **Does your hearing situation cause you to become irritable?** | 1 | 2 | 3 | 4 | 5 |
| 1. **How often does your hearing cause you to become frustrated with members of the family?** | 1 | 2 | 3 | 4 | 5 |
| 1. **How often does your hearing cause you to avoid parties or social events?** | 1 | 2 | 3 | 4 | 5 |
| 1. **Does your hearing cause you to feel stupid or dumb?** | 1 | 2 | 3 | 4 | 5 |
| 1. **How often do you have difficulty hearing when somebody speaks in a whisper?** | 1 | 2 | 3 | 4 | 5 |
| 1. **Do you feel handicapped by a hearing problem?** | 1 | 2 | 3 | 4 | 5 |
| 1. **How often do you have difficulty listening to the TV or radio?** | 1 | 2 | 3 | 4 | 5 |
| 1. **Do you feel that any difficulty with your hearing limits or hampers your personal or social life?** | 1 | 2 | 3 | 4 | 5 |
| 1. **How often does your hearing cause you difficulty in a restaurant with relatives and friends?** | 1 | 2 | 3 | 4 | 5 |
| 1. **How often do communication difficulties cause you feel left out in a group of people?** | 1 | 2 | 3 | 4 | 5 |

Do you wear Hearing Aids? YES / NO If YES, on average day, how long for? ............... Hours

On a scale of 1-10 **(1= unsatisfied, 10= most satisfied)** what is your overall satisfaction with the hearing aids?

**1 2 3 4 5 6 7 8 9 10**

## Appendix 3 – The mini mental state examination (MMSE)

## Appendix 4 – The short cognitive evaluation battery (SCEB)

Temporal Orientation

**What month is it** – 5 points for each month of difference (Maximum = 30)

**What is todays date** – 1 point for each day of difference (maximum = 15)

**What year is it** – 10 points for each year of difference (maximum = 60)

**Which day of the week is it** – 1 point for each day of the week of difference (maximum = 3)

**What time is it** – 1 point for every 30 minutes of difference (maximum = 5)

Total degrees of error score: / 113

1. 5 word test

Read the 5 words, and match to the semantic cue

Lemonade – fizzy drink made of lemons

Museum – a building where objects of permanent value are kept and displayed

Lorry – large vehicle used to transport goods

Pan – tool used in cooking on a hob

Butterfly – insect that started its life as a caterpillar

Remove the list and recall the items (if not spontaneously recalled give semantic cue)

1. Clock Drawing task

Draw the clock with all of the numbers in and put the hands at 20 minutes to 4.

Score 1-7 (Solomon et al., 1998)

2.5 Recall the 5 items asked you to remember

Delayed recall (sum of cued and free recall) – after clock drawing test score: / 5

Score 1-7 (Solomon et al., 1998) (draw the time of 3:40)

Verbal fluency

Animals

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## Appendix 5 – Verbal fluency tasks

Semantic verbal fluency

Animals Fruits Cities

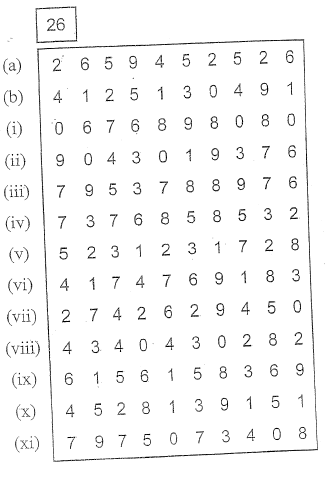
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Phonemic Fluency

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## Appendix 6 – Digit cancellation



## Appendix 7 – House Visual Span

**House visual span**

**SPAN 1**

a)  

b)  

c)  

**SPAN 2**

a)    

b)    

c)    

**SPAN 3**

a)      

b)      

c)   ****   ****

**SPAN 4**

1. **   **

**b)**    

1.    

**SPAN 5**

**a)     **

**    **

**b)**     

**c)**     

**SPAN 6**

1.      

****     

**RECALL SPAN 6**

1.      

****     

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **1** |  |  | **2** |  |  | **3** |  |  | **4** |  |  | **5** |  |  | **6** |  | **Time** | **Score** | **Delay** |
|  | **A** | **B** | **C** | **A** | **B** | **C** | **A** | **B** | **C** | **A** | **B** | **C** | **A** | **B** | **C** | **A** |  |  |  |  | **6A** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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