Age-Related Hearing Loss & Neurocognitive Function: Normal and Pathological Processes in Cognitive Ageing

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By

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DECLARATION

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David Loughrey

Abstract

This thesis investigates age-related hearing loss (ARHL) as a potential biomarker and risk factor for cognitive decline and dementia. Two reviews were conducted to examine the evidence for an association in the epidemiological and experimental literature. Both reviews found sufficient support for an association and, in particular, a mechanistic association whereby ARHL affects cognitive function. Based on these two reviews, a hypothetical model termed Neurocognitive Implicit-Explicit Asymmetric Decline (NIEAD), whereby ARHL mechanistically causes cognitive decline, was posited. This model postulates that ARHL will be associated with decline in implicit or bottom-up cognitive processes but relative maintenance in explicit cognitive processes. This hypothesis was assessed in three studies in which a sample of older adults with hearing loss was compared to a control group using indices of implicit and explicit function. The results from these studies indicated support for this model. The overall conclusion of this thesis is that further research is warranted into the association between ARHL and cognitive ageing.

List of Publications

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SUMMARY

This thesis investigates age-related hearing loss (ARHL) as a potential biomarker and treatable risk factor for cognitive decline and dementia and attempts to explore and identify a cognitive profile of older adults with ARHL using neuropsychological assessment.

Chapter 1 gives an overview of the literature on cognitive ageing, theoretical perspectives, pathological cognitive ageing, and ARHL. Epidemiological research on the possible link between age-related hearing loss (ARHL) and cognitive decline and dementia has produced inconsistent results and the basis for their possible association remains unclear.

Chapter 2 describes a systematic review and meta-analysis to estimate the association between age-related hearing loss (ARHL) as assessed by pure-tone (PT) audiometry and cognitive function, cognitive impairment and dementia to clarify this association in epidemiological studies. A small but significant association was found for ARHL within all domains of cognitive function. A significant association was found for both cognitive impairment and dementia, but not for Alzheimer's disease and vascular dementia subgroups. The pattern of results in cognitive ageing indicated a possible mechanistic association via impaired speech perception.

Chapter 3 describes a narrative review of possible pathological processes that represent either a common aetiological cause for both conditions or a mechanistic pathway by which ARHL leads to neurocognitive decline. A review of the evidence suggests that the relationship between ARHL and neurocognitive aging is most likely to be multifactorial with several processes contributing including behavioural and neuroimaging support for a possible speech-based mechanistic association.

Chapter 4 describes a hypothetical model for a mechanistic association whereby ARHL causes cognitive decline based on the reviews reported in the previous two chapters and the methods used to collect data for the empirical chapters in this thesis. This hypothetical model, termed Neurocognitive Implicit-Explicit Asymmetric Decline (NIEAD), describes the maintenance of explicit, executive cognitive processes but decline in implicit, automatic cognitive processes in ARHL patients.

Chapter 5 examines differences in markers of processing speed and intra-individual variability between a group of older adults with and without hearing loss and differences in markers of higher cognitive control and neural arousal. It was found that older adults with hearing loss had maintained explicit processes but increased decline in a marker for neural arousal levels. It was suggested that this accounted for a similar accuracy score but longer reaction latencies on a test of sustained attention.

Chapter 6 describes an analysis based on fluency tasks examining how ARHL may be associated with differences in stored semantic and phonological representations and in retrieval of these representations. The results suggested that the hearing loss group had maintained explicit retrieval but impaired semi-automatic retrieval of representatives in memory.

Chapter 7 presents the results from an analysis of differences in feature binding in short-term episodic memory, a semi-automatic cognitive process. It was found that the HL had maintained short-term memory for single feature items but impaired feature binding in short-term episodic memory.

A general discussion of the findings, the limitations and their implications are presented in Chapter 8.

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CHAPTER 1 COGNITIVE AGEING AND AGE-RELATED HEARING LOSS

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List of Abbreviations

AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
ANSI	American National Standards Institute
APOE	Apolipoprotein E
ARHL	Age-related Hearing Loss
Aβ	Beta Amyloid
BBB	Blood-Brain Barrier
BDNF	Brain-derived neurotrophic factor
BLB	blood-labyrinth barrier
BMI	Body Mass Index
BNT	Boston Naming Test
BSA	British Society of Audiology
CAEP	Cortical Auditory Evoked Potentials
CAMCOG	Cambridge Cognitive Examination
CAMDEX	Cambridge Mental Disorders of the Elderly Examination
CESD	Center for Epidemiologic Studies Depression
CI	Confidence Interval
CMA	Comprehensive Meta-Analysis
CNS	Central Nervous System
CRP	C-reactive protein
CRT	Choice Reaction Time
CV	Coefficient of Variation
DAN	Dorsal Attention Network
dB	Decibel
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
EEG	Electroencephalogram
ELU	Ease of Language Understanding
FCSRT	Free and Cued Selective Reminding Test
FFT	Fast Fourier Transform
FFV	Fast Frequency Variability
fMRI	Functional Magnetic Resonance Imaging
FPCN	Frontoparietal Control Network
GCs	Glucocorticoids
GM-CSF	Granulocyte-macrophage Colony-stimulating Factor
GRM	Glutamate Receptor, Metabotropic
GSTs	Glutathione S-transferases
HADS	Hospital Anxiety and Depression Scale
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
HHIE-S	Hearing Handicap Inventory for the Elderly-Screening
HLG	Hearing Loss Group
HPA	hypothalamic-pituitary-adrenal
HR	Hazard ratios
IIV	Intra-individual variability
IL	Interleukin
IGF	Insulin-like growth factor
ISD	Individual Standard Deviation
ISHAA	Irish Society of Hearing Aid Audiologist
ISI	Inter-stimulus Interval
kHz	Kilohertz
MAPK	Mitogen-activated Protein Kinases
MCG	Medical College of Georgia

MCI	Mild Cognitive Impairment
MCS	Mean Cluster Size
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
MTHFR	Methylenetetrahydrofolate Reductase
NART	National Adult Reading Test
NEIL	Neuro-Enhancement for Independent Lives
NFT	Neurofibrillary Tangles
OR	Odds Ratios
OXPHOS	Oxidative Phosphorylation
PAR	Population Attributable Risk
PASA	Posterior-Anterior Shift in Ageing
PET	Positron emission tomography
PFC	Prefrontal Cortex
PON1	Paraoxonase/arylesterase
PRISMA	Primary Reporting Items for Systematic Reviews and Meta-analyses
PSQI	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
PTA	Pure-tone Average
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
RT	Reaction Time
SAM	Sympathetic-adrenal-medullary
SART	Sustained Attention to Response Task
SD	Standard Deviation
SFV	Slow Frequency Variability
SHAA	Irish Society of Hearing Aid Audiologists
SHARE	Survey of Health, Ageing and Retirement in Europe
SPSS	Statistical Package for Social Sciences
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TILDA	The Irish Longitudinal Study on Ageing
TNF	Tumour Necrosis Factor
VaD	Vascular Dementia
VEGF	Vascular Endothelial Growth Factor
VEP	Visual Evoked Potentials
VRFs	Vascular Risk Factors
WHO	World Health Organisation
WMHs	White Matter Hyperintensities
WMS	Wechsler Memory Scale

Chapter 1 Cognitive ageing and age-related hearing loss

1.1 General Introduction

This thesis aims to explore the potential association between age-related hearing loss (ARHL) and neurocognitive decline with a view to explicating the causal pathways that underpin this association. A demographic shift towards an increasingly larger proportion of older adults in the human population is projected to lead to an exponential increase in the prevalence of dementia (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007; Ferri et al., 2005; Suzman & Beard, 2011). In the absence of an effective treatment for dementias such as Alzheimer's disease (AD) (Thies & Bleiler, 2013), there is a strong need to identify potential risks factors that influence and modify the rate of age-associated cognitive decline and the onset of dementia (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014; Sperling, Mormino, & Johnson, 2014). Cohort studies indicate that age-related hearing loss (ARHL) may precede the onset of clinical dementia by five to 10 years, and is therefore a possible non-invasive biomarker (Albers et al., 2015). It has been further suggested that modification or prevention of sensory decline may offer a treatment pathway to alter clinical outcomes (Albers et al., 2015; Lin & Albert, 2014).

The importance of clarifying the association between ARHL and cognitive decline is profound. It is estimated that dementia affects 46·8 million people worldwide and is projected, due to demographic trends and longer lifespan, to increase in global prevalence to approximately 131·5 million in 2050 (Prince et al., 2015). The global cost of dementia in 2015 was US$818 billion and this is projected to increase to US$2 trillion by 2050 (Prince et al., 2015). Current pharmaceutical approaches which target neuropathologies such as Alzheimer's disease (AD) offer limited benefit with symptom modifying effects at best (Thies & Bleiler, 2013). Reduction of risk factors such as social isolation may contribute to a cognitive reserve which in turn moderates the impact of neuropathology to maintain optimal cognitive function (Stern, 2009, 2012; Valenzuela & Sachdev, 2006; Wilson et al., 2013). This approach may be more beneficial than pharmacological intervention after clinical expression of neuropathology (Barnes & Yaffe, 2011), and lead to significant reductions in medical costs (Lin, Yang, Fillit, Cohen, & Neumann, 2014). This thesis will explore the evidence in the literature for ARHL as a risk factor for cognitive decline and dementia and will examine a possible mechanistic basis for this association. This chapter will give an overview of the literature on cognitive ageing, theoretical perspectives of cognitive ageing, cognitive decline, and on ARHL.

1.2 Cognitive Ageing

1.2.1 Normal cognitive ageing

One of the earliest findings in cognitive ageing research has been that normal cognitive ageing is associated with differential decline across domains of cognitive functions (See Figure 1.1) (Christensen, 2001; Coubard et al., 2011; Deary et al., 2009; Hayden & Welsh-Bohmer, 2012; Kray & Lindenberger, 2000; Meijer, van Boxtel, Van Gerven, van Hooren, & Jolles, 2009; Salthouse, 2004, 2010a; Salthouse, Atkinson, & Berish, 2003; Toepper, 2017; Tucker-Drob, Johnson, & Jones, 2009; Verhaeghen & Salthouse, 1997). Cognitive functions such as vocabulary and general knowledge show little decline until after the age of 60 whereas others such as aspects of memory, executive functions, processing speed and reasoning begin to decline much earlier, from the age of 20 onwards on a curvilinear trajectory with a sharper decline at older ages (Toepper, 2017). This differential pattern of cognitive ageing is usually summarised in the literature by classifying those functions based on the accumulation of knowledge and experiences, such as vocabulary, as crystallised intelligence and functions such as processing speed as fluid intelligence (Salthouse, 2010a). Several hypotheses (outlined further below) suggest that there is a primary component underpinning cognitive ageing including decline in a fundamental cognitive resource such as processing speed (Salthouse, 1996) or attentional resources (Craik & Byrd, 1982). It is most likely that multiple pathways contribute, reflecting the effects of various neurological changes and pathophysiological processes (Andrews-Hanna et al., 2007; Deary et al., 2009; DeCarlo, Tuokko, Williams, Dixon, & MacDonald, 2014; Toepper, 2017; Whalley, Deary, Appleton, & Starr, 2004).

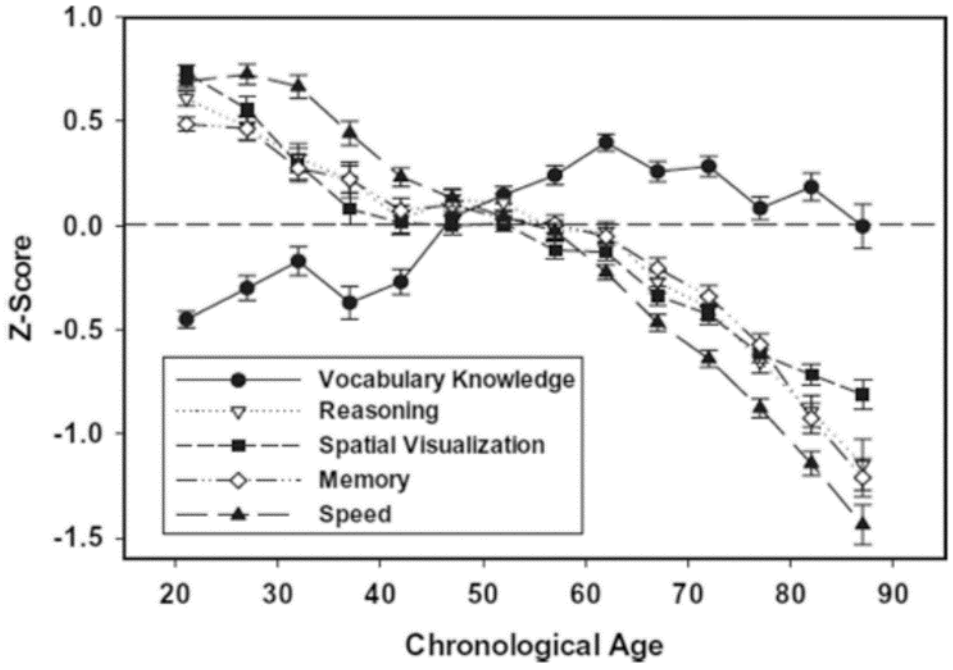

Figure 1.1: Change in cognitive domains with age (Salthouse, 2010b).

Vocabulary, considered a form of crystallised intelligence, increases into late middle age then gradually declines. In contrast, fluid intelligence linearly declines from young adulthood.

1.2.2 Structural changes in cognitive ageing

Modern brain imaging research approaches, such as task-evoked brain response studies, have contributed further to understanding by exploring how non-pathological cognitive ageing is mediated by changes in the neuroanatomical structure and function of the brain (Dennis & Cabeza, 2011; Fjell & Walhovd, 2010). Volumetric reductions in regional brain grey matter, particularly in the prefrontal cortex and medial temporal lobe regions, are associated with decline in executive function and memory respectively (Buckner, 2004; Dennis & Cabeza, 2011; Fjell, McEvoy, Holland, Dale, & Walhovd, 2013; Hedden & Gabrieli, 2004; Jagust, 2013; Yuan & Raz, 2014). This loss is more likely due to shrinkage of neurons, reductions of synaptic spines and loss of synapses rather than neuronal loss (Fjell & Walhovd, 2010). Studies assessing functional connectivity report decline in white matter integrity associated with slower information processing speed and consequent body mass index (BMI).

Due to their classical roles in executive and memory functions respectively, the frontal and temporal lobes and their sub-regions have received more focused examination (Dennis & Cabeza, 2011; Tisserand et al., 2004). Deterioration in various sub-regions of the frontal lobes has been linked to deficits in executive functions (Cardenas et al., 2011; Gunning-Dixon & Raz, 2003; Zimmerman et al., 2006) and to other functions including memory particularly due to greater reliance on these regions to compensate for age-related declines in other cognitive domains (Buckner, 2004; Dennis & Cabeza, 2011). Sub-regions of the temporal lobes also exhibit

differential rates of decline (Dennis & Cabeza, 2011). In non-pathological ageing, the hippocampus undergoes substantial atrophy whereas the entorhinal cortex does not (Raz et al., 2005) which is of interest as the entorhinal cortex is one of the first affected by AD neuropathology (Braak & Braak, 1997). Shrinkage in the entorhinal cortex was also found to be associated with episodic memory decline over a five-year period while the hippocampus was not, suggesting that the entorhinal cortex may be a sensitive marker of memory decline in normal ageing (Rodrigue & Raz, 2004). The perirhinal and entorhinal areas are selectively involved in familiarity-based recognition while the hippocampus is associated with more explicit recollection of stimuli (Bowles et al., 2007; Bowles et al., 2010; Martin, Bowles, Mirsattari, & Kohler, 2011).

Cellular and molecular neuroscience examining neurochemical and metabolic influences on cognitive ageing have contributed further to understanding (Dennis & Cabeza, 2011). For example, the neurotransmitter norepinephrine (Robertson, 2013) and its substrate dopamine (Backman, Lindenberger, Li, & Nyberg, 2010) underpin alterations in brain metabolic pathways, influence neurogenesis and modify the deteriorative effects of pro-inflammatory mediators and neuropathological substrates on neurons. Consequently, their decline is associated with deficits in episodic memory, executive functions and processing speed and clinical expression of AD (Backman et al., 2010; Dennis & Cabeza, 2011; MacDonald, Karlsson, Rieckmann, Nyberg, & Backman, 2012; Robertson, 2013). Altered neurometabolism, particularly glucose regulation and oxygen metabolic rate, is also associated with cognitive decline and AD (Dennis & Cabeza, 2011; Lourenco, Ledo, Dias, Barbosa, & Laranjinha, 2015). Dysfunction in cellular processes leads to production and accumulation of neuropathological substrates (Joshi & Pratico, 2014). Beta amyloid (Aβ) peptide which forms neuritic plaques and hyperphosphorylated tau-based neurofibrillary tangles (NFT) accumulating in medial temporal lobe and limbic regions are characteristic signatures of AD (Braak & Braak, 1991; Hyman et al., 2012) although they are also observed in samples exhibiting normal cognition (Aizenstein et al., 2008; Mintun et al., 2006; Oh et al., 2011; Rowe et al., 2007). While their accumulation is still associated with loss in neurons and connectivity between brain regions, leading to disruption in neurocognitive networks in the normal ageing population (Dennis & Thompson, 2014; Oh et al., 2011), the presence and quantity of these substrates alone is not predictive of clinical outcomes (Stern, 2009, 2012).

1.2.3 Functional changes in cognitive ageing

Ageing is also associated with functional changes in the brain as older adults demonstrate different patterns of neural activity compared to younger counterparts when performing cognitive tasks (Dennis & Cabeza, 2011; Stern, 2012; Stern et al., 2005; Toepper, 2017). Task-evoked brain imaging studies in older adults typically find decreased activation in task-related regions compared to younger controls (Dennis & Cabeza, 2011; Grady, 2012). Concomitant with this decrease, studies report increased activity in frontal and parietal regions as well as decreasing asymmetry in frontal region neural activity (Dennis & Cabeza, 2011) possibly reflecting decline in neural

specificity and increased recruitment of higher order cognitive processes to complete tasks (Grady, 2012; Stern, 2012). This is supported in neurocognitive studies which find that such shifts in neural activation are reflected behaviourally in decreased reaction times for older adults but comparable levels of accuracy compared to young adult controls (Grady, 2012; Grady et al., 1994). Studies examining changes in neural activity with age have generally noticed two neural patterns across a wide range of domains (Dennis & Cabeza, 2011). The first is referred to as Posterior-Anterior Shift in Ageing (PASA) which posits that older adults compensate for decrease in neural activity in posterior regions by recruiting prefrontal cortex regions (Grady et al., 1994). The second is referred to as the Hemispheric Asymmetry Reduction in OLDer Adults (HAROLD) and describes how older adults show less hemispheric lateralisation in prefrontal cortical activity (Cabeza, 2002). This was originally conceptualised by Cabeza as a compensatory mechanism. An alternative explanation, the dedifferentiation hypothesis, suggests that this more diffuse activation is due to an age-related difficulty in engaging specialised neural mechanisms (de Frias, Lovden, Lindenberger, & Nilsson, 2007). However, research has generally found stronger support for the HAROLD model (Batterham, Christensen, & Mackinnon, 2011; Cabeza, Anderson, Locantore, & McIntosh, 2002; Reuter-Lorenz et al., 2000; Rosen et al., 2002).

Increasing integration of cognitive and neuroscience research methods has led to the view that cognitive processes depend on networks between interconnected neural regions rather than specific neuroanatomic regions (Andrews-Hanna, Smallwood, & Spreng, 2014; Andrews-Hanna et al., 2007; Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Choi, Yeo, & Buckner, 2012; Leech, Kamourieh, Beckmann, & Sharp, 2011; Raichle, 2010; Tisserand & Jolles, 2003; Yeo et al., 2011). Neuroplastic adjustments in neural networks have been related to age-associated cognitive changes independent of AD neuropathology and in clinical outcomes (Andrews-Hanna et al., 2007; Fjell et al., 2013; Klaassens et al., 2017; Shaw, Schultz, Sperling, & Hedden, 2015). The default mode network (DMN) underpins social and internally directed cognitive activities (Andrews-Hanna, 2012; Andrews-Hanna et al., 2014; Buckner, Andrews-Hanna, & Schacter, 2008; Li, Mai, & Liu, 2014; Raichle, 2015). Disrupted connectivity in the DMN has been observed in normal cognitive ageing (Andrews-Hanna et al., 2007; Huang, Hsieh, et al., 2015), amnestic MCI (Bai et al., 2008; De Vogelaere, Santens, Achten, Boon, & Vingerhoets, 2012; Weiler et al., 2014) and AD (Dennis & Thompson, 2014; Greicius, Srivastava, Reiss, & Menon, 2004). Decline has also been observed in executive control networks which underpin the executive domains of cognition enabling top-down regulation of cognitive function in normal and MCI samples (Cai et al., 2017; Shaw et al., 2015). As segregation between these networks has been viewed as favourable for optimal cognitive performance (Anticevic et al., 2012; Fox et al., 2005; Samu, Campbell, Tsvetanov, Shafto, & Tyler, 2017; Sonuga-Barke & Castellanos, 2007) a third network, called the salience network, has been proposed which modulates the interaction between these two networks (Chand & Dhamala, 2016; Seeley et al., 2007; Uddin, 2015). Disrupted modulation by this network has been associated with

MCI and with performance on the Montreal Cognitive Assessment (MoCA) (Chand, Wu, Hajjar, & Qiu, 2017).

1.2.4 Cognitive decline and impairment

With increasing age, comes a higher risk for developing age-related cognitive pathologies or dementia, the most common of which is Alzheimer's disease (AD) (Salthouse, 2010a). Interposed between these two conditions is an intermediate stage of cognitive impairment, usually termed Mild Cognitive Impairment (MCI), which represents a decline in cognitive function greater than expected for the person's age but which does not yet meet criteria for dementia (Petersen, 2004). While it has been hypothesised that forms of dementia such as AD might reflect simply an accelerated ageing process, qualitative differences in cognitive and neuro-imaging profiles suggest that these conditions, particularly AD, represent a distinctive, separate condition (Toepper, 2017). Mild cognitive impairment was originally characterised by a decline in memory which had no identifiable aetiology and did not interfere with daily function (Petersen et al., 1999). This concept has been expanded to include other variations of cognitive impairment and to reflect subtle changes in function seen in this condition (Morris et al., 2001) such as amnestic and nonamnestic forms of impairment and within one or multiple cognitive domains (Petersen & Morris, 2005; Winblad et al., 2004). Originally used to describe a prodromal phase of AD, subsequent work has found that MCI precedes other age-associated conditions such as VaD (Hayden & Welsh-Bohmer, 2012). Though estimates vary according to diagnostic criteria, MCI has an increasing prevalence with age in the older adult population and is associated with an increased risk of conversion to dementia (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003; de Souza-Talarico, de Carvalho, Brucki, Nitrini, & Ferretti-Rebustini, 2016).

1.2.5 Assessment and prediction of pathological cognitive decline

As some level of cognitive decline is normal with ageing, one of the challenges for researchers is distinguishing between cognitive changes due to age and those due to underlying neuropathology in the preclinical stages (Backman, Jones, Berger, Laukka, & Small, 2004; Belleville, Fouquet, Duchesne, Collins, & Hudon, 2014; Sperling et al., 2014). As neuropathologies, such as AD, often have a long prodromal phase of years if not decades, before clinical symptoms are manifest (see Figure 1.2) (Backman, Jones, Berger, Laukka, & Small, 2005; Caldwell, Yao, & Brinton, 2015; Elias et al., 2000; Linn et al., 1995; Morris, 2005), researchers often use longitudinal studies to separate the data of those who developed dementia from those who age successfully, in order to identify patterns associated with normal cognitive ageing and the neuropsychological signatures of pathological cognitive decline such as those associated with dementia (Hayden & Welsh-Bohmer, 2012). Biomarkers such as APOE e4 genotype, medial temporal lobe atrophy or accumulation of amyloid beta (Aβ) may have predictive value for future incident dementias such as AD but often healthcare providers have limited access to such diagnostic techniques which are currently

expensive and inefficient for large-scale screening assessments (Albert et al., 2011; Logie, Parra, & Della Sala, 2015).

In contrast, neuropsychological assessment is comparably easier to administer and studies suggest that it has good if not greater predictive value compared to biomarkers (Belleville et al., 2014; Landau et al., 2010; Logie et al., 2015). Identification of patterns of strengths and weaknesses can aid in differentiating between different forms of cognitive impairment and dementias and in earlier identification of those at risk (Jacobson, Delis, Bondi, & Salmon, 2002; Nestor, Scheltens, & Hodges, 2004; Twamley, Ropacki, & Bondi, 2006). In normal and pathological ageing, there is decline in memory, executive function and processing speed (Toepper, 2017). However, prodromal AD is associated with deficits in episodic and semantic memory and with subtle deficits in executive function, whereas decline with normal ageing is more accentuated in executive functions and processing speed but is associated with maintained semantic memory (Buckner, 2004; Toepper, 2017).

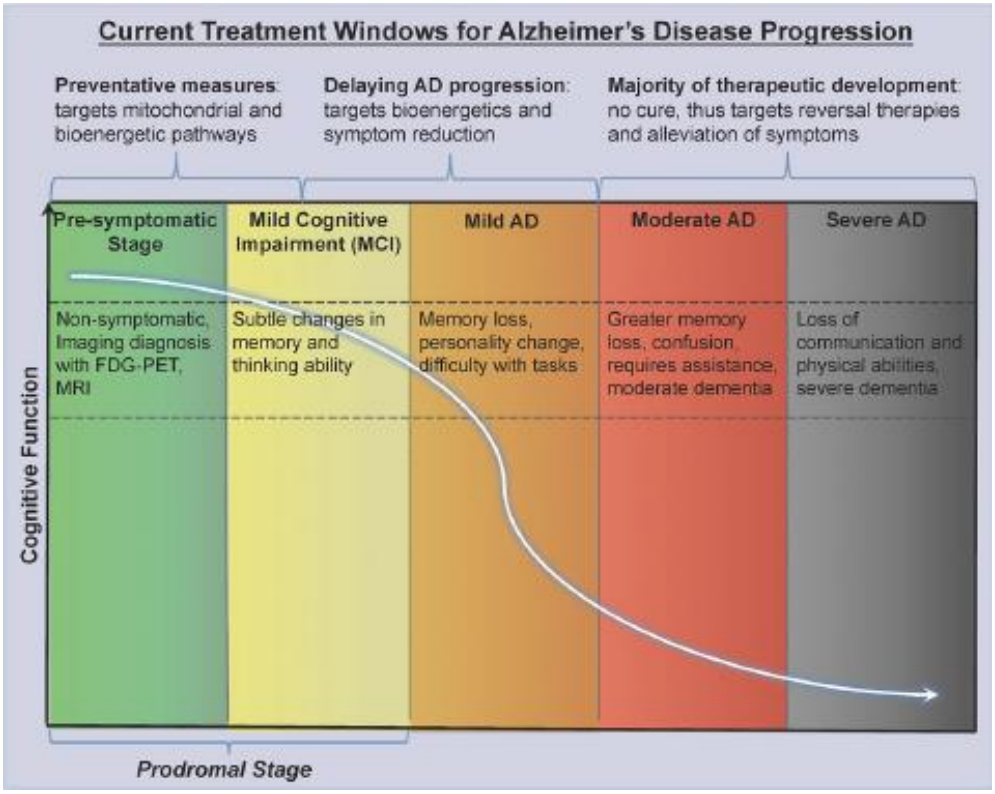

Fig 1.2: Progression of AD from pre-symptomatic stage to incident AD (Caldwell et al., 2015).

1.2.6 Treatment and prevention of pathological cognitive decline

Current pharmacological treatments for AD, the most common dementia, offer only moderate symptom relief (Thies & Bleiler, 2013). Drug trials attempting to halt or reverse cognitive decline, usually by reversing AD amyloid pathology, have produced limited results (Feldman et al., 2014;

Folch et al., 2015; Karran, Mercken, & De Strooper, 2011; Thies & Bleiler, 2013). As early diagnosis is a factor in successfully managing dementia, the long prodromal stage of AD offers an opportunity for earlier identification and prevention and may provide the most effective avenue to reduce the burden and prevalence of AD (Bateman et al., 2012; Lin, Yang, et al., 2014; Sperling et al., 2014; Villemagne et al., 2013). However, overlap between cognitive deficits and pathophysiological substrates due to AD pathology and the benign effects of ageing make it challenging to distinguish prodromal AD cases from the normal ageing population (Belleville et al., 2014; Bondi et al., 2008). Investigative efforts are increasingly focused on identifying the unique biomarkers and cognitive signatures of this disease and the modifiable factors which delay AD incidence (Caldwell et al., 2015; Norton et al., 2014) and may also allow for more successful cognitive ageing among the normal ageing population (Beydoun et al., 2014). Switching to a strategy of earlier identification and prevention would significantly reduce prevalence and the associated cost (Lin, Yang, et al., 2014). Interventions that delay the onset of dementia by one year would lead to a decrease of more than 10% in the global prevalence of dementia in 2050 (Brookmeyer et al., 2007). ARHL may be one such modifiable risk factor or a predictive marker for age-associated neurocognitive decline and disease (Deal et al., 2015; Gallacher et al., 2012; Lin, Metter, et al., 2011; Panza, Solfrizzi, & Logroscino, 2015).

1.3 Theoretical perspectives

There has been much debate as to what factors are most fundamental in explaining age-related variance in cognitive function with some researchers attempting to explain this phenomenon in terms of a single factor or a small number of factors (Dennis & Cabeza, 2011). Multiple theories have been proposed attempting to account for cognitive ageing - a few of the main ones are described briefly below.

1.3.1 Sensory Deficit

According to sensory deficit theory, age-related changes can be explained in terms of changes in sensory processing (Lindenberger & Baltes, 1994). The main support for this view comes from evidence of strong correlations between age-related differences in sensory and cognitive measures (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994). Further support for this view comes from neuroimaging studies (Dennis & Cabeza, 2011) where it was found that older adults recruited higher cognitive functions (pre-frontal cortex increase) to compensate for visual processing deficits (occipital decrease) demonstrating that decline in sensory functioning has a broader impact on brain function (Grady et al., 1994). These findings were confirmed in a study which demonstrated this pattern of neural compensation in the same occipital and PFC regions across working memory, visual attention and episodic retrieval tasks (Cabeza et al., 2004). Older adults who demonstrated the weakest occipital activations demonstrated the strongest PFC activations.

1.3.2 Frontal Lobe

The frontal lobe hypothesis describes how age-related atrophy in the prefrontal cortex leads to decline in the executive functions: monitoring, sequencing, initiation of action, inhibiting pre-potent responses, formulating goals, focusing attention and generating response alternatives (Miller & Cohen, 2001; West, 2000). As these functions mediate performance between age and general cognitive capacities (Salthouse et al., 2003), it is argued that age-related cognitive decline may arise from impaired or inefficient deployment of cognitive control processes due to age-related degeneration of frontal lobe structures (Braver & Barch, 2002; Crawford, Smith, Maylor, Della Sala, & Logie, 2003; Glisky, 2007; Greenwood, 2000; Rodriguez-Aranda & Sundet, 2006; West, 2000). This view is supported by neurological evidence which finds that the frontal lobes typically demonstrate the fastest rate of decline compared to other regions (Raz et al., 2005; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003).

1.3.3 Speed of Processing

This theory posits that cognitive deficits in older adults can be attributed to a reduction in the speed of processing (Salthouse, 1996). There is strong evidence to support this view because processing speed shares a large proportion of variance with age related deficits in cognitive measures and declines steadily with age. A possible neural mechanism for this decline is white matter deterioration because several studies have found a correlation between decline in processing speed and WMHs (white matter hyperintensities) and DTI (diffusion tensor imaging) measures of white matter integrity (Dennis & Cabeza, 2011). Performance on tasks assessing speed of processing, executive functioning and visual detection reaction time were found to have a significant relationship with DTI measures in frontal and frontal striatal areas (Madden et al., 2004; O'Sullivan et al., 2001; Persson et al., 2006). Periventricular WMHs were associated with slower motor speed (Soderlund, Nyberg, Adolfsson, Nilsson, & Launer, 2003). Older adults may compensate for these deficits by recruiting PFC regions and increasing speed performance on tasks (Reuter-Lorenz et al., 2000).

1.3.4 Resources

Craik and colleagues (Craik, 1986; Craik, a. Routh, & Broadbent, 1983; Craik & Byrd, 1982) propose that a decline in the available attentional resources leads to age-related deficits in cognitive performance. This has been supported by behavioural studies which have found that when attentional resources are reduced in younger adults they show similar deficits in cognitive function to older adults (Anderson, Craik, & Naveh-Benjamin, 1998; Jennings & Jacoby, 1993). In a PET study of an encoding and retrieval task, Anderson et al. (2000) demonstrated that younger adults show the same pattern of neural activity as older adults under divided attention. Based on Craik's (1983) proposal that deficits in processing due to age were linked to a reduction in the efficiency of frontal lobe function, Dennis & Cabeza (2008) further expand on this theory. They propose that older adults will show reduced activity in PFC regions typically engaged by younger adults and

that they will compensate for this deficit by recruiting contralateral PFC regions thus tapping into other cognitive resources. Neuroimaging studies have found that older adults typically show reduced activation in PFC regions normally engaged by younger adults on visuospatial working memory, and on episodic encoding and retrieval tasks (Grady et al., 1994; Schiavetto, Kohler, Grady, Winocur, & Moscovitch, 2002). Supporting the second proposal, studies have also found that older adults recruit contralateral regions to support performance on tasks assessing multiple cognitive domains (Cabeza et al., 2002; Reuter-Lorenz et al., 2000).

1.3.5 Inhibition

This theory proposes that decline in inhibitory control in working memory allows goal-irrelevant information to interfere with working memory processes, leading to deficits in cognitive performance (Hasher & Zacks, 1988; Zacks, Hasher, & Li, 2000). Extending these assumptions to a neural context, Dennis and Cabeza (2011) propose that older adults should demonstrate weaker neural activity in inhibitory control regions and greater activity in inhibited regions. These assumptions have been supported by neuroimaging research (Cabeza et al., 1997; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Jonides et al., 2000). Additionally, older adults show bilateral PFC activations during inhibitory tasks compared to younger adults suggesting that they compensate for this deficit by recruiting other neural regions (Nielson, Langenecker, & Garavan, 2002).

1.3.6 Brain Reserve & Cognitive Reserve

Brain reserve posits that those with a greater brain size and number of neurons are able to tolerate greater damage to the brain, either from age-related changes, injury or neuropathology before manifesting clinical symptoms (Stern, 2012). With the advent of normal ageing or neuropathology such as Alzheimer's disease, comes a volumetric shrinkage in various brain structures (Desikan et al., 2009; Raz et al., 2005). Brain reserve is essentially a passive model, presuming that the clinical manifestation of these neuropathological or age-related neuronal changes exists once a threshold of neuronal damage has been reached. Research has found links between the clinical effects of neuropathology and brain size, head circumference and number of synapses (Bigio, Hynan, Sontag, Satumtira, & White, 2002; Mori et al., 1997; Mortimer, Snowdon, & Markesbery, 2003).

Cognitive reserve, in contrast, is an active model and describes how individual differences in neurocognitive functioning result in differences in the clinical manifestation of neural changes associated with ageing and neurodegenerative disease (Stern, 2012). Stern (Stern, 2009) outlines two mechanisms through which the brain does this. Neural reserve refers to how differences in the efficiency, capacity, or flexibility of the neuronal networks underlying cognitive functions lead them to be more or less resilient to neuronal damage. Neuronal compensation refers to the capacity of the brain to recruit structures or networks not normally used to help maintain or improve performance. Studies examining inter-individual variation in efficiency of task-related neural processing using fMRI have provided evidence to support this concept (Holtzer et al., 2009; Stern,

2012; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007). Proxies of cognitive reserve have been found to be associated with cognitive function independently of neuropathology (Wilson et al., 2013) and atrophy (Vaughan et al., 2014; Vuoksimaa et al., 2013).

1.4 Risk factors & mechanisms

Another trend that has emerged in the literature is that there is considerable variability in the level of cognitive functioning between individuals of the same age, even within the normal cognitive ageing population (Salthouse, 2010a) and in fluid intelligence and memory rather than in crystallised intelligence (Christensen, 2001). Based on evidence from a meta-analysis by Verhaeghen and Salthouse (1997) in population samples ranging from 18 to 80 years of age, Salthouse (2010a) points out that age accounts for between only 4% to 36% of the variance in cognitive function. This differential decline may be mediated and determined by multiple biological, environmental and lifestyle factors which modify the trajectory of cognitive ageing (Beydoun et al., 2014; Bozzali et al., 2015; Deary et al., 2009; Depp, Harmell, & Vahia, 2012; Hayden & Welsh-Bohmer, 2012; Stern, 2012) and modify risk of incident dementia (Barnes & Yaffe, 2011; Norton et al., 2014; Sperling et al., 2014).

This variance has led to a diverse range of research approaches assessing various biomarkers which may aid prediction of cognitive decline and potential risk factors that can be modified or treated to alter outcomes. For example, research on specific genetic markers have found associations between cognitive health and genetic markers regulating cardiovascular health (e.g. PON1, APOE), cell metabolism and oxidative stress (e.g. SIRT3), inflammatory processes (e.g. IL6, IL10) (Depp et al., 2012; Glatt, Chayavichitsilp, Depp, Schork, & Jeste, 2007; Zubenko, Hughes, Zubenko, & Maher, 2007).

Apart from biological processes, there are also several lifestyle factors such as education and social network size that influence cognitive ageing (Depp et al., 2012) and that can predict clinical outcomes and contribute significantly to the onset of dementias, including AD, independently of neuropathologic substrates (Bennett, Schneider, Tang, Arnold, & Wilson, 2006; Norton et al., 2014; Stern, 2012). These modifiable factors possibly impart a ‘reserve’ against neuropathology (Stern, 2009, 2012) and provide a potential avenue for interventions to reduce prevalence (Norton et al., 2014). Additionally, cardiovascular risk factors related to lifestyle, such as atherosclerosis, produce grey and white matter lesions contributing significantly to cognitive decline and dementia pathology including AD (Qiu & Fratiglioni, 2015). Chronic stress influences a network of physiological processes that often result in neuronal degradation (Depp et al., 2012) and is associated with damage to the brain particularly in relation to the hippocampus, inflammatory cytokines and decreased immune response (McEwen, 2000, 2002, 2008). Observational studies have generally found that greater exercise participation is associated with reduced risk for dementia (Larson et al., 2006) possibly by reducing oxidative stress and inflammation as well as altering posterior brain regions (Kramer, Erickson, & Colcombe, 2006; Prakash et al., 2011). Calorie

restriction has been linked to significantly improved memory performance in older adults (Witte, Fobker, Gellner, Knecht, & Floel, 2009).

1.5 ARHL & its impact on the health of older adults

1.5.1 Overview

ARHL generally begins at the higher frequencies in young adulthood and progresses gradually, bilaterally and symmetrically towards the lower frequencies (<3 kilohertz (kHz)), becoming more noticeable in older age when severe enough to affect speech understanding (Gates & Mills, 2005). As hearing loss progresses in severity, it leads to impairment of social (Gopinath et al., 2012) and daily function (Lopez-Torres Hidalgo et al., 2009). It is a highly prevalent condition in the older adult population with at least a mild hearing loss affecting roughly 25-30% of older adults aged between 50-59 years increasing to more than 50% of adults aged over 60 years with significant increases per decade (Agrawal, Platz, & Niparko, 2008; Gopinath, Rochtchina, et al., 2009; Lin, Thorpe, Gordon-Salant, & Ferrucci, 2011; Nash et al., 2011; Raynor et al., 2009; Wilson et al., 1999). The World Health Organisation estimates that one-third of adults over the age of 65 years have a moderate or disabling hearing loss (World Health Organisation, 2015). Acquired hearing loss most likely represents a mixture of pathophysiological processes - primarily genetic factors and environmental exposures such as noise and ototoxic factors (Fetoni, Picciotti, Paludetti, & Troiani, 2011; Gates & Mills, 2005; McMahon, Kifley, Rochtchina, Newall, & Mitchell, 2008; Viljanen et al., 2007; Wingfield et al., 2007; Yamasoba et al., 2013). Regardless of specific pathophysiology, functional outcomes are similar and are characterised by an increase in hearing thresholds and poorer frequency resolution, initially experienced as a loss of perception of speech in noisy backgrounds (Barrenas & Wikstrom, 2000; Dubno et al., 2008; Gates & Mills, 2005; Yamasoba et al., 2013).

1.5.2 Anatomy & pathophysiological processes

Decline in peripheral hearing function is primarily due to dysfunction of the cochlea in the inner ear, the most complex part of the peripheral hearing structure, which transduces incoming mechanical sound into neurochemical signals for processing in the auditory cortex (Gates & Mills, 2005; Yamasoba et al., 2013). Primary sites of ARHL pathology in the cochlea are the stria vascularis, auditory hair cells and spiral ganglion neurons (Fetoni et al., 2011; Kamogashira, Fujimoto, & Yamasoba, 2015; Ohlemiller, 2004; Schmiedt, 2010; Schuknecht & Gacek, 1993; Yamasoba et al., 2013).

The stria vascularis is a highly vascularised epithelium with an intense aerobic metabolism that lines the outer wall of the cochlear duct (*scala media*) where the organ of Corti is located (Gates & Mills, 2005; Schmiedt, 2010). It contains Na^+ K^+ ATPase pumps and produces endolymph, maintaining the endocochlear potential needed for initiating signalling in cochlear hair cells. Deterioration of this structure, termed strial or metabolic presbycusis (Schuknecht & Gacek, 1993),

consequently leads to loss of endocochlear potential with a flat increase in decibel threshold across low frequencies and a sloping increase on high frequencies (Schmiedt, Lang, Okamura, & Schulte, 2002; Schuknecht & Gacek, 1993; Suzuki et al., 2006).

The outer and inner auditory hair cells are located in the organ of Corti, a sensory epithelium on the basilar membrane of the cochlea (Gates & Mills, 2005; Schmiedt, 2010; Yamasoba et al., 2013). Displacement of outer hair cells by sound waves propagating in the endolymph amplifies the waves and extends the frequency range. Outer hair cells are more susceptible to damage than inner hair cells and their loss, termed 'sensory presbycusis' (Schuknecht & Gacek, 1993), results in a rise in hearing decibel threshold progressing from the higher frequencies downwards and poorer frequency selectivity (Davis, Ahroon, & Hamernik, 1989). Displacement of inner hair cells opens transduction ion channels allowing an influx of potassium (K^+) and calcium (Na^+) ions into the hair cell, depolarising the cell and triggering the release of neurotransmitters, thereby transducing mechanical sound waves into neurochemical signals. These signals are transmitted to the auditory cortex through release of the neurotransmitter glutamate by inner hair cell synapses to afferent spiral ganglion neurons. Little is known about the behavioural consequences of inner hair cell deterioration, the loss of which does not seem to substantially lower hearing threshold (Lobarinas, Salvi, & Ding, 2013).

The spiral ganglion, formed by the cell bodies of the cochlear (auditory) nerve, transports signals from the hair cells to the auditory cortex in the temporal lobe (Gates & Mills, 2005; Schmiedt, 2010; Yamasoba et al., 2013). Deterioration in the afferents, termed 'neural presbycusis' (Schuknecht & Gacek, 1993), is associated with poorer temporal and frequency coding and speech perception in noise (Lopez-Poveda, 2014; Sergeyenko, Lall, Liberman, & Kujawa, 2013; Yamasoba et al., 2013).

Deterioration in hearing function can also originate in the central auditory cortex independently of observed changes in the peripheral structure (Ouda, Profant, & Syka, 2015). Decline in these structures leads to poorer auditory perceptual function as characterised by poorer understanding of degraded or rapid speech without apparent deterioration in peripheral pathways (Gates & Mills, 2005). This may be due to age related neurodegeneration or neuropathology (Gates, Anderson, McCurry, Feeney, & Larson, 2011; Sinha, Hollen, Rodriguez, & Miller, 1993; Wong et al., 2009). Data from epidemiological ageing studies suggest that disabling central auditory dysfunction independent of peripheral function has a low rate of prevalence in the adult population (Gates & Mills, 2005). Central auditory dysfunction usually occurs secondary to longer-term peripheral dysfunction in the later stages of the pathological process (Gates & Mills, 2005).

1.5.3 Assessment

Hearing loss is primarily assessed using pure-tone audiometry: the criterion standard, which consists of administering a pure-tone sound monaurally at different decibel levels across a range of

frequencies to measure pre-tone thresholds (Bagai, Thavendiranathan, & Detsky, 2006). However, it does not detect decline in a multitude of peripheral hearing functions such as frequency selectivity or localising of sound sources which also contribute to hearing status and may precede threshold elevation (Bharadwaj, Masud, Mehraei, Verhulst, & Shinn-Cunningham, 2015; Kujawa & Liberman, 2015; Sergeyenko et al., 2013; Wayne & Johnsrude, 2015). Future research using multiple alternative assessments of peripheral functions, such as speech-in-noise perception or temporal processing (Humes, Busey, Craig, & Kewley-Port, 2013; Humes, Kidd, & Lentz, 2013), may give further insight into whether these functions have unique associations with cognitive function independent of pure-tone audiometry (Wayne & Johnsrude, 2015).

1.5.4 Association with other health concerns in the ageing population

Hearing loss has been associated with a wide range of health and neuropsychiatric conditions typically reported with ageing and dementia. These include poorer health-related quality of life (Appollonio, Carabellese, Frattola, & Trabucchi, 1996; Dalton et al., 2003; Genther, Frick, Chen, Betz, & Lin, 2013; Sugawara et al., 2011), functional impairment (Appollonio et al., 1996; Chen, Genther, Betz, & Lin, 2014; Dalton et al., 2003; Marsiske, Klumb, & Baltes, 1997; Strawbridge, Wallhagen, Shema, & Kaplan, 2000; Wahl et al., 2013), reduced social participation (Appollonio et al., 1996; Chen, Genther, et al., 2014; Gopinath et al., 2012; Kramer, Kapteyn, Kuik, & Deeg, 2002; Marsiske et al., 1997; Strawbridge et al., 2000), apathy (Sugawara et al., 2011), depression (Jayakody, Friedland, Eielboom, Martins, & Sohrabi, 2017; Kramer et al., 2002), anxiety (Jayakody et al., 2017), frailty (Kamil, Li, & Lin, 2014), sleep dysfunction (Nakajima, Kanda, Hosobuchi, & Suwa, 2014), change in personality (reduced extraversion) (Berg & Johansson, 2013), increased risk of falls (Lin & Ferrucci, 2012), increased numbers of hospitalisations (Genther et al., 2013) and greater risk of mortality (Appollonio et al., 1996; Karpa et al., 2010; Wahl et al., 2013).

1.5.5 ARHL & cognitive ageing

ARHL and decline in cognitive functioning both follow similar patterns of incidence and progression across the lifespan with some data suggesting that they can be co-morbid processes (Lindenberger & Baltes, 1994; Wayne & Johnsrude, 2015). Sensory functioning is a strong late-life predictor of individual differences in intellectual functioning (Lindenberger & Baltes, 1994, 1997). Data from multiple epidemiological studies using samples from the general population have linked severity of acquired hearing loss, as measured by audiometry, with poorer outcomes in multiple cognitive domains (Bush, Lister, Lin, Betz, & Edwards, 2015; Deal et al., 2015; Lin, Ferrucci, et al., 2011) and accelerated cognitive decline (see Figure 1.3) (Lin et al., 2013). Severity of ARHL has also been linearly associated with dementia (See Figure 1.4) (Lin, Metter, et al., 2011). This relationship was found to remain after controlling for a range of other risk factors including age, gender, education and vascular factors (Bush et al., 2015; Deal et al., 2015; Lin, 2011; Lin, Ferrucci, et al., 2011; Lin et al., 2013). However, other similar studies have found no connection

between audiometric acquired hearing loss and cognition (Humes, Busey, Craig, & Kewley-Port, 2009; Lin et al., 2004). Likewise, some studies have associated hearing loss with cognitive impairment (Karpa et al., 2010; Kiely, Gopinath, Mitchell, Luszcz, & Anstey, 2012; Lin et al., 2013; Lopez-Torres Hidalgo et al., 2009; Quaranta et al., 2014) while others have not (Gates et al., 1996; Kurniawan et al., 2012; Tay, Kifley, et al., 2006).

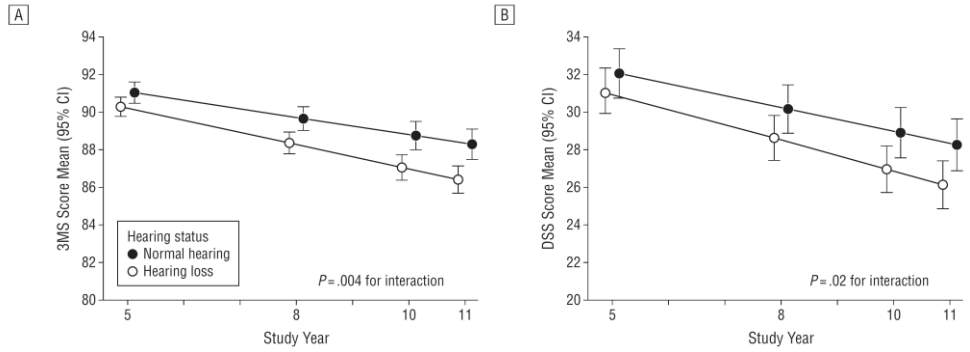

Figure 1.3: Relationship between hearing loss and cognitive decline.

Note: tasks assess a) global cognition, b) processing speed (Lin et al., 2013)

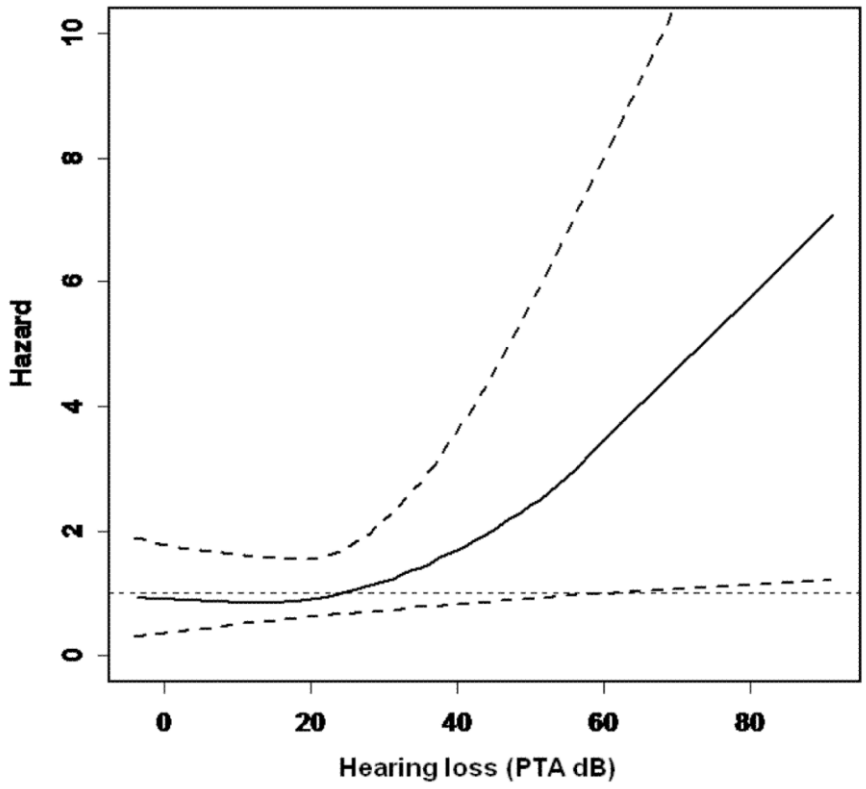

Figure 1.4: Relationship between hearing loss and risk of incident dementia (Hazard ratio) (Lin, Metter, et al., 2011).

Variance in findings may be due to suboptimal audiometric assessment, limited audiometric criteria (excluding higher speech frequencies) or cognitive tests using auditory stimuli (Gallacher et al., 2012). However, studies that aimed to assess decline in cognitive function using visual tests have reported significant decline in executive function and episodic memory (Gallacher et al., 2012; Jayakody et al., 2017). Neuroimaging studies researching both conditions have found further support for an association, finding that pure-tone thresholds were linked with increased atrophy of both regional (Eckert, Cute, Vaden, Kuchinsky, & Dubno, 2012; Husain, Medina, et al., 2011; Lin, Ferrucci, et al., 2014) and global brain grey matter (Lin, Ferrucci, et al., 2014) and white matter alterations (Eckert et al., 2013; Husain, Medina, et al., 2011). Additionally, a small number of intervention trials have reported improved cognitive outcomes following audiological rehabilitation (Acar, Yurekli, Babademez, Karabulut, & Karasen, 2011; Mosnier et al., 2015; Mulrow et al., 1990).

1.5.6 Hypotheses & causal factors

Hypotheses on the cause of this association include a common aetiology, such as alterations in the vascular system affecting cochlear and neural function (Lin, Ferrucci, et al., 2014; Lindenberger & Baltes, 1994; Malgrange, Varela-Nieto, de Medina, & Paillasse, 2015) or a more general association as part of frailty syndrome (Panza, Solfrizzi, & Logroscino, 2015). Other hypotheses suggest that the association may be mechanistic with hearing loss affecting cognition (Lin, Ferrucci, et al., 2014; Lin, Metter, et al., 2011; Lindenberger & Baltes, 1994). Potential mechanisms include loss of cognitive stimulation (Peelle, Troiani, Grossman, & Wingfield, 2011; Wilson et al., 2013), increased cognitive effort in speech perception (Peelle et al., 2011) leading to poorer memory encoding (Tun, McCoy, & Wingfield, 2009) and depletion of cognitive reserve (Campbell & Sharma, 2013, 2014), or psychosocial stress and altered immunological function (Reader et al., 2015) due to factors such as impaired daily function (Chen, Betz, et al., 2014) or depression (Schmaal et al., 2015) and loneliness (Cole et al., 2007; Wilson, Begeny, Boyle, Schneider, & Bennett, 2011; Wilson, Krueger, et al., 2007). As it is not clear which pathways are dominant in this relationship, ARHL may be either a predictive symptomatic marker or modifiable risk factor for dementia or both (Lin, Metter, et al., 2011; Panza, Solfrizzi, & Logroscino, 2015).

Lack of clarity as to the causal nature of this relationship has perhaps led to a lack of theoretical models for predicting specific long-term outcomes for different cognitive systems following ARHL (Wayne & Johnsrude, 2015) apart from research examining the perceptual-cognitive link in speech processing (Peelle et al., 2011; Pichora-Fuller, 2003; Ronnberg et al., 2013). One model, the Ease of Language Understanding (ELU) model, is a complex framework incorporating multiple aspects of listening under adverse conditions in older adults (Ronnberg et al., 2013). Broadly, it posits that mismatch between degraded acoustic information and stored phonological representations of words leads to explicit, effortful processing of speech resulting in poorer encoding and retrieval from long-term memory (Ronnberg et al., 2013). This is predicted to lead to a more pronounced decline

in long-term episodic and semantic memory systems through disuse compared to recruited cognitive functions such as working memory and immediate recall (Ronnberg et al., 2011; Ronnberg, Hygge, Keidser, & Rudner, 2014; Ronnberg et al., 2013).

1.6 Summary and conclusions

There is projected to be a significant increase in the prevalence of dementia in the next few decades (Brookmeyer et al., 2007; Ferri et al., 2005; Suzman & Beard, 2011). However, there is currently no effective treatment for these dementias such as AD (Thies & Bleiler, 2013). Conditions such as ARHL may offer predictive biomarkers for dementia, assisting with development of public health policy and with selection for future clinical trials. Furthermore, modification of risk factors such as hearing loss may influence the rate of age-associated cognitive decline and the time of onset of dementia (Albers et al., 2015; Norton et al., 2014; Sperling et al., 2014). Neuropsychological assessment is the primary method used by researchers and clinicians to assess and predict the development of dementia (Belleville et al., 2014; Landau et al., 2010; Logie et al., 2015). Further research is required to continue the development of neuropsychological tests that detect subtle changes in cognition to promote earlier diagnosis of cognitive impairment. In particular, more research is needed to assess how different risk factors may contribute to differences in patterns of cognitive decline. Given the prevalence of ARHL, the identification of a pattern of neuropsychological changes associated with it may benefit diagnosis and facilitate intervention. Additionally, it may give insight into the causal factors underlying the possible association between ARHL and cognitive decline.

1.7 Thesis outline

This thesis took an exploratory approach to assessing the association between ARHL and cognitive function and the possible causal mechanism underpinning this association. Chapter 2 describes a systematic review and meta-analysis of this association in epidemiological studies to examine and estimate the extent of the association between age-related hearing loss (ARHL) and cognitive function, cognitive impairment and dementia. Epidemiological research on the possible link between age-related hearing loss (ARHL) and cognitive decline and dementia has produced inconsistent results. Chapter 3 describes another review of possible pathological processes that represent either a common aetiological cause for both conditions or a mechanistic pathway by which ARHL leads to neurocognitive decline. Chapter 4 describes a hypothetical model for a mechanistic association whereby ARHL causes cognitive decline and outlines the methods used to collect data for the empirical chapters in this thesis. Chapter 5 describes differences in markers of processing speed and intra-individual variability between a group of older adults with and without hearing loss and differences in markers of higher cognitive control and neural arousal. Chapter 6 describes an analysis based on fluency tasks examining how ARHL may be associated with differences in stored semantic and phonological representations and in retrieval of these representations. Chapter 7 presents the results from an analysis of differences in feature-binding in

short-term episodic memory. A general discussion of the findings, the limitations and their implications are presented in Chapter 8.

Chapter 2 The Association of Age-Related Hearing Loss with Cognition Function, Cognitive Impairment and Dementia: A Systematic Review with Meta-Analysis

2.1 Introduction

This chapter reports on a systematic review and meta-analysis conducted to examine the association between age-related hearing loss (ARHL) and cognitive decline and dementia. Meta-analysis is a powerful tool to examine associations between potential risk factors and health outcomes as it is based on a larger sample size than an individual cohort study (Borenstein, Hedges, Higgins, & Rothstein, 2011). Further statistical analysis using moderator analysis and meta-regression allows for exploration of potential confounders that may explain the association between risk factors and outcomes as well as the influence of potential biases (e.g. publication bias). Pooling data from multiple independent studies could allow for a more robust estimate of the strength of the association between ARHL and cognitive decline, thus potentially informing design of future cohort studies as well as randomised controlled trials. Compared to other risk factors for dementia, there has been very little research examining the effects of ARHL on cognitive health outcomes despite its prevalence (Lin & Albert, 2014). Approximately one-third of adults over 65 experience a disabling hearing loss (Wilson, Tucci, Merson, & O'Donoghue, 2017; World Health Organisation, 2015). It is easily diagnosed and treated and half of all cases are preventable; it would therefore be a serviceable risk factor (Albers et al., 2015; Lin & Albert, 2014). Prior reviews have either not included a meta-analysis of this association or have included different measures of hearing impairment and studies of different designs (Cherko, Hickson, & Bhutta, 2016; Gennis, Garry, Haaland, Yeo, & Goodwin, 1991; Schmulian Taljaard, Olaithe, Brennan-Jones, Eikelboom, & Bucks, 2015).

Epidemiological findings have been inconsistent (Gallacher et al., 2012; Lin, Ferrucci, et al., 2011; Wayne & Johnsrude, 2015), possibly due to different audiometric criteria (e.g. self-report) or suboptimal methodology (e.g. no sound treated room or audio cognitive tests) (Dupuis et al., 2015; Gallacher et al., 2012; Lin, Ferrucci, et al., 2011; MacDonald, Joyson, Lee, Seymour, & Soiza, 2012). However, neuroimaging studies have linked ARHL with increased global (Lin, Ferrucci, et al., 2014) and regional grey matter atrophy, particularly regions associated with speech processing (Eckert et al., 2012; Husain, Medina, et al., 2011; Lin, Ferrucci, et al., 2014; Peelle et al., 2011), and with white matter hyperintensities (Eckert et al., 2013; Husain, Medina, et al., 2011). Additionally, a small number of intervention trials have reported improved cognitive outcomes following audiological rehabilitation (Acar et al., 2011; Mosnier et al., 2015).

This chapter reports on a systematic review and meta-analysis to investigate the association between ARHL and cognitive function, cognitive impairment and dementia in cohort observational studies. Qualitatively different search and audiometric criteria were used compared to other reviews of this topic (Cherko et al., 2016; Gennis et al., 1991; Schmulian Taljaard et al., 2015). To reduce conceptual heterogeneity, only observational cross-sectional and cohort studies that assessed hearing loss using pure-tone audiometry (the criterion standard) were included. Subgroup analyses were conducted to investigate the effects of various study, demographic, audiometric and lifestyle factors and to explore possible explanations for heterogeneity. An examination of whether cognitive reserve mediated cognitive outcomes for ARHL was completed.

2.2 Methods

This systematic review was performed according to an a priori established protocol (PROSPERO: CRD42015026052) and adhered to the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (Liberati et al., 2009). It also met the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). Six *a priori* meta-analyses were planned across two levels of study design and three levels of cognitive outcome: (1) cross-sectional studies of ARHL & cognitive function; (2) cohort studies of ARHL & cognitive function; (3) cross-sectional studies of ARHL & cognitive impairment; (4) cohort studies of ARHL & cognitive impairment; (5) cross-sectional studies of ARHL & dementia; and (6) cohort studies of ARHL & dementia. All analyses were conducted using Comprehensive Meta-Analysis (CMA; version 3).

2.2.1 Data sources and searches

Studies published up to August 26, 2015 were retrieved from four electronic databases: (1) PubMed; (2) Cochrane Library; (3) EMBASE; and (4) SCOPUS. Keywords included: 'hearing', 'cognition', 'dementia' and 'Alzheimer's disease' (several papers included had been published online prior to publication of the print version). Search terms and strategy are provided in Appendix A. Results were updated on April 15, 2016. Cross-referencing for potentially eligible papers was conducted using retrieved study papers and the author's personal files.

2.2.2 Study selection criteria

The inclusion criteria were as follows: (1) cross-sectional and cohort studies; (2) published studies (any language); (3) minimum age of sample ≥18 years; (4) baseline sample included general, community-dwelling population rather than special groups at risk e.g. coronary heart disease patients; (5) main exposure variable was the individual's peripheral hearing status (as assessed by pure-tone audiometric assessment); (6) full inclusion of hearing loss sample i.e. no pure-tone audiometric cut-off point; (7) assessment of one or more of the following outcomes: (a) cognitive function; (b) cognitive impairment; (c) dementia; (8) exposure and outcome measurements taken by health professionals or trained investigators i.e. not based on self-report data.

Primary outcomes of interest were cognitive function, cognitive impairment and dementia. Cognitive function was a continuous variable and was sub-divided into 10 cognitive domains including attention, delayed recall, fluency, global function, immediate recall, processing speed, reasoning, semantic memory, visuospatial ability and working memory (Lezak, 2004). Cognitive impairment and dementia were dichotomous variables. A secondary outcome of interest was any data that examined subgroups (e.g. AD) among dementia studies.

2.2.3 Data extraction and quality assessment

Two researchers independently screened for eligible studies and conducted data extraction using a codebook. If consensus could not be reached, one author acted as arbitrator for study inclusion. The same author was consulted regarding data extraction. Multiple publication bias was avoided by using data from the most recently published study. Data from different papers that examined the same cohort were included provided they were for different cognitive outcomes and were treated as separate studies in analysis. Priority was given to outcomes that were maximally adjusted for covariates. The first and second author independently assessed the quality of reporting for each paper using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument (Vandenbroucke et al., 2014). Using Cohen's kappa coefficient (Cohen, 1968), agreement was excellent (0.91) prior to correcting discrepant items.

2.2.4 Calculation of effect sizes

Pearson's *r* correlation coefficient was chosen as the effect size of the linear association between pure-tone audiometric hearing loss and cognitive function. Negative scores indicated that greater hearing loss was associated with poorer cognitive functioning. Odds ratios (OR) were used for cognitive impairment and dementia.

If the required outcome metric was not reported in the paper, *r* or OR values were calculated using available data. Where the predictor variable was continuous, unstandardized Beta (β) values were standardised by dividing them by the standard error. Where the standard error was not available, the β values, provided they were within $\pm$0.5, were converted to *r* using the Peterson and Brown formula (Peterson & Brown, 2005). Standardised β values were converted to *r* by dividing them by the square root of the sample size. If the predictor variable was categorical, β values were entered into CMA as either raw mean differences or as Cohen's *d* as appropriate. Hazard ratios (HR), where the rate of incidence of outcome was less than 10%, were interpreted as OR (Zhang & Yu, 1998). If this rate exceeded 10%, HR were still treated as OR and a sensitivity analysis with the study deleted from the model was conducted to see if it had a significant impact on the overall results. Other effect sizes, (e.g. Chi-square, mean scores, etc.) were converted in CMA.

2.2.5 Statistical analysis

Random-effects, method-of-moments models that incorporate heterogeneity into the overall estimate were used to pool effect sizes from each study (DerSimonian & Laird, 1986). All

outcomes from each study were converted to either Fisher's *Z* or log ORs for analysis purposes and then converted back to the original metric i.e. *r* and OR respectively. For the meta-analyses of cognitive function, multiple tests of the same cognitive domain from the same study were collapsed into one effect size and subgroups were analysed independently as separate effect sizes. Heterogeneity was examined using the *Q* test and any *p*-value ≤0·10 was considered statistically significant (Higgins, Thompson, Deeks, & Altman, 2003). Inconsistency was examined using I^2 and the following grades were applied: <25% (very low), 25% to <50% (low), 50% to <75% (moderate) and >75% (large) (Higgins et al., 2003).

Small-study effects were examined using funnel plots and the regression-intercept approach of Egger and colleagues (Egger, Davey Smith, Schneider, & Minder, 1997) provided there were at least ten effect sizes (Egger et al., 1997; Sterne et al., 2011). To examine the effects of each result on the overall findings, outcomes were analysed by deleting each study from the model once. Cumulative meta-analysis, ranked by year, was used to examine the accumulation of evidence over time (Lau, Schmid, & Chalmers, 1995). An *ad hoc* analysis was conducted to project the effect of hearing loss treatment and prevention on dementia prevalence using the population attributable risk (PAR) formula (Barnes & Yaffe, 2011; Levin, 1953), the WHO estimate of hearing loss prevalence in older adults (one-third) (World Health Organisation, 2015), and our cohort dementia OR (the more conservative estimate). The number of cases of dementia potentially prevented with 10%-25% reduction in ARHL was also calculated (Barnes & Yaffe, 2011).

2.2.6 Subgroup analyses (moderator and meta-regression analyses)

Subgroup analyses were conducted to examine whether heterogeneity between studies was caused by differences in study samples and methods. Planned variables included (1) study characteristics, (2) subject characteristics, (2) Audiometric factors, (3) cognitive measures and (4) statistical analysis (see Appendix A for a list of each planned variable). For continuous variables, simple weighted least squares meta-regression (random-effects, method of moments approach) were used (Borenstein et al., 2011). Missing data for different variables from different studies was anticipated; therefore, only simple meta-regression was planned and performed. Meta-regression was performed only on covariates for which there were at least four effect sizes.

Between-group differences (Q_b) in effect size for categorical variables were examined using mixed effects ANOVA-like models for meta-analysis (Borenstein et al., 2011). These consisted of a random-effects model for combining studies within each subgroup and a fixed effect-model across subgroups (Borenstein et al., 2011). Study-to-study variance (tau-squared) was considered to be unequal for all subgroups. This value was computed within subgroups but not pooled across subgroups. Moderator analysis was conducted only between categories for which there were at least three effect sizes for each category. If effect sizes that had been collapsed into one effect size differed on a categorical variable prior to collapse, they were separated for moderator analysis. All

meta-regression and moderator analyses were considered to be exploratory (Littell, Corcoran, & Pillai, 2008).

2.3 Results

The characteristics of included studies are shown in Table 2.1. Of the 1,185 citations reviewed, 40 studies met the inclusion criteria (Figure 2.1). An excluded studies table is available upon request. Study quality results are shown in Table 2.1 and Appendix A. More than 80% of the included papers met the criteria for 16 out 22 STROBE items.

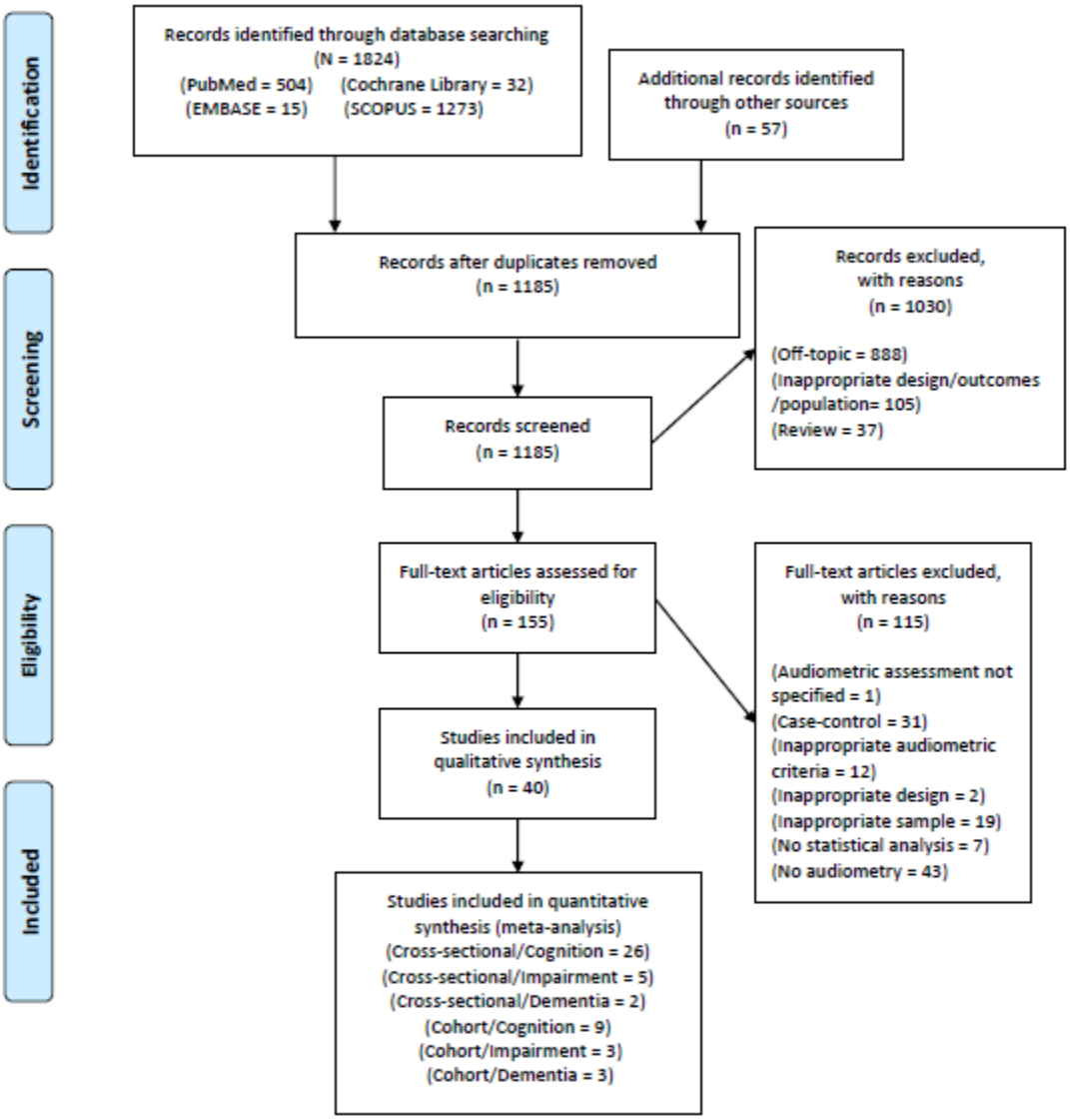

Figure 2.1: PRISMA flow diagram

2.3.1 Hearing loss & cognitive function

Twenty-six studies with 15,620 participants were included in the cross-sectional/cognitive function analysis (Anstey, 1999; Anstey, Luszcz, & Sanchez, 2001a; Anstey & Smith, 1999; Baltes & Lindenberger, 1997; Bucks et al., 2016; Clark, 1960; Deal et al., 2016; Deal et al., 2015; Dupuis et al., 2015; Era, Jokela, Qvarnberg, & Heikkinen, 1986; Gussekloo, De Craen, Oduber, Van Boxtel, & Westendorp, 2005; Harrison Bush, Lister, Lin, Betz, & Edwards, 2015; Helzner et al., 2005; Heron & Chown, 1967; Hofer, Berg, & Era, 2003; Hong, Mitchell, Burlutsky, Liew, & Wang, 2016; Li, Jordanova, & Linberger, 1998; Lin, 2011; Lin, Ferrucci, et al., 2011; Lin et al., 2013; Lindenberger & Baltes, 1994, 1997; MacDonald, Dixon, Cohen, & Hazlitt, 2004; Schaie, Baltes, & Strother, 1964; Sugawara et al., 2011; Thomas et al., 1983; Valentijn et al., 2005; van Boxtel et al., 2000). Nine studies with 8,233 participants were included in the cohort/cognitive function analysis (Anstey, Hofer, & Luszcz, 2003; Anstey, Luszcz, & Sanchez, 2001b; Deal et al., 2016; Deal et al., 2015; Gallacher et al., 2012; Hong et al., 2016; Lin et al., 2013; Lindenberger & Ghisletta, 2009; Valentijn et al., 2005). The cohort studies had a follow-up length ranging from two to 23 years (mean 10·4 years).

There was a small but statistically significant association between ARHL and all of the ten cognitive domains of interest in cross-sectional studies including; global cognition (r, -0.15, $p<0.001$), executive functions (r, -0.08 to -0.18, $p<0.001$), episodic memory (r, -0.1 to -0.14, $p\leq0.002$), processing speed (r, -0.13, $p<0.001$), semantic memory (r, -0.14, $p<0.001$) and visuospatial ability (r, -0.107, $p=0.01$). Similar results were observed in seven of eight domains in cohort studies, excluding fluency which approached significance (r, -0.067, $p=0.07$). These included global cognition (r, -0.14, $p<0.001$), executive functions (r, -0.06 to -0.1, $p<0.048$), episodic memory (r, -0.06 to -0.1, $p\leq0.004$), processing speed (r, -0.08, $p=0.002$) and semantic memory (r, -0.14, $p=0.003$). There was no cohort data for visuospatial ability or working memory. All domains in cross-sectional and cohort studies were also collapsed into an overall score of cognitive function which was significant. Forest plots of correlations are shown in Figures 2.2 & 2.3 and Appendix A.

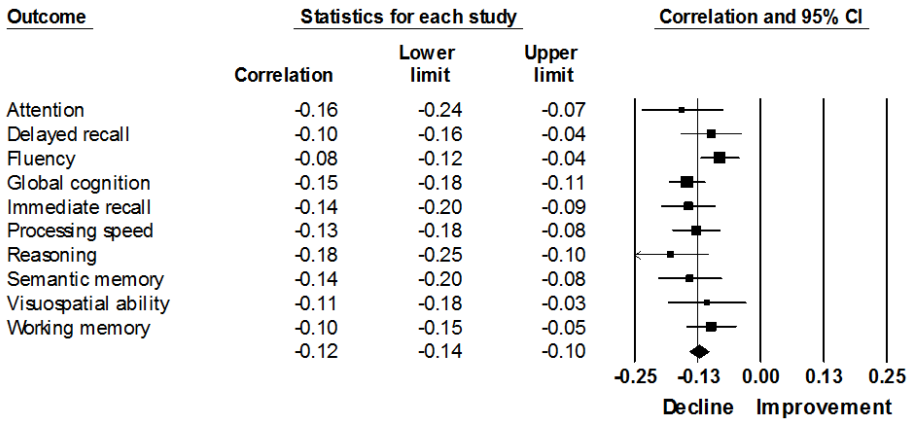

Figure 2.2: Forest plot of correlation *r* values for cognition/cross-sectional outcomes.

The black squares represent the *r* value while the lines represent the corresponding 95% confidence intervals. The middle of the black diamond represents the overall *r* value while the left and right extremes of the diamond represent the corresponding 95% confidence intervals.

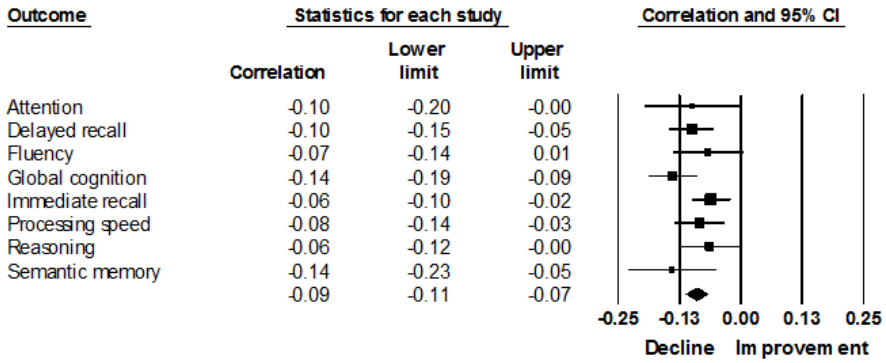

Figure 2.3: Forest plot of correlation *r* values for cognition/cohort outcomes.

Heterogeneity was significant in all domains except fluency and visuospatial ability. Inconsistency across studies ranged from very low to large. Qualitative analysis of small-study effects demonstrated moderate to no asymmetry across studies (Appendix A). Quantitative analysis with Egger's Test of the Intercept found statistically significant small-study effects for cross-sectional semantic memory (Appendix A). With each included study deleted from the model once, results remained statistically significant across all deletions for all domains with the exception of Clark (1960) (Clark, 1960) for cross-sectional visuospatial ability (Appendix A). The difference between the largest and smallest values, having deleted each group once, ranged from 16.6% to 60.2%. Cumulative meta-analysis demonstrated that ARHL has been significantly related to cognitive function since between 1960 and 2012 (Appendix A).

2.3.2 Hearing loss & cognitive impairment

Five studies with 6,582 participants were included in the cross-sectional/cognitive impairment analysis (Dupuis et al., 2015; Karpa et al., 2010; Kiely et al., 2012; Kurniawan et al., 2012; Lopez-Torres Hidalgo et al., 2009; Quaranta et al., 2014; Tay, Wang, et al., 2006). Three studies with 7,817 participants were included in the cohort/cognitive impairment analysis (Gallacher et al., 2012; Kiely et al., 2012; Lin et al., 2013). The cohort studies had a follow-up length ranging from six to 18 years (mean 11.7 years).

There was a statistically significant association between ARHL and cognitive impairment across cross-sectional (OR 2.00, 95% CI 1.39-2.89, $p<0.001$) and cohort studies (OR 1.22, 95% CI 1.09-1.36 $p<0.001$) (Appendix A). Forest plots are shown in Figures 3 and 4. Statistically significant heterogeneity and a large amount of inconsistency was observed in cross-sectional but not cohort studies. Adults with cognitive impairment totalled 797 (12.2%) in cross-sectional studies and 1,395 (20.4%) in cohort studies.

Small-study effects were not examined because there were less than ten effect sizes. With each group deleted from the model once, results remained statistically significant across all deletions (Appendix A). The difference between the largest and smallest values with each group deleted was 0.45 (20.1%) for cross-sectional studies and 0.04 (3.4%) for cohort studies. Cumulative meta-analysis demonstrated that cognitive impairment has been significantly related to ARHL since the completion of the first cross-sectional study in 2009 and cohort study in 2012 (Appendix A).

2.3.3 Hearing loss & dementia

Two studies with 741 participants were included in the cross-sectional/dementia analysis (Herbst & Humphrey, 1980; Quaranta et al., 2014). One assessed dementia (Herbst & Humphrey, 1980) and the other assessed AD (Quaranta et al., 2014). Three studies with 3,585 participants were included in the cohort/dementia analysis (Deal et al., 2016; Gallacher et al., 2012; Lin, Metter, et al., 2011). All three reported incident dementia outcomes, two for an AD subset (Gallacher et al., 2012; Lin, Metter, et al., 2011) and one for a vascular dementia (VaD) subset (Gallacher et al., 2012). The follow-up period ranged from nine to 18 years (mean 15 years).

There was a significant association between ARHL and dementia in both cross-sectional (OR 2.42, 95% CI 1.24-4.72, p=0.01) and cohort studies (OR 1.28, 95% CI 1.02-1.59, p=0.03) (Appendix A). There was no statistically significant association between ARHL and AD for cross-sectional (OR 1.80, 95% CI 0.58 – 5.60, p=0.31) or cohort studies (OR 1.69, 95% CI 0.72-4.00, p=0.23). Forest plots are shown in Appendix A. No statistically significant heterogeneity or inconsistency was observed for cross-sectional studies. For cohort studies, statistically significant heterogeneity was observed as well as a moderate amount of inconsistency. Adults with dementia totalled 59 (8.7% of the total sample) in cross-sectional studies and 366 (10.6% of the total sample) in cohort studies. The PAR estimate using OR for cohort dementia was 8·38% (95% CI: 0.79-16.39) or 3.92 million cases (95% CI: 0.37-7.67).

When AD subgroups were examined as a secondary outcome of interest, there was no statistically significant association between ARHL and AD for cross-sectional or cohort studies (Appendix A). In the one cross-sectional study, there were 20 (4.6% of total sample) adults with AD and in two cohort studies there were 78 (5.2% of total sample) adults with AD. Only one study (a cohort study) reported the association of ARHL with vascular dementia (VaD). There were 38 cases (4.4% of total sample) and the effect size approached significance (Table 10).

No other analyses were conducted for cross-sectional dementia studies because only two studies were included. Small-study effects were not examined in cohort dementia studies because there were less than ten effect sizes. With each group deleted from the model once, results remained statistically significant only when the study by Gallacher et al. (2012) was deleted (Appendix A). This study did not control for any vascular risk factors (VRFs) which may have contributed to the larger effect size and wider confidence intervals. The difference between the largest and smallest

values with each group deleted was 0.53 (31.4%). Cumulative meta-analysis demonstrated that results were statistically significant since 2011 (Appendix A). The PAR estimate using OR for cohort dementia was 8.38% (95% CI: 0.79-16.39) or 3.92 million cases (95% CI: 0.37-7.67). A reduction in hearing loss among older adults of 10%-25% could potentially prevent more than 390,000-970,000 dementia cases worldwide.

2.3.4 Subgroup analyses (moderator and meta-regression analyses)

Summary data of moderator and meta-regression analyses are presented in Appendix A. Detailed results of the respective Fisher's Z values (moderator analysis), slope (meta-regression), standard errors and confidence intervals for each variable are available in Appendix A.

Study characteristics: Associations were weaker for studies conducted in the USA compared to Australia and Europe and for samples with mixed race compared to those in which the breakdown by race was not declared. The association between ARHL and cognition generally became weaker with later publication date and higher STROBE score. Results for journal impact factor were mixed. The association for cohort global cognition became significantly weaker with increasing length to follow-up.

Subject characteristics: Cross-sectional associations between hearing loss and cognition were weaker for studies that declared exclusion of participants with cognitive impairment and dementia and inclusion of cardiovascular risk participants. Conversely, in cohort studies there was generally a stronger association for those that removed cognitively impaired and dementia participants at baseline. The baseline mean and maximum age of the sample generally had mixed and non-significant results. Increased minimum age significantly weakened the association for cross-sectional attention and reasoning. The effect size for cohort global cognition became stronger with baseline mean and minimum age. Results were otherwise mixed and non-significant. Associations for female participants at baseline and education (mean years) were mixed and non-significant. Primary education strengthened the association with cross-sectional processing speed, whereas tertiary education usually weakened the association and secondary education results were mixed. Increased proportion of white race usually strengthened the association whereas black race usually significantly weakened the association and associations for other race were non-significant. Current or previous smoking had significant associations with global cognition and processing speed.

Audiometric factors: A stronger association was usually found when auditory function was assessed with both ears (compared to only the better ear) and when frequencies >4 kHz were excluded. There was no significant difference whether or not a hearing loss categorical criteria of >25 decibel (dB) (compared to hearing as a continuous variable) was used. A weaker association was generally found when studies used a sound-treated room/booth or followed the WHO criteria. Inclusion of hearing aid users (compared to those that did not declare inclusion/exclusion of hearing aid users) weakened the association for immediate recall and semantic memory. The

sample PTA significantly weakened the associations with cross-sectional attention and immediate recall. Results for other domains were mixed and non-significant. Inclusion of a higher proportion of participants with a hearing loss in the sample generally made the associations weaker, significantly so with cross-sectional immediate recall. Hearing aid user results were mixed and non-significant.

Cognitive measures: Results were mostly minor and inconsistent with respect to whether the cognitive test was accessible to a hearing loss sample. The only significant result found a stronger association for non-biased tests.

Statistical analysis: A stronger association was generally found for studies that used correlation as the statistical model compared to those that used linear regression or linear mixed models. Those that reported results as significant generally had significantly stronger associations for all assessed domains. Those that used age, sex, race, education and vascular factors as a covariate reported weaker associations, sometimes significantly so. This same trend was observed for those that controlled for stroke, hypertension, diabetes and current or previous smokers, preferentially for global cognition, processing speed and semantic memory. Controlling for depression significantly weakened the association with cross-sectional attention. Results for pre-morbid IQ were mixed and non-significant except for cohort global cognition. There was a significantly stronger association with cohort processing speed for studies that included participants with cognitive impairment or dementia in the analysis (compared to those that either excluded them or did not declare inclusion/exclusion).

Because of a lack of data, no other *a priori* variables were examined for cognitive function. Other variables were reviewed *ad hoc*. A significantly weaker association was generally found for those that controlled for study site. Subgroup analyses were not conducted for cognitive impairment and dementia outcomes because of an insufficient number of studies with the exception of cross-sectional cognitive impairment studies (Appendix A). Year of publication, age (mean and minimum), sex (% female), sample PTA, hearing loss (%), cognitive impairment (%), impact factor and STROBE were assessed. No association was statistically significant.

2.4 Discussion

In this meta-analysis, ARHL was significantly associated with accelerated multi-domain cognitive decline, cognitive impairment and dementia, supporting further consideration of ARHL as a risk factor for these outcomes (Albers et al., 2015; Barnes & Yaffe, 2011; Lin & Albert, 2014). The non-significant association found between ARHL and AD may be due to small sample sizes. Alternatively, the association with dementia but not AD may be due to causal factors such as impaired speech perception affecting neurological function independent of AD aetiology (Albers et al., 2015; Lin, Ferrucci, et al., 2014). AD substrate has been found in the auditory neural regions but not in the peripheral ear and cochlear structures (Albers et al., 2015).

The results show that the strength of the association between ARHL and cognitive decline and dementia compares in size and significance to other risk factors (Barnes & Yaffe, 2011) including cardiovascular risk (DeRight, Jorgensen, & Cabral, 2015), type 2 diabetes (Cheng, Huang, Deng, & Wang, 2012; Gudala, Bansal, Schifano, & Bhansali, 2013; Monette, Baird, & Jackson, 2014), hypertension (Gifford et al., 2013), smoking (Peters, Poulter, et al., 2008; Zhong, Wang, Zhang, Guo, & Zhao, 2015), sleep dysfunction (Almondes, Costa, Malloy-Diniz, & Diniz, 2016; Lo, Groeger, Cheng, Dijk, & Chee, 2016), and physical inactivity (Blondell, Hammersley-Mather, & Veerman, 2014). Additionally, the findings indicate that cognitive reserve, assessed by proxy measures education and pre-morbid IQ (Valenzuela & Sachdev, 2006), may moderate the association between ARHL and cognition with some evidence of a dose-response effect.

Study quality assessment showed that reporting was generally of very good quality across included papers, suggesting a low level of bias in results. However, there was poor reporting of attrition rates which may conceal a greater decline in cognition and a greater risk of dementia in older cohorts due to higher drop-outs among those with poorer health (Knopman et al., 2014). In subgroup analysis, no bias was found for verbal or audio cognitive tests. However, there was some potential bias in results as substandard audiometric assessment was associated with a stronger effect size. Significant small-study effects were observed only for semantic memory in cross-sectional studies. The lack of small study effects lends support to the findings of the meta-analysis overall. The association with cognition became weaker with later publication date and higher STROBE score, possibly due to more stringent statistical analysis particularly inclusion of more covariates such as vascular risk factors.

2.4.1 Causal mechanisms for ARHL and cognition

The relationship between ARHL and cognition remains unclear (Lin, Metter, et al., 2011; Panza, Solfrizzi, & Logroscino, 2015; Wayne & Johnsrude, 2015). One hypothesis is a common aetiology such as decline in the vascular system (Lin, Ferrucci, et al., 2014; Lindenberger & Baltes, 1994; Wayne & Johnsrude, 2015) while other hypotheses suggest that the association may be mechanistic, with ARHL causing cognitive decline (Lin, Metter, et al., 2011; Lindenberger & Baltes, 1994). Alternatively, it is possible that the association between ARHL and cognitive decline is not causal and rather they are comorbid conditions as part of a broader physiological decline due to ageing. ARHL has been associated with multiple other indices of advanced ageing in common with cognitive decline and could be a marker for shared underlying risk factors, possibly as part of a frailty syndrome (Panza, Solfrizzi, & Logroscino, 2015).

The analysis in this study indicated both common causal and mechanistic pathways. Vascular risk factors (VRFs) contributed significantly to the association for global cognition and processing speed. However, the pooled effect size of studies controlling for VRFs in these outcomes remained significant, suggesting other contributing factors such as depression and speech perception. Depression significantly moderated the association with attention. This supports previous research

showing that cognitive function might be impacted by psychosocial stress and altered immunological function (Reader et al., 2015) due to factors such as loneliness (Cole et al., 2007; Wilson, Begeny, et al., 2011; Wilson, Krueger, et al., 2007) or depression (Mener, Betz, Genther, Chen, & Lin, 2013; Schmaal et al., 2015).

The pattern of cognitive decline observed in this study suggested some support for a causal mechanism whereby impaired speech perception concomitant with ARHL affects cognitive decline. The relationship between ARHL and decline in executive function and memory is consistent with behavioural and neuroimaging research which typically report increased recruitment of executive functions to perceive speech following acquired hearing loss (Campbell & Sharma, 2014; Cardin, 2016; Erb & Obleser, 2013; Peelle et al., 2011; Pichora-Fuller, 2003; Ronnberg et al., 2013; Wingfield & Grossman, 2006). This is predicted to lead to relative maintenance in executive functions and short-term memory but greater decline in long-term memory systems through disuse (Ronnberg et al., 2013). In support of this prediction, stronger associations were found in longitudinal compared to cross-sectional studies between executive function, immediate recall and ARHL; whereas associations between delayed and semantic memory and ARHL were similar across cohort and cross sectional designs. Furthermore, semantic memory, usually maintained in older age relative to episodic memory (Salthouse, 2010b), demonstrated a similar or greater degree of decline to episodic memory. Interestingly, neuroimaging research in ARHL samples report neural atrophy and reduced connectivity in regions associated with semantic memory and speech processing, including the parahippocampal and perisylvian regions (Husain, Medina, et al., 2011; Li, Booth, et al., 2013; Lin, Ferrucci, et al., 2014; Peelle et al., 2011).

Further support for a speech based causal mechanism was found in subgroup analyses. The association between ARHL and attention and immediate recall significantly weakened with a higher level of hearing loss. This was consistent with neuroimaging research reporting failure of executive functions to compensate for hearing loss beyond a perceptible auditory threshold (Erb & Obleser, 2013). Therefore, increased hearing loss beyond an auditory threshold and individual cognitive capacity to compensate may lead to more pronounced impairment in executive functions due to disuse (Erb & Obleser, 2013) and may be increasingly less predictive of further decline above a common vascular pathology. Among cohort studies of fluency and immediate recall, those that controlled for VRFs had insignificant effect sizes (Deal et al., 2016; Deal et al., 2015) whereas outcomes were generally significant for those that did not (Anstey et al., 2003; Gallacher et al., 2012; Lindenberger & Ghisletta, 2009; Valentijn et al., 2005). Decline in processing speed may reflect advanced ageing (Panza, Solfrizzi, & Logroscino, 2015). Alternatively, reallocation of executive processes to support accuracy in speech perception may lead to decline in performance speed as observed in older adults with visual processing deficits (Grady et al., 1994).

The weaker association between ARHL and cognitive decline with inclusion of frequencies >4 kHz may be due to more common decline at these frequencies and loss at lower frequencies being indicative of more progressive ARHL (Gates & Mills, 2005) which may mechanistically impair verbal communication (Lindenberger & Baltes, 1994; Tun et al., 2009). Alternatively, different pure-tone audiometric profiles may be indicative of different aetiologies for ARHL (Gates & Mills, 2005) with possible implications for cognition. For example, vascular disease has been associated with both low-frequency hearing loss and white-matter hyperintensities (Eckert et al., 2013).

2.4.2 Implications for clinicians, policy makers and future research

Even though the results of this study indicate an association between ARHL and cognitive decline, cognitive impairment and dementia, they cannot indicate causality. Further research is required to determine whether a causal relationship exists. Furthermore, the results indicated that the use of hearing aids may benefit short-term and semantic memory. In intervention studies, cognitive benefits have been noted with hearing aids or cochlear implants (Acar et al., 2011; Mosnier et al., 2015). As hearing aid production currently meets less than 10% of global need, this could have implications for public health resources (World Health Organisation, 2015).

Future epidemiological research could consider whether demographic factors influence the relationship between ARHL and cognitive function. Apart from age, the association between ARHL and cognitive decline was stronger for men than for women. Race also had a significant effect; the association was stronger for whites compared to blacks possibly due to selective survival (Kim & Miech, 2009). Weaker associations between ARHL and cognitive function were consistently reported in the USA compared to Europe and Australia possibly due to differences in prevalence of ARHL or of cognitive ageing (Skirbekk, Loichinger, & Weber, 2012) and dementia (Prince et al., 2013). Epidemiological research could also assess if increased demand on reserve may lower the threshold for expression of age-associated decline or neuropathology (Stern, 2009); and also if ARHL is associated with cognitive decline independently of neuropathologic hallmarks of dementia (Stern, 2009); and if there is a mediator of this association e.g. loneliness. Neuroimaging studies examining reduced cognitive compensation for speech tasks with hearing aids would be of clinical interest. Additionally, impairment in lexical/semantic functions, episodic memory and executive functions are used as markers for diagnosing AD and vascular dementias (Salmon, 2012). Further research is needed to examine how ARHL may possibly contribute to decline in these domains apart from neuropathologies.

2.4.3 Strengths & limitations

To the best of their knowledge, the authors of this study believe that this is the first systematic review and meta-analysis of ARHL and cognitive decline using only pure-tone thresholds as the audiometric criteria, the criterion standard. The strict inclusion criteria of only ageing studies using pure-tone audiometry and objective outcome assessment allowed the authors to reduce conceptual heterogeneity in study design and measurement. This provided the most accurate quantitative

measure of their association. All eligible studies retrieved from the search were included in the meta-analyses, except those with duplicate data.

Despite low levels of heterogeneity in study design and measurement, there was considerable heterogeneity across most outcomes. Future reviews would benefit from a more stringent inclusion criteria requiring a minimum level of adjustment. However, in any adjusted estimate of effect size for risk factors derived from cohort ageing studies, there will be residual confounding as ARHL and cognitive decline are reported to be influenced by multiple biological and environmental factors (Caldwell et al., 2015; Deary et al., 2009; Fortunato et al., 2016; Stern, 2009). Where possible, extensive subgroup analyses were conducted to investigate whether the association differed by important participant, study, measurement and analysis factors including covariates adjusted for. This provided additional insights into the potential basis of this association for future experimental and clinical trials and how these studies may reduce bias.

It was not possible to examine whether studies controlled for aetiology of hearing loss e.g. congenital/pre-lingual deafness. However, given the extremely low prevalence (<2%) of hearing impairment in those under 40 years of age (Lin, Niparko, & Ferrucci, 2011) this was considered to be insignificant. In some of the meta-analyses, there was a very low number of effect sizes. It was not possible to examine other planned moderators and covariates, such as income or attrition rate, due to lack of data. For meta-analyses of dementia subgroups, the number of cases was very small.

Furthermore, as these were meta-analyses of observational studies, support for any inferences regarding the causal nature of the association is limited and cannot provide direct evidence for policy recommendations (Balshem et al., 2011). However, the analyses of prospective studies of cognitive function, cognitive impairment and dementia give an indication of the temporal order of the association consistent with a causal effect. Due to the large number of statistical tests conducted, some of the findings could have been the result of chance. However, the authors did not want to risk missing potentially important findings that could be tested in future original studies (Rothman, 1990). Finally, as is the case with any aggregate data meta-analysis, the potential for ecological fallacy exists.

2.5 Conclusions

In conclusion, ARHL is a potential risk factor for cognitive decline, cognitive impairment and dementia. The effect sizes for all three main outcomes were small but they compared strongly with estimates for other risk factors more commonly investigated in this population. Further research, including intervention trials, is warranted.

Table 2.1 (a): Characteristics of Included Studies

Ref. Author (year)	Population	Study Design/ STROBE	Baseline demographics	Audiometric assessment
Anstey (1999)	Population based sample of community dwelling women aged 60-90 years in Australia.	Cross-sectional 14	N = 180 Age: 70.56 (7.13) 100% female	PTA 2, 4, 8 kHz in both ears.
Anstey & Smith (1999)	Population based sample of community dwelling women aged 60-90 years in Australia.	Cross-sectional 17	N = 180 Age: 70.56 (7.13) 100% female	PTA 2, 4, 8 kHz in both ears.
Anstey et al. (2001a)	ALSA: population based sample of community dwelling adults aged 70-98 years in Australia.	Cross-sectional 17	N = 894 Age: 77.7 (5.6) 49% female	PTA 0.5, 1, 2, 3, 4 kHz in both ears.
Anstey et al. (2001b)	ALSA: population based sample of community dwelling adults aged ≥65 years in Australia. Duration: 2 years	Cohort 15	N = 2,087 Age: NA 49.4% female	PTA 0.5, 1, 2 kHz or PTA 3, 4 kHz or PTA 6, 8 kHz in both ears.
Anstey et al. (2003)	ALSA: population based sample of community dwelling adults aged ≥70 years in Australia. Duration: 8 years	Cohort 20	N = 1,823 Age: 77.77 (6.56) 48.8% female	PTA of lesser PTT at 2, 3, 4 kHz in either ear.
Baltes & Lindenberger (1997)	Composite sample of BASE participants and younger adults aged 25-101 years in Germany.	Cross-sectional 17	N = 315 Age: 64.9 (22) Gender ratio: NA	PTA 0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz in both ears.
Bucks et al. (2016)	BHAS: Population based sample of community-dwelling adults aged 45-66 years in Australia.	Cross-sectional 21	N = 1,969 Age: 56.2 (5.5) 53.8% female	PTA 0.5, 1, 2, 4 kHz in the better ear in a sound-treated booth.
Clark (1960)	Population based sample of community dwelling adults aged 20-70 years in the USA.	Cross-sectional 11	N = 102 Age: NA Approx. 50% female	PTA 3 kHz in both ears.
Deal et al. (2015)	ARIC Study: population based sample of community dwelling adults aged 45–64 years in the USA.	Cohort Cross-sectional 22	N = 253 Age: 56.6 (5.3) 60.9% female	PTA >25dB, >40dB 0.5, 1, 2, 4 kHz in the better ear in a soundproof booth.
Deal et al. (2016)	HABC Study: random sample of community dwelling Medicare beneficiary adults aged 70–79 years in the USA.	Cohort Cross-sectional 22	N = 1,889 Age: 75.5 (3) 52.73% female	PTA 0.5, 1, 2, 4 kHz in the better ear in a sound-attenuating booth.
Dupuis et al. (2015)	Population based sample of community dwelling older adults in Canada.	Cross-sectional 20	N = 301 Age: 71.13 (7.4) 64% female	PTA >25dB 0.5, 1, 2 kHz in the worse ear in a soundproof booth.
Era et al. (1986)	Compared population based samples of community dwelling men across three age ranges (31-35, 51-55, 71-75 years) in Finland.	Cross-sectional 17	N = 547 Age: NA 0% female	PTA 0.5, 1, 2 kHz & PTT 4 kHz in the better ear in a soundproof room.

Table 2.1 (b): Characteristics of Included Studies

Ref. Author (year)	Covariates	Cognitive domains assessed	Clinical outcomes (criteria)
Anstey (1999)	Age, grip strength, forced expiratory volume, vibration sense & vision.	Attention Processing speed	None
Anstey & Smith (1999)	Age.	Processing speed Reasoning Semantic memory Visuospatial ability Working memory	None
Anstey et al. (2001a)	None.	Immediate recall Processing speed Semantic memory	None
Anstey et al. (2001b)	Age.	Immediate recall Processing speed Semantic memory	None
Anstey et al. (2003)	Age, gender, education, depression, self-rated health & number of medical conditions.	Immediate recall Processing speed Semantic memory	None
Baltes & Lindenberger (1997)	Age.	Fluency Global cognition Immediate recall Processing speed Reasoning Semantic memory	None
Bucks et al. (2016)	Age, gender, education, depression & pre-morbid IQ.	Attention Delayed recall Fluency Processing speed Working memory	None
Clark (1960)	None.	Attention Immediate recall Processing speed Reasoning Visuospatial ability	None
Deal et al. (2015)	Age, gender, education, smoking, hypertension, diabetes, pre-morbid IQ & depression.	Attention Delayed recall Fluency Global cognition Processing speed Semantic memory	None
Deal et al. (2016)	Age, gender, race, education, study site, smoking, hypertension, diabetes & stroke.	Immediate recall Processing speed	Dem (diagnosis, medication use or race-stratified 3MS decline more than 1.5 SDs from the baseline mean)
Dupuis et al. (2015)	None.	Global cognition	CI (MoCA)
Era et al. (1986)	None.	Fluency Reasoning Visuospatial ability Working memory	None

Table 2.1 (a) (Continued): Characteristics of Included Studies

Ref. Author (year)	Population	Study Design/ STROBE	Baseline demographics	Audiometric assessment
Gallacher et al. (2012)	CaPS: population based sample of community dwelling men aged ≥45 years in Wales. Duration: 17 years	Cohort 21	N = 1,057 Age: 56.1 (4.4) 0% female	PTA 0.5, 1, 2, 4 kHz in both ears (binaural).
Gussekloo et al. (2005)	Leiden 85+ Study: population based sample of community dwelling adults aged 85 years in the Netherlands.	Cross-sectional 17	N = 459 Age: 85 (0) 66% female	PTA 1, 2, 4 kHz in both ears in participants' homes.
Harrison Bush et al. (2015)	SKILL Study: population based sample of community dwelling adults aged 62-98 years in the USA.	Cross-sectional 21	N = 894 Age: 73.47 (6) 57.8% female	PTA 0.5, 1, 2 kHz in the better ear.
Helzner et al. (2005)	HABC Study: random sample of community dwelling Medicare beneficiary adults aged 73–84 years in the USA.	Cross-sectional 19	N = 2,052 Age: 77.5 (2.8) 52.7% female	PTA >25dB 0.5, 1, 2 kHz in the worse ear.
Herbst & Humphrey (1980)	Sample of community dwelling adults registered with a group practise, aged ≥70 years, in the UK.	Cross-sectional 14	N = 253 Age: NA 64% female	PTA ≥35dB 1, 2, 4 kHz in the better ear.
Heron & Chown (1967)	Sample of community dwelling adults aged 20-79 years in the UK.	Cross-sectional 22	N = 540 Age: NA 44.44% female	PTA 1 kHz in both ears.
Hofer et al. (2003)	NORA Study: population based sample of community-dwelling adults aged 75 years in Denmark, Finland and Sweden.	Cross-sectional 18	N = 1,041 Age: 75 (0) 57.26% female	PTA 0.25 kHz, PTA 0.5, 1, 2 kHz & PTA 4, 8 kHz in both ears in a soundproof room.
Hong et al. (2016)	BMES: population based sample of adults aged >49 years in Australia. Duration: 10 years	Cohort Cross-sectional 20	N = 2,334 Age: NA Gender ratio: NA	PTA >40dB 0.5, 1, 2, 4 kHz in the worse & the better ear in a sound-proof booth.
Karpa et al. (2010)	BMHS: population based sample of adults aged >49 years in Australia.	Cross-sectional 20	N = 2,815 Age: 66.6 (9.3) 56.7% female	PTA >25dB 0.5, 1, 2, 4 kHz in the better ear in a sound-treated room.
Kiely et al. (2012)	ALSA & BMES: population based samples of community dwelling adults aged 50–103 years in Australia. Duration: 11 years	Cohort Cross-sectional 20	N = 4,221 Age: 73.6 (8.9) 53.7% female	PTA 0.5, 1, 2, 4 kHz in the better ear (ALSA & BMES) and in a sound-treated booth (BMES).
Kurniawan et al. (2012)	Leiden 85+ study: population based sample of adults aged 85 years in the Netherlands.	Cross-sectional 19	N = 435 Age: 85 (0) 66.7% female	PTA >35 dB 1, 2, 4 kHz in better ear in participants' homes.

Table 2.1 (b) (Continued): Characteristics of Included Studies

Ref. Author (year)	Covariates	Cognitive domains assessed	Clinical outcomes (criteria)
Gallacher et al. (2012)	Age, social class, anxiety, baseline cognitive function (*cognitive function only*) & premorbid IQ (*clinical outcomes only*).	Delayed recall Global cognition Immediate recall Processing speed Reasoning	CI (NINCDS-AIREN/DSM-IV & no functional impairment) Dem (DSM-IV or NINCDS-AIREN) AD (DSM-IV, most met criteria for NINCDS-ADRDA) VaD (NINCDS-AIREN)
Gussekloo et al. (2005)	Gender & education.	Attention Delayed recall Global cognition Immediate recall Processing speed	None
Harrison Bush et al. (2015)	Age, gender, education, race, diabetes, heart disease, hypertension, stroke & depression.	Attention Global cognition Immediate recall Processing speed Working memory	None
Helzner et al. (2005)	Age, gender, education, household income, study site, blood pressure, diabetes, cardiovascular disease, cerebrovascular disease, hip bone mineral density, history of ear surgery, alcohol use, smoking, walking calorie expenditure, ototoxic medication & occupational noise exposure.	Global cognition	None
Herbst & Humphrey (1980)	None.	None	Dem (CARE)
Heron & Chown (1967)	None.	Attention Immediate recall Processing speed Reasoning Semantic memory	None
Hofer et al. (2003)	None.	Fluency Immediate recall Processing speed Reasoning Working memory	None
Hong et al. (2016)	None (*cross-sectional*) Age & gender.	Global cognition	None
Karpa et al. (2010)	None.	None	CI (MMSE)
Kiely et al. (2012)	Age, years in study, gender, education, diabetes, stroke, hypertension, workplace noise exposure & high-frequency audiometric noise notches.	None	CI (MMSE)
Kurniawan et al. (2012)	None.	None	CI (MMSE)

Table 2.1 (a) (Continued): Characteristics of Included Studies

Ref. Author (year)	Population	Study Design/ STROBE	Baseline demographics	Audiometric assessment
Li et al. (1998)	Sample of community-dwelling older adults aged 30-51 years in Germany.	Cross-sectional 17	N = 179 Age: NA 51.96% female	PTA 0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz in both ears.
Lin (2011a)	NHANES: population based sample of community dwelling adults aged 60-69 years in the USA.	Cross-sectional 20	N = 605 Age: 64.1 (2.9) 52.9% female	PTA 0.5, 1, 2, 4 kHz in the better ear in a sound-treated room.
Lin et al. (2011b)	BLSA: population based sample of community dwelling adults aged ≥55 years in the USA.	Cross-sectional 19	N = 347 Age: 71 (7.2) 35.2% female	PTA 0.5, 1, 2, 4 kHz in the better ear in a sound-attenuating chamber.
Lin et al. (2011c)	BLSA: population based sample of community dwelling adults aged 36-90 years in the USA. Duration: 18 years	Cohort 21	N = 639 Age: NA 43.7% female	PTA 0.5, 1, 2, 4 kHz in the better ear in a soundproof booth.
Lin et al. (2013)	HABC Study: random sample of community dwelling Medicare beneficiary adults aged 70–79 years in the USA. Duration: 6 years	Cohort Cross-sectional 20	N = 1,984 Age: 77.4 (2.76) 52.1% female	PTA >25dB 0.5, 1, 2, 4 kHz in the better ear in a sound-treated booth.
Lindenberger & Baltes (1994)	BASE: population based sample of community dwelling and Institutionalized adults aged 70-103 years in Germany.	Cross-sectional 18	N = 156 Age: 84.9 (9) 50% female	PTA 0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz in both ears in participants' homes or in a clinic.
Lindenberger & Baltes (1997)	BASE: population based sample of community dwelling and Institutionalized adults aged 70-103 years in Germany.	Cross-sectional 17	N = 516 Age: 84.9 (8.7) 50% female	PTA 0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz in both ears in participants' homes or in a clinic.
Lindenberger & Ghisletta (2009)	BASE: population based sample of community dwelling and Institutionalized adults aged 70-103 years in Germany. Duration: 13 years.	Cohort 18	N = 516 Age: 84.9 (8.7) 50% female	PTA 2, 3, 4, 6 kHz in both ears.
Lopez-Torres Hidalgo et al. (2009)	Random sample of public health card holder registry aged 65-96 years in Spain.	Cross-sectional 20	N = 1,161 Age: 73.3 (5.9) 55.9% female	PTA ≥40dB 1, 2 kHz in one ear, or PTA ≥40dB 1 or 2 kHz in both ears in a health care centre.
MacDonald et al. (2004)	VL Study: population based sample of community dwelling adults aged 67-95 years in Australia.	Cross-sectional 18	N = 125 Age: 78.9 (3.12) 61.6% female	PTA 0.5, 1, 2 kHz in both ears.
Quaranta et al. (2014)	GA Study: sample of older adults aged >65 years in Italy.	Cross-sectional 17	N = 488 Age: 72.8 (6.2) 39.3% female	PTA >35dB 0.5, 1, 2 kHz in both ears in a soundproof chamber.
Schaie et al. (1964)	Sample of retired community dwelling adults aged 70-88 years in the USA.	Cross-sectional 15	N = 47 Age: 76.4 (NA) 48.9% female	PTA 0.128, 0.256, 0.512, 1.024, 2.048, 4.096, 8.192 kHz in both ears.

Table 2.1 (b) (Continued): Characteristics of Included Studies

Ref. Author (year)	Covariates	Cognitive domains assessed	Clinical outcomes (criteria)
Li et al. (1998)	Age.	Fluency Immediate recall Global cognition Processing speed Reasoning Semantic memory	None
Lin (2011a)	Age, gender, hearing aid, income, education, race & cardiovascular risk factors (*diabetes, hypertension, smoking & stroke*).	Processing speed	None
Lin et al. (2011b)	Age, gender, race, education, diabetes, smoking & hypertension.	Attention Fluency Global cognition Immediate recall Processing speed Semantic memory	None
Lin et al. (2011c)	Age, gender, race, education, diabetes, smoking, hypertension & baseline cognitive function.	None	Dem (DSM-III) AD (NINCDS-ADRDA)
Lin et al. (2013)	Age, gender, education, race/ethnicity, study site, hypertension, diabetes, smoking & stroke.	Global cognition Processing speed	CI (3MSE <80 or decline >5 from baseline)
Lindenberger & Baltes (1994)	Age & vision.	Global cognition	None
Lindenberger & Baltes (1997)	Age.	Global cognition	None
Lindenberger & Ghisletta (2009)	Age, time to death & risk of dementia.	Fluency Immediate recall Processing speed	None
Lopez-Torres Hidalgo et al. (2009)	None.	None	CI (SPMSQ)
MacDonald et al. (2004)	None.	Immediate recall Processing speed Reasoning Semantic memory Working memory	None
Quaranta et al. (2014)	Age, gender & education.	None	CI (Neuropsychological assessment/Petersen (2004)) Dem (DSM-V)
Schaie et al. (1964)	Age.	Global cognition	None

Table 2.1 (a) (Continued): Characteristics of Included Studies

Ref. Author (year)	Population	Study Design/ STROBE	Baseline demographics	Audiometric assessment
Sugawara et al. (2011)	Population based sample of community dwelling adults aged ≥50 years in Japan.	Cross-sectional 18	N = 846 Age: 63.9 (8.3) 63.4% female	PTA >25dB 0.5, 1, 2 kHz in the better ear.
Tay et al. (2006)	BMES: population based sample of community dwelling adults aged ≥50 years in Australia.	Cross-sectional 22	N = 3,509 Age: 66.7 (NA) 57% female	PTA >40dB 0.5, 1, 2, 4 kHz in the better ear in a sound-treated room.
Thomas et al. (1983)	Population based sample of healthy community dwelling adults aged 60-89 years in the USA.	Cross-sectional 13	N = 259 Age: 72 (NA) 54% female	PTA 0.5, 1, 2 kHz in the better ear.
Valentijn et al. (2005)	MAAS: sample of community dwelling adults aged 55-83 years recruited from network of patients attending general practises in the Netherlands. Duration: 6 years	Cohort Cross-sectional 20	N = 391 Age: 65.1 (6.6) 48.6% female	PTA 1, 2, 4 kHz in the better ear.
van Boxtel et al. (2000)	MAAS: sample of community dwelling adults aged 23-82 years recruited from network of patients attending general practises in the Netherlands.	Cross-sectional 18	N = 453 Age: 51.4 (16.5) 50.8% female	PTA 1, 2, 4 KHz in the better ear.

3MSE – Modified Mini-Mental State Examination; ACC Study – Aged Care Client Study; ACT study – Adult Changes in Thought Study; ALSA – Australian Longitudinal Study of Ageing; ARIC Study – Atherosclerosis Risk in Communities Neurocognitive Study; BASE – Berlin Aging Study; BHAS – Busselton Healthy Ageing Study; BLSA – Baltimore Longitudinal Study of Aging; BMES – Blue Mountains Eye Study; BMHS – Blue Mountains Hearing study; CARE – Comprehensive Assessment and Referral Evaluation; CI –Cognitive Impairment; CaPS - Caerphilly Prospective Study; Dem – Dementia; DSM – Diagnostic and Statistical Manual of Mental Disorders; FH Study – Framingham Heart Study; GA Study – Great Age Study; HABC Study – Health, Aging and Body Composition Study; HL – Hearing Loss; MAAS – Maastricht Aging Study; MoCA – Montreal Cognitive Assessment; MMSE – Mini–Mental State Examination; NH – Normal Hearing; NHANES – National Health and Nutritional Examination Survey; NINCDS-ADRDA – National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; NINCDS-AIREN – National Institute of Neurological and Communicative Disorders and Stroke–Association Internationale pour la Recherché et l'Enseignement en Neurosciences; NORA Study – Nordic Research on Aging Study; PTA – Pure-Tone Average; PTT – Pure Tone Threshold; SKILL Study – Staying Keen in Later Life Study; SOF – Study of Osteoporotic Fractures; SPMSQ – Short Portable Mental Status Questionnaire; VL Study – Victoria Longitudinal Study.

Table 2.1 (b) (Continued): Characteristics of Included Studies

Ref. Author (year)	Covariates	Cognitive domains assessed	Clinical outcomes (criteria)
Sugawara et al. (2011)	Age, gender & education.	Global cognition	None
Tay et al. (2006)	Age, gender, education & history of stroke.	None	CI (MMSE)
Thomas et al. (1983)	None.	Delayed recall Global cognition Reasoning Working memory	None
Valentijn et al. (2005)	None (*cross-sectional*) Age, gender, education & baseline hearing and cognitive function.	Attention Delayed recall Fluency Immediate recall Processing speed	None
van Boxtel et al. (2000)	Age, gender & education. Processing speed (*delayed and immediate recall only*).	Delayed recall Immediate recall Processing speed	None

3MSE – Modified Mini-Mental State Examination; ACC Study – Aged Care Client Study; ACT study – Adult Changes in Thought Study; ALSA – Australian Longitudinal Study of Ageing; ARIC Study – Atherosclerosis Risk in Communities Neurocognitive Study; BASE – Berlin Aging Study; BHAS – Busselton Healthy Ageing Study; BLSA – Baltimore Longitudinal Study of Aging; BMES – Blue Mountains Eye Study; BMHS – Blue Mountains Hearing study; CARE – Comprehensive Assessment and Referral Evaluation; CI –Cognitive Impairment; CaPS - Caerphilly Prospective Study; Dem – Dementia; DSM – Diagnostic and Statistical Manual of Mental Disorders; FH Study – Framingham Heart Study; GA Study – Great Age Study; HABC Study – Health, Aging and Body Composition Study; HL – Hearing Loss; MAAS – Maastricht Aging Study; MoCA – Montreal Cognitive Assessment; MMSE – Mini–Mental State Examination; NH – Normal Hearing; NHANES – National Health and Nutritional Examination Survey; NINCDS-ADRDA – National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; NINCDS-AIREN – National Institute of Neurological and Communicative Disorders and Stroke–Association Internationale pour la Recherché et l'Enseignement en Neurosciences; NORA Study – Nordic Research on Aging Study; PTA – Pure-Tone Average; PTT – Pure Tone Threshold; SKILL Study – Staying Keen in Later Life Study; SOF – Study of Osteoporotic Fractures; SPMSQ – Short Portable Mental Status Questionnaire; VL Study – Victoria Longitudinal Study.

Chapter 3 Age-related hearing loss, cognitive decline and dementia: Review of common aetiological factors and mechanistic pathways

3.1 Introduction

Multiple epidemiological studies have reported a link between age-related hearing loss (ARHL) and accelerated cognitive decline and dementia providing support for a reliable association between ARHL and cognition (Wayne & Johnsrude, 2015). The direction of the relationship is not clear but several hypotheses have emerged to account for these findings (Lin, Ferrucci, et al., 2011; Lin, Metter, et al., 2011; Lindenberger & Baltes, 1994; Wayne & Johnsrude, 2015). The aim of this chapter is to provide a comprehensive outline of common causal factors and mechanistic pathways emerging in the literature that potentially link ARHL with pathological cognitive ageing. This review will examine the evidence for each and their significance for future interventions, with implications for future research and public health care policy.

3.2 Theoretical views

There are several theoretical views as to the basis of the association between ARHL and cognitive decline (See Fig 3.1) (Lin, Ferrucci, et al., 2011; Lindenberger & Baltes, 1994; Wayne & Johnsrude, 2015). One possibility, the "cognitive load on perception" hypothesis, posits that cognitive decline may affect hearing function due to a loss of cognitive resources needed for auditory perception (Wayne & Johnsrude, 2015). There is evidence that a decline in cognitive resources has a deteriorative effect on perceptual function (Mattys & Palmer, 2015; Wingfield, Amichetti, & Lash, 2015; Wong et al., 2009). However, this does not account for the association between pure-tone loss and cognitive decline. Additionally, central dysfunction of the auditory cortex usually occurs secondary to peripheral hearing loss (Gates & Mills, 2005). Also, no evidence of neuropathologic substrate associated with Alzheimer's disease has been found in the peripheral auditory structures (Baloyannis, Mauroudis, Manolides, & Manolides, 2009; Sinha et al., 1993). Pure-tone audiometry is a reliable assessment of peripheral function that does not significantly rely on higher auditory cortical processing (Pickles, 2008), and is robust to cognitive ageing (Marshall, 1991) and dementia (Uhlmann, Rees, Psaty, & Duckert, 1989). There is little support for this hypothesis from longitudinal studies (Kiely et al., 2012; Wayne & Johnsrude, 2015) and this hypothesis will not be a focus of this review.

There may be a *common aetiology* underpinning both ARHL and cognitive ageing - the "common cause" hypothesis (Lindenberger & Baltes, 1994; Wayne & Johnsrude, 2015). The primary risk factor for both ARHL and age-related cognitive decline is age (Panza, Solfrizzi, & Logroscino, 2015). Therefore a common pathophysiology intrinsic to the ageing process may affect both the

cochlea (Fetoni et al., 2011; Yamasoba et al., 2013) and the brain (Deary et al., 2009; DeCarlo et al., 2014; Karlamangla et al., 2014). Observational studies have linked both ARHL and cognitive ageing with indices of physical ageing such as slower gait (Callisaya et al., 2015; Li, Simonsick, Ferrucci, & Lin, 2013; Viljanen, Kaprio, Pyykko, Sorri, Koskenvuo, et al., 2009), increased incidence of falls (Lin & Ferrucci, 2012; Semenov, Bigelow, Xue, Lac, & Agrawal, 2015; Viljanen, Kaprio, Pyykko, Sorri, Pajala, et al., 2009), increased risk of hospitalisations (Genther et al., 2013; Wilson, Rajan, et al., 2014) and also with mortality (Amirian et al., 2010; Anstey, Luszcz, Giles, & Andrews, 2001; Karpa et al., 2010; Smits, Deeg, Kriegsman, & Schmand, 1999). This association may be due to a frailty syndrome (Panza, Solfrizzi, Barulli, et al., 2015; Panza, Solfrizzi, & Logroscino, 2015; Robertson, Savva, & Kenny, 2013). Additionally, structural equation modelling data from observational studies suggest that a common age-related factor underlies auditory and cognitive decline (Anstey et al., 2003; Humes, Busey, et al., 2013); see (Wayne & Johnsrude, 2015) for a review.

Alternatively, deterioration in hearing function may have direct implications for neurocognitive functioning via a *mechanistic pathway* (Lindenberger & Baltes, 1994; Wayne & Johnsrude, 2015). Decline in auditory acuity may lead to potentially reversible decline in cognitive performance due to temporary reallocation of cognitive resources to compensate for loss of hearing acuity - the "information-degradation" hypothesis (Pichora-Fuller, 2003; Wayne & Johnsrude, 2015) or permanent decline through impact on neuroplastic adjustments - the "sensory deprivation" hypothesis (Lin, Metter, et al., 2011). In contrast to the common cause hypothesis, further statistical analysis of observational data has suggested that hearing acuity influences cognitive function independently of any age-related processes (Anstey, Luszcz, et al., 2001a; Humes, Busey, et al., 2013; Wayne & Johnsrude, 2015). Neuroimaging studies report that neural correlates of auditory and speech processes are preferentially affected by acquired hearing loss providing further support for a mechanistic pathway (Campbell & Sharma, 2013; Eckert et al., 2012; Husain, Carpenter-Thompson, & Schmidt, 2014; Lin, Ferrucci, et al., 2014; Peelle et al., 2011).

Evidence suggests that the link between ARHL and cognitive decline is due to a mixture of both a common aetiology and a mechanistic association (Wayne & Johnsrude, 2015). As ARHL is a common condition that is easily detected and managed (Bagai et al., 2006), it may provide a potential avenue for better detection and treatment of age-associated cognitive decline and dementia (Lin, Metter, et al., 2011; Lin et al., 2013).

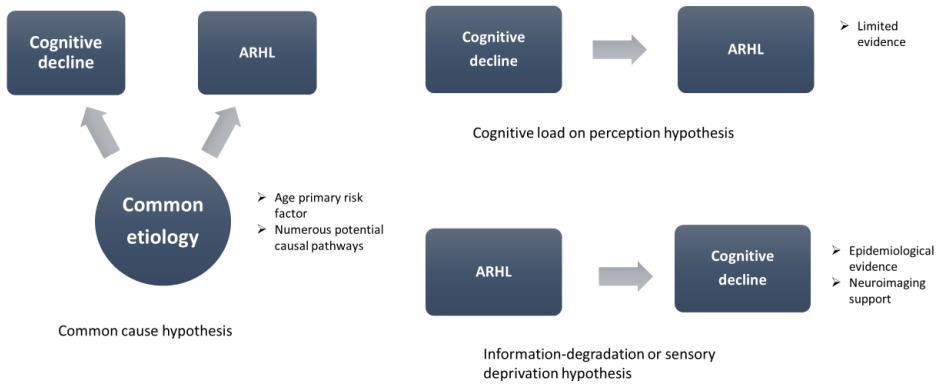

Figure 3.1: Theoretical views of relationship between ARHL and cognitive decline (Lin, Ferrucci, et al., 2011; Lindenberger & Baltes, 1994; Wayne & Johnsrude, 2015).

3.3 Common aetiologies

Both ARHL and cognitive ageing are complex conditions that share multiple underlying pathophysiological processes and common risk factors (Deary et al., 2009; DeCarlo et al., 2014; Fetoni et al., 2011; Panza, Solfrizzi, & Logroscino, 2015; Whalley et al., 2004; Yamasoba et al., 2013). Epidemiological and experimental research from human and animal studies point to several possible underlying aetiological causes. This section focuses on key processes and biomarkers which have been implicated in both age-related neurodegeneration and otopathy. See Figure 3.2 for an outline of these pathways.

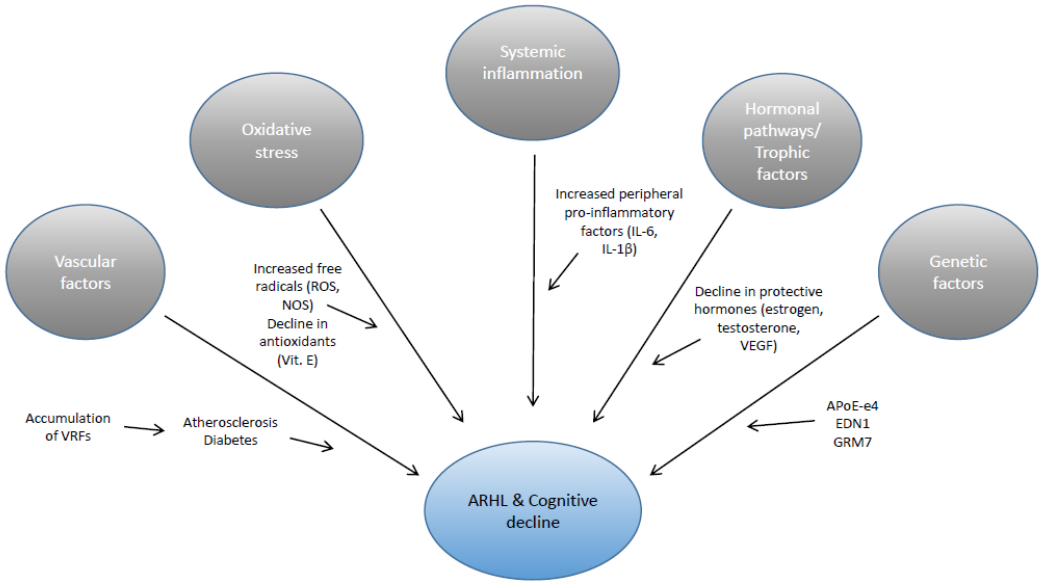

Figure 3.2: Map of common aetiologies between ARHL and cognitive decline.

3.3.1 Cardiovascular and cardiometabolic factors

Vascular pathophysiologies may link ARHL and neurodegenerative cognitive decline. Evidence from observational studies and reviews suggest that ARHL, cognitive decline and dementia share common vascular risk factors (VRFs) including obesity (Anstey, Cherbuin, Budge, & Young,

2011; Cruickshanks et al., 2015; Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Helzner et al., 2011), diabetes mellitus (Akinpelu, Mujica-Mota, & Daniel, 2014; Bainbridge, Cheng, & Cowie, 2010; Cruickshanks et al., 2015; Cukierman-Yaffee, 2009; Helzner et al., 2005; Li, Shao, et al., 2014; Sridhar, Lakshmi, & Nagamani, 2015), alcohol consumption (Gopinath, Flood, McMahon, et al., 2010; Peters, Peters, Warner, Beckett, & Bulpitt, 2008), smoking (Cruickshanks et al., 2015; Helzner et al., 2005; Helzner et al., 2011; Peters, Poulter, et al., 2008), hypertension (Gates, Cobb, D'Agostino, & Wolf, 1993; Helzner et al., 2011; Qiu, Winblad, & Fratiglioni, 2005; Reitz et al., 2010), cholesterol (Anstey, Lipnicki, & Low, 2008; Helzner et al., 2011) and hyperlipidaemia (Deckers et al., 2015; Lee et al., 2015). VRFs are heavily implicated in neurodegenerative cognitive decline, accounting for the majority of modifiable risks factors for dementia (Barnes & Yaffe, 2011; Norton et al., 2014). AD patients commonly present with a mixture of cerebrovascular pathology and neuropathological substrates at post-mortem (Qiu & Fratiglioni, 2015). Additionally, ARHL is a predictor for cardiovascular disorder (Friedland, Cederberg, & Tarima, 2009; Karpa et al., 2010), cerebrovascular disease (Helzner et al., 2005) and vascular dementia (Gallacher et al., 2012).

Studies commonly report VRFs as having a cross-sectional association with prevalence of acquired hearing loss but find that they are not predictive of incidence of hearing loss (Gopinath, Flood, McMahon, et al., 2010; Gopinath, Schneider, Rochtchina, Leeder, & Mitchell, 2009; Kiely et al., 2012; Mitchell et al., 2009). Interestingly, systematic reviews report a strong association between risk of dementia and VRFs in mid-life but less so in later life (Anstey et al., 2011; Novak & Hajjar, 2010; Qiu & Fratiglioni, 2015; Qiu et al., 2005; Tolppanen, Solomon, Soininen, & Kivipelto, 2012). This may be due to a cumulative effect of VRFs over the lifespan leading to an incremental increase in risk of disorder (Qiu & Fratiglioni, 2015). This may have a similar effect on peripheral vascular structures, e.g. moderate alcohol consumption has been associated with protective effects in both the cochlea (Dawes et al., 2014; Gopinath, Flood, McMahon, et al., 2010) and the brain (Peters, Peters, et al., 2008).

In epidemiological studies, multiple cardiovascular disorders and diseases have been linked with both ARHL and cognitive decline or dementia. These include coronary heart disease (Eggermont et al., 2012; Erkan et al., 2015; Gates et al., 1993; Newman et al., 2005; Perez Villa, Perez Villa, Morello, Betriu, & Traserra, 1995; Susmano & Rosenbush, 1988), stroke (Cumming, Marshall, & Lazar, 2013; Karpa et al., 2010; Levine et al., 2015; Rostamian, Mahinrad, Stijnen, Sabayan, & de Craen, 2014), angina, previous myocardial infarction (Haring et al., 2013; Karpa et al., 2010; Newman et al., 2005; Torre, Cruickshanks, Klein, Klein, & Nondahl, 2005), heart failure (Gure et al., 2012; Hajduk, Kiefe, Person, Gore, & Saczynski, 2013; Saczynski et al., 2013) and atherosclerosis (Fischer et al., 2015; van Oijen et al., 2007; Yarchoan et al., 2012; Zhong et al., 2012). Disorders in cardiovascular function may cause injury to both the cochlea and the brain through similar pathophysiological mechanisms including hypoperfusion, hypoxia, hypoglycaemia

and emboli (Qiu & Fratiglioni, 2015) with consequent deterioration in capillary structures, endothelial dysfunction, basement membrane thickening (Morris, Carare, Schreiber, & Hawkes, 2014; Thomopoulos, Spicer, Gratton, & Schulte, 1997), ischemic injury and atrophy in brain and cochlea parenchyma (Attems & Jellinger, 2014; Fetoni et al., 2011; Olivetto, Simoni, Guaran, Astolfi, & Martini, 2015; Oron, Elgart, Marom, & Roth, 2014; Qiu & Fratiglioni, 2015). This can trigger a heightened local inflammatory response, increase oxidative stress and cause mitochondrial dysfunction leading to further degeneration in tissue (Blass, Sheu, & Gibson, 2000; Dai et al., 2004; Joshi & Pratico, 2014; Khan, Szczepek, Haupt, Olze, & Mazurek, 2010; Kim et al., 2012; Quintanilla, Orellana, & von Bernhardi, 2012; Raz, Knoefel, & Bhaskar, 2015; Rosales-Corral, Reiter, Tan, Ortiz, & Lopez-Armas, 2010; Sochocka, Koutsouraki, Gasiorowski, & Leszek, 2013). Capillary degeneration or small vessel disease may lead to dysfunction and breakdown of the blood-brain barrier (Attems & Jellinger, 2014; Grinberg & Thal, 2010), and the blood-labyrinth barrier in the stria vascularis (Neng et al., 2015). Ischemic processes can also trigger glutamate excitotoxicity which is associated with deterioration of the spiral ganglion neurons (Malgrange et al., 2015) and neurodegeneration and apoptosis in the brain (Brassai, Suvanjeiev, Ban, & Lakatos, 2015).

Multiple regions in the cochlea are affected by these vascular pathophysiological mechanisms. The stria vascularis, a highly vascularised structure, may be preferentially affected by vascular pathology (Gates & Mills, 2005) because deterioration in microvasculature leads to atrophy of the stria vascularis in animal models (Fetoni et al., 2011; Gratton & Schulte, 1995). Another animal model found that hypoxia and ischemia cause deafness through hair cell loss (Olivetto et al., 2015). A human histopathological study found that lumen narrowing of the auditory artery was associated spiral ganglion atrophy (Makishima, 1978). Additionally, another study found ischemic brainstem lesions in the auditory pathways of ischemic heart disease patients (Perez Villa, Perez Villa, Morello, Betriu, & Traserra, 1996). Based on animal studies, hearing loss due to degeneration of the stria vascularis results in a distinctive audiometric pattern of a flat and low slope toward the higher frequencies, compared to sensory loss which typically has a much steeper slope with a dip in the higher frequencies (Fetoni et al., 2011; Gates & Mills, 2005; Olivetto et al., 2015; Schmiedt et al., 2002). This form of hearing loss is the most typical finding in cohort studies examining ARHL (Gates, Cooper, Kannel, & Miller, 1990; Gates & Mills, 2005; Wilson, Noe, Cruickshanks, Wiley, & Nondahl, 2010) and is significantly correlated with cardiovascular status (Friedland et al., 2009) and with white matter hyperintensities (Eckert et al., 2013). Furthermore, a histopathological study using human samples found a correlation between age and stria vascularis deterioration (Suzuki et al., 2006) suggesting that it is the most prominent anatomic characteristic of age-related cochlear dysfunction (Gates & Mills, 2005). In the brain, cerebrovascular dysfunction can lead to neurodegeneration both globally and locally through accumulation of infarcts or haemorrhagic lesions and can subsequently cause cognitive decline (Attems & Jellinger, 2014; Qiu & Fratiglioni, 2015). A study found that participants with higher vascular risk factors demonstrated lower neural

efficiency on a cognitive task of inhibition (Chuang et al., 2014). Additionally, it may play a key role in AD through affecting cholinergic dysfunction (Roman & Kalaria, 2006), impairing removal of neuropathological substrate (Attems & Jellinger, 2014; Tarasoff-Conway et al., 2015) and amyloidogenesis (Reed et al., 2012).

Obesity, as assessed by body mass index (BMI), is associated with hearing loss (Cruickshanks et al., 2015; Helzner et al., 2011) atrophy of grey (Gustafson, Lissner, Bengtsson, Bjorkelund, & Skoog, 2004) and white matter (Bettcher et al., 2013) and is a significant risk factor for dementia (Gustafson et al., 2003). A systematic review found that obesity is linked with impairment across all cognitive domains (Prickett, Brennan, & Stolwyk, 2015). This may be due to peripheral white adipose tissue causing elevated pro-inflammatory factors and reduced gut microbial diversity (Heneka et al., 2015; Kiliaan, Arnoldussen, & Gustafson, 2014; Rosano, Marsland, & Gianaros, 2012). An animal study found that diet-induced obesity was associated with degeneration of the spiral ganglion and spiral ligament via hypoxia, inflammation, and apoptosis signalling pathway (Hwang, Hsu, Yu, Liu, & Yang, 2013).

Age-related cardiometabolic changes can lead to deterioration in peripheral vasculature. A recent review of animal and human histopathological studies found that diabetes was associated with changes in the basement membrane of the stria vascularis, and less consistently, with loss of spiral ganglion neurons, organ of Corti cells, and atrophy in the stria vascularis (Akinpelu, Ibrahim, Waissbluth, & Daniel, 2014). It is associated with reduced global and regional (frontal and temporal lobes and anterior cingulate) brain volume, white matter hyperintensities, altered functioning and breakdown of the blood-brain barrier (Lee et al., 2014; Sato & Morishita, 2014; Serlin, Levy, & Shalev, 2011). The mechanisms are not clear but there are several possible common pathways (Hong, Buss, & Thomas, 2013; Yang & Song, 2013). Hyperglycaemia may lead to microangiopathy in the cochlea (Hong et al., 2013) and the brain (Sato & Morishita, 2014). Chronic hyperglycaemia and hyperinsulinemia may lead to increased oxidative stress and mitochondrial dysfunction (Brownlee, 2001). Advanced glycation end products due to hyperglycaemia may lead to disruption of cochlear endolymph homeostasis or endothelial damage (Hong et al., 2013) and to neurodegeneration (Salahuddin, Rabbani, & Khan, 2014; Yang & Song, 2013). Hypoglycaemia can also disrupt cochlear endolymph homeostasis (Mendelsohn & Roderique, 1972) and impair neuronal metabolism and insulin signalling (Sato & Morishita, 2014) with consequences for neuroplasticity (Mainardi, Fusco, & Grassi, 2015). Hyperglycaemia may lead to higher levels of angiotensin, a potent vasoconstrictor, which can lead to strial dysfunction (Meyer Zum Gottesberge, Massing, Sasse, Palma, & Hansen, 2015). Blockage of the angiotensin II receptor was found to ameliorate the effects of hyperglycaemia in diabetic rats (Meyer Zum Gottesberge et al., 2015). Interestingly, treatment of angiotensin and its associated axis (the renin-aldosterone-angiotensin axis) can ameliorate the effects on cognition in patients with hypertension (Yagi et al., 2011) and with AD (Ashby & Kehoe, 2013). Additionally, hyperinsulinemia may

disrupt clearance of amyloid-beta through depletion of insulin-degrading enzyme (Farris et al., 2003).

Both high and low cholesterol levels are associated with impaired cognition and dementia (Anstey et al., 2008). Hypercholesterolemia (or hyperlipidaemia) may increase the risk of vascular pathology such as stroke or arthrosclerosis (Bhatnagar, Soran, & Durrington, 2008). In the brain, cholesterol plays a key role in neuronal structure and function, synaptic function and plasticity (Leoni & Caccia, 2013; Pfrieger & Ungerer, 2011; Segatto, Leboffe, Trapani, & Pallottini, 2014) and interacts with neuroinflammation and oxidative stress to play a crucial role in amyloidogenesis (Gamba et al., 2015; Gamba et al., 2012; Segatto et al., 2014). Little is known about the effects of cholesterol levels on cochlear cholesterol homeostasis but it may possibly be linked to ARHL through similar mechanisms (Malgrange et al., 2015).

Age-associated elevation in levels of homocysteine, possibly due to poorer absorption of B-vitamins, is associated with damage to nervous and vasculature structures (Ansari, Mahta, Mallack, & Luo, 2015; de Jager, 2014; Sharma, Tiwari, & Tiwari, 2015). In epidemiological studies, hyperhomocysteimia has been linked to ARHL (Gopinath, Flood, Rochtchina, McMahon, & Mitchell, 2010), cognitive decline (Agrawal et al., 2015) and from meta-analysis, with AD (Beydoun et al., 2014). This is possibly through multiple mechanisms including oxidative stress, inflammation, endothelial dysfunction and excitotoxicity (Humpel, 2011; Kamat, Vacek, Kalani, & Tyagi, 2015; Sharma et al., 2015; Tyagi, Lominadze, & Roberts, 2005). It was mechanistically linked with deterioration in the cochlea of mice through oxidative stress (Martinez-Vega et al., 2014). In a randomised controlled trial, reduced homocysteine levels by treatment with B vitamins slowed the rate of accelerated brain atrophy in MCI (Smith et al., 2010). Additionally, in a prospective study, intake of folic acid and vitamin B12 was associated with reduced conversion to dementia in an MCI population (Blasko et al., 2012).

As VRFs are modifiable risk factors that are heavily implicated in both dementia (Norton et al., 2014) and ARHL (Gates & Mills, 2005) they are a strong pathway for intervention and treatment of both conditions. VRFs possibly have a cumulative effect over the lifespan and may no longer be risk factors in older adults (Kiely et al., 2012; Qiu & Fratiglioni, 2015). Therefore, future clinical trials in this area should focus on modifying these VRFs while taking into account that there may be a limited window of opportunity for intervention (Qiu & Fratiglioni, 2015). Several studies report that the link between ARHL and cognitive decline/dementia was independent of vascular factors (Bush et al., 2015; Deal et al., 2015; Helzner et al., 2005; Kiely et al., 2012; Lin, 2011; Lin, Ferrucci, et al., 2011; Lin, Metter, et al., 2011; Lin et al., 2013; Teipel et al., 2015) suggesting that other processes contribute to their association.

3.3.2 Oxidative stress and mitochondrial dysfunction

The ageing process is associated with a systemic accumulation of defects in cellular metabolism leading to increasing oxidative stress and mitochondrial dysfunction within the cell (Fetoni et al., 2011; Huang, Leu, & Zou, 2015; Kamogashira et al., 2015; Wang, Wang, et al., 2014). It has been posited that this accumulation has a causal role in the ageing process (Harman, 1956; Lenaz, 2012; Linnane, Marzuki, Ozawa, & Tanaka, 1989; Wang, Wu, Wu, & Wei, 2013), ARHL (Fetoni et al., 2011; Fetoni, Troiani, Petrosini, & Paludetti, 2015; Kamogashira et al., 2015), cognitive decline (Berr, Balansard, Arnaud, Roussel, & Alperovitch, 2000; Gao et al., 2007; Huang, Leu, et al., 2015; Torres et al., 2011) and neurodegenerative diseases (Gamba et al., 2015; Moreira, Carvalho, Zhu, Smith, & Perry, 2010; Revel et al., 2015).

The mitochondria serve the energetic needs of the cell through aerobic oxidative phosphorylation (OXPHOS) a by-product of which is production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Fetoni et al., 2011; Kamogashira et al., 2015; Moreira et al., 2010). ROS and RNS are toxic, free radicals that serve crucial functions such as signalling molecules in intracellular processes and are neutralised through antioxidant mechanisms (Fetoni et al., 2011; Wang et al., 2013). Both the brain and cochlea have an intense aerobic metabolism and consequentially have increased production of these free radicals (Fetoni et al., 2011; Kamogashira et al., 2015; Moreira et al., 2010). An excessive amount of ROS and RNS due to an imbalance in their production and detoxification leads to oxidative stress, a state which has a deteriorative effect on cellular function by causing mitochondrial dysfunction, disruption of intracellular signalling pathways and oxidative damage of surrounding cellular structures (Wang et al., 2013; Wang, Wang, et al., 2014; Yamasoba et al., 2013). It is hypothesised to cause mutation or deletion of mitochondrial DNA, impairing OXPHOS activity and inducing cellular calcium (Ca^{2+}) dyshomeostasis, which leads to further ROS production, forming a vicious downward spiral (Kamogashira et al., 2015; Wang et al., 2013; Wang, Wang, et al., 2014; Wong & Ryan, 2015). This is compounded by age-associated decline in level of antioxidants such as vitamins A and C and antioxidant enzymes (Kamogashira et al., 2015; Venkateshappa, Harish, Mahadevan, Srinivas Bharath, & Shankar, 2012; Wang et al., 2013; Wang, Wang, et al., 2014). Additionally, mitochondrial DNA replicates independently of the cell cycle making it susceptible to increased accumulation of mutations compared to chromosomal DNA (Kamogashira et al., 2015; Wang, Wang, et al., 2014).

The excess of free radicals triggers the opening of mitochondrial inner membrane permeability transition pores which decreases membrane potential and releases pro-apoptotic factors (Fetoni et al., 2011; Kamogashira et al., 2015; Wang et al., 2013). Defective mitochondria are normally eliminated by autophagy and mitophagy which protect against cellular apoptosis, but this function declines with the ageing process (Wang et al., 2013; Yuan et al., 2015). Ultimately, cellular death occurs through necrotic processes and both intrinsic (mitochondrial) and extrinsic (cell death

receptor) apoptotic pathways, which in excess leads to tissue dysfunction (Kamogashira et al., 2015; Wang et al., 2013; Yamasoba et al., 2013).

Oxidative stress is intimately linked with vascular and neuronal inflammatory processes (Gamba et al., 2015; Kamogashira et al., 2015; Wang et al., 2013). A heightened state of oxidative stress can trigger a vascular inflammatory response, cause endothelium dysfunction and mediate the necrotic action of leukocytes (Cahill-Smith & Li, 2014; Iadecola, 2004; Menardo et al., 2012; Rosano et al., 2012) as well as induce neuroinflammatory response from microglia and neurons (Gamba et al., 2015). Oxidative by-products such as isoprostanes are potent vasoconstrictors and can induce ischemia in the cochlea (Miller, Brown, & Schacht, 2003) and the brain (Hoffman, Moore, & Ellis, 1997). Additionally, intracellular calcium ($Ca2^{+}$) concentration drives endothelium cells in regulating perfusion and consequently $Ca2^{+}$ dyshomeostasis may impair endothelium function and precede cardiovascular disease (Socha et al., 2015).

Animal studies examining oxidative stress have linked its pathophysiological effects across multiple sites in the cochlea, including hair cells, stria vascularis, and the spiral ganglion (Fetoni et al., 2011; Kamogashira et al., 2015). Age-associated decline in oxidative stress defence mechanisms may compound this effect (Kamogashira et al., 2015; Wang et al., 2013; Wang, Wang, et al., 2014). Mice lacking antioxidant enzymes demonstrated age-related cochlear hair cell loss, reduced thickness of stria vascularis and degeneration of the spiral ganglion (Fetoni et al., 2011; Kamogashira et al., 2015; Yamasoba et al., 2013). Upregulation of VEGF expression which is triggered by oxidative stress and protective against its effects on the cochlea was substantially lower in aged mice (Picciotti et al., 2004). Damage related to noise exposure triggering oxidative stress may be compounded by decline in these defences (Kamogashira et al., 2015).

A longitudinal study found an association for increased risk of global cognitive decline with peripheral markers of systemic oxidative stress (Odds Ratio (OR) = 2.25; confidence interval (CI 95% = 1.26-4.02) and antioxidants (OR = 1.58; CI 95% = 1.08-2.31) (Berr et al., 2000). Other studies have supported this association with cognition including decline in episodic memory and executive function (Gao et al., 2007; Torres et al., 2011). Neurons are especially vulnerable to the neurotoxic action of ROS and RNS (Gamba et al., 2015). Furthermore, oxidative modification of protein signalling pathways and induced Ca^{2+} dyshomeostasis may also disrupt cellular processes essential for synaptic plasticity (Butterfield et al., 2006; Paula-Lima, Adasme, & Hidalgo, 2014). Therefore, oxidative stress may impair neurogenesis and alter dendritic networks contributing to atrophy (Huang, Leu, et al., 2015). The frontal cortex and medial temporal lobe, including the hippocampus, show preferential age-associated increase in oxidative stress and decreased mitochondrial activity (Huang, Leu, et al., 2015; Venkateshappa et al., 2012). They also demonstrate preferential loss of antioxidant enzyme activities. Compared to normal controls, MCI/early AD patients demonstrate increased oxidative imbalance in hippocampus, parahippocampus and superior and middle temporal gyrus (Butterfield et al., 2006; Keller et al.,

2005; Williams, Lynn, Markesbery, & Lovell, 2006). Interestingly, these regions were also preferentially affected and associated with ARHL in a longitudinal imaging study (Lin, Ferrucci, et al., 2014).

AD brains demonstrate a high state of oxidative stress (Gamba et al., 2015; Wang, Wang, et al., 2014), which along with associated neuroinflammation, plays a key part in the pathophysiology of the disease (Emerit, Edeas, & Bricaire, 2004). Peripheral markers of oxidative stress correlated strongly with cognitive outcomes in AD patients (Pratico et al., 2000) and can predict further cognitive decline (Revel et al., 2015) and increased risk of medial temporal lobe atrophy (Zito et al., 2013). The pathological downward cycle between oxidative stress and mitochondrial dysfunction may also be a primary progenitor in the pathogenesis of AD occurring preceding neuropathology (Bonda et al., 2010; Gamba et al., 2015; Nunomura et al., 2001; Swerdlow & Khan, 2004, 2009; Wang, Wang, et al., 2014). Mitochondrial oxidative stress can trigger hyperphosphorylation of tau (Melov et al., 2007; Su et al., 2010) possibly through activation of the mitogen-activated protein kinases (MAPK) p38 signalling pathway (Giraldo, Lloret, Fuchsberger, & Vina, 2014; Su et al., 2010). It has been hypothesised that end products of oxidised cholesterol and lipids, oxysterol and 4-hydroxynonenal respectively, may enhance production and accumulation of Aβ (Dias et al., 2014; Gamba et al., 2014; Gamba et al., 2015). Aβ, a potent generator of ROS and RNS, induces further oxidative stress leading to further neurodegeneration (Gamba et al., 2015).

There are potential therapeutic targets for both ARHL and neurocognitive decline through this pathway (Caldwell et al., 2015; Martinez-Vega et al., 2014). Supplementation of antioxidant molecules or enzymes has been found to ameliorate the effects of oxidative stress on the cochlea (Fetoni et al., 2011; Kamogashira et al., 2015) and cognitive function in humans (Witte et al., 2009) and on cognitive function in AD mice (Yu et al., 2015). Caloric restriction, associated with lower incidence of hearing loss in several animal studies, better cognitive function, and longer lifespan is thought to be primarily mediated by its effects on oxidative stress and increased autophagy (Sohal & Forster, 2014; Wang et al., 2013).

3.3.3 Immunosenescence and inflammaging

Age-related changes in the immune system (*immunosenescence*), primarily due to lifelong antigenic stress, is associated with decline in adaptive immunity and conservation or upregulation in innate immunity (Gruver, Hudson, & Sempowski, 2007; Martorana et al., 2012; Michaud et al., 2013; Weiskopf, Weinberger, & Grubeck-Loebenstein, 2009). This is observed in the form of decreased numbers of regulatory and naïve T lymphocytes and in numbers and diversity of B lymphocytes with an increase in memory T lymphocytes (Martorana et al., 2012; Michaud et al., 2013). This shift to a chronic, low-grade, systemic inflammatory state is termed inflammaging (Franceschi et al., 2000; Franceschi & Campisi, 2014) and is characterised by an increase of pro-inflammatory cytokines (e.g. interleukin (IL)-6, IL-1β and tumour necrosis factor (TNF)-α),

chemokines (e.g. IL-8) and acute phase proteins (C-reactive protein (CRP)) (Martorana et al., 2012; Michaud et al., 2013; Rosano et al., 2012). While the inflammatory response is adaptive, enabling elimination of immune challenges, prolonged, systemic exposure may lead to deterioration in tissue and damage of multiple organs including the cochlea and brain (Martorana et al., 2012).

In a cross-sectional study of older adults, Verschuur et al. (2012) reported that hearing thresholds were significantly correlated with multiple indicators of inflammatory status including white blood cell count, neutrophil count, IL-6 and CRP. Nash et al. (2014), examining a longitudinal study of a large cohort (n=1,073), reported that younger (<60) but not older participants with high or increasing levels of serum CRP had nearly twice the risk (hazard ratio: 1.96, 95% confidence interval: 1.19, 3.23) of developing hearing loss over a ten year timeframe. Several cross-sectional (Gunstad et al., 2006; Heringa et al., 2014; Wright et al., 2006) and longitudinal studies (Heringa et al., 2014; Marioni et al., 2009; Rafnsson et al., 2007; Tilvis et al., 2004; Weaver et al., 2002; Yaffe et al., 2003) have also found a significant link between peripheral markers IL-6 and CRP with impairment or decline in multiple cognitive domains including memory, executive functions and processing speed. Furthermore, observational research has found associations between inflammatory markers with MCI and AD (Galimberti et al., 2006; Holmes et al., 2009; Leung et al., 2013). A prospective study found that IL-1 and TNF-α were significant predictors of AD incidence over a mean follow-up of seven years (Tan et al., 2007). In healthy older adults, neuroimaging studies (Frodl & Amico, 2014) have also linked peripheral markers to reduced volume in grey and white matter (Bettcher et al., 2012; Jefferson et al., 2007; Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008; Marsland et al., 2015; Taki et al., 2013; Wersching et al., 2010). Additionally, inflammatory markers were associated with atrophy in medial temporal lobes in AD populations (Matsumoto et al., 2008) and together with MRI measures were predictive of conversion from MCI to AD (Furney et al., 2011).

Both the cochlea and the central nervous system (CNS) have blood diffusion barriers with similar structures and functions that selectively exclude most blood-borne substances and protect them from influences in the systemic vasculature (Rosano et al., 2012; Trune & Nguyen-Huynh, 2012). However, the advent of sickness behaviour following systemic stimuli suggests communication between the immune system and the CNS (Holmes, 2013; Rosano et al., 2012). Rodent studies report an exaggerated central inflammatory response to peripheral inflammatory stressors in older brains even in the absence of neuropathology (Dilger & Johnson, 2008; Rosano et al., 2012). Hearing loss is a common incidence in systemic autoimmune diseases and the cochlea is often the first organ affected (Berrocal & Ramirez-Camacho, 2002; Kastanioudakis et al., 2002; Nacci et al., 2010; Roverano et al., 2006; Trune & Nguyen-Huynh, 2012).

There are several pathways through which increased pro-inflammatory cytokines may affect these organs (Rosano et al., 2012; Trune & Nguyen-Huynh, 2012; Zhang, 2008). They may induce endothelial cells to downregulate production of tight junction proteins and cause greater endothelial

permeability and erosion of the blood barriers thus allowing infiltration into the parenchyma (Rosano et al., 2012; Trune & Nguyen-Huynh, 2012; Zhang, 2008) or through passive diffusion through nude areas of the blood-brain barrier (Rosano et al., 2012). Endothelial cells may produce adhesion molecules providing attachment sites to facilitate transport of inflammatory cells through the blood barrier into the extra-capillary space (Trune & Nguyen-Huynh, 2012; Yang, Shang, Zhao, Fang, & Chen, 2013). Endothelial cells themselves are producers of pro-inflammatory factors including cytokines and chemokines (Rosano et al., 2012). The recent discovery that the brain is connected to the peripheral immune system through meningeal lymphatic vasculature suggests another pathway (Louveau et al., 2015).

Following entrance into the CNS and cochlea parenchyma, pro-inflammatory mediators such as IL-6 and TNF-α can induce regional inflammation (Rosano et al., 2012; Trune & Nguyen-Huynh, 2012) even in the absence of local antigens (Martorana et al., 2012; Rosano et al., 2012; Trune & Nguyen-Huynh, 2012; Wong & Ryan, 2015). These mediators have a cytotoxic action through multiple pathways including ROS and RNS production (McGeer & McGeer, 2004; Rosano et al., 2012; Sarkar & Fisher, 2006). TNF-α can activate the extrinsic cell receptor apoptotic pathways (Wilde, Pringle, Sundstrom, Mann, & Iannotti, 2000; Wong & Ryan, 2015; Zelova & Hosek, 2013). Cytokines and ROS also activate intracellular mitogen-activated protein (MAPK) signalling pathways (Rosano et al., 2012; Wong & Ryan, 2015). MAPK pathways, key mediators of inflammatory and apoptotic responses, are implicated in ARHL (Fransen et al., 2015; Wong & Ryan, 2015) and dementia (Munoz & Ammit, 2010). Long-term inflammation induces cellular death via apoptotic and necrotic pathways and oxidises and erodes surrounding tissue triggering further inflammatory action (Currais, 2015; Rosano et al., 2012; Uchida, Sugiura, Ueda, et al., 2014; Wong & Ryan, 2015; Zhang, 2008). This perpetuates the inflammatory response, sustaining a vicious cycle which can lead to decline in organs (Currais, 2015; Rosano et al., 2012; Uchida, Sugiura, Ueda, et al., 2014; Wong & Ryan, 2015).

When stimulated by inflammatory mediators, resident brain macrophages, termed ‘microglia’, release inflammatory molecules and free radicals (Gamba et al., 2015; Michelucci, Heurtaux, Grandbarbe, Morga, & Heuschling, 2009) and activate astrocytes which enhances the inflammatory response (Gamba et al., 2015; Jo, Law, & Chung, 2014; Vallieres, Campbell, Gage, & Sawchenko, 2002). Also, neurons themselves serve as sources of pro-inflammatory factors (Gamba et al., 2015; Tchelingerian, Vignais, & Jacque, 1994). Activated microglia can recruit monocytes from the periphery through the blood-brain barrier (D'Mello, Le, & Swain, 2009; Reader et al., 2015). Apart from deterioration of cerebrovasculature (Jo et al., 2014), chronic inflammation can alter neuroplasticity (Frodl & Amico, 2014; McAfoose & Baune, 2009; Rosano et al., 2012) through impairment of neurogenesis (Vallieres et al., 2002), disruption of long-term potentiation (Murray & Lynch, 1998) and synaptic dysfunction (Khairova, Machado-Vieira, Du, & Manji, 2009). Neuroinflammation has been implicated in the formation of amyloid plaques through enhancing

levels of amyloid precursor protein and of amyloidgenesis (Frodl & Amico, 2014; Gamba et al., 2015; Heneka et al., 2015). In animal models, pharmaceutical modulation of the immunological processes of microglia can significant reduce Aβ deposition (Lim, Rodriguez-Ortiz, & Kitazawa, 2015). The effects of Aβ are also mediated by inflammation. Non-demented patients with high levels of Aβ deposition demonstrated lower microglial inflammation response to Aβ than patients with dementia (Perez-Nievas et al., 2013).

Similar processes may hypothetically activate target immune cells in several regions of the cochlea to release cytokines (Fujioka, Okano, & Ogawa, 2014; Murillo-Cuesta et al., 2015; Trune & Nguyen-Huynh, 2012; Wong & Ryan, 2015). Inflammation has been demonstrated to be a key mechanism through which noise and ischemia affect hearing loss (Abi-Hachem, Zine, & Van De Water, 2010; Murillo-Cuesta et al., 2015). The blood-labyrinth barrier (BLB) in the stria vascularis contains perivascular macrophage-like melanocytes which are essential for maintaining endocochlear potential (Trune & Nguyen-Huynh, 2012; Zhang et al., 2015; Zhang et al., 2012). Inflammatory exposure may degenerate the stria vascularis and BLB leading to loss of endocochlear potential (Tagaya et al., 2011; Trune & Nguyen-Huynh, 2012) and may also suppress genes regulating ion homeostasis (Trune, 2010; Trune & Nguyen-Huynh, 2012). Additionally, the spiral ligament has been found to contain cochlear macrophages which may regulate microvasculature response to noise and facilitate repair (Dai & Shi, 2011; Fujioka et al., 2014; Hirose, Discolo, Keasler, & Ransohoff, 2005). Treatment with glucocorticoids has shown much success in reversing inflammatory-mediated hearing loss (Abi-Hachem et al., 2010; Trune & Nguyen-Huynh, 2012).

Chronic, systemic inflammation is implicated in the pathophysiological process of most, if not all, age-associated diseases (Vasto & Caruso, 2004). These include disorders linked to both ARHL and pathological cognitive ageing such as atherosclerosis (Casserly & Topol, 2004; Fischer et al., 2015), rheumatoid arthritis (Ferraccioli, Carbonella, Gremese, & Alivernini, 2012; Murdin, Patel, Walmsley, & Yeoh, 2008), diabetes (Schmidt et al., 1999; Ulu et al., 2014) and mitochondrial dysfunction (Currais, 2015). Additionally, obesity is linked to both conditions (Kiliaan et al., 2014), most likely as adipose tissue is a key source of peripheral IL-6 (Mohamed-Ali et al., 1997). Pharmacological inhibition of the p38 MAPK pathway may prevent inflammatory-mediated hearing loss (Wong & Ryan, 2015) and AD (Munoz & Ammit, 2010). A higher inflammatory state can be triggered via biopsychosocial factors such as chronic stress, depression and loneliness and associated with the hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Hawkley & Capitanio, 2015; Reader et al., 2015; Rosano et al., 2012).

3.3.4 Hormonal & trophic factors

Hormonal and trophic factors play a key role in regulation and initiation of multiple physiological processes and intracellular signalling pathways where they exert their functions (Ebner, Kamin, Diaz, Cohen, & MacDonald, 2014). Altered expression of certain hormones as part of the ageing

process can occur due to reduced secretion by glands or changes in the nervous system which regulates release of these hormones (Chahal & Drake, 2007; Colciago, Casati, Negri-Cesi, & Celotti, 2015; Ebner et al., 2014). Consequently, this can lead to disruption of physiological processes and change in structure and function of multiple organs including the brain and cochlea (Colciago et al., 2015; Conrad & Bimonte-Nelson, 2010; Ebner et al., 2014).

There is increasing evidence that sex steroid hormones play key roles in the ageing process (Ebner et al., 2014; Li & Singh, 2014) and possibly explain the common finding of sex differences in ARHL (Agrawal et al., 2008; Lin, Thorpe, et al., 2011) and cognitive ageing (Colciago et al., 2015; Li & Singh, 2014). Loss of estrogen, primarily estradiol E2, during menopause is associated with higher risk of cognitive decline and dementia (Colciago et al., 2015) and higher rate of hearing loss (Svedbrant, Bark, Hultcrantz, & Hederstierna, 2015). In the cochlea, estrogen is implicated in the maintenance of the organ of Corti (McCullar & Oesterle, 2009). Estrogen may exert strong protective effects on the cochlea and brain through similar processes, including through its antioxidant effects, protection of mitochondrial function, maintenance of calcium homeostasis and anti-apoptotic effects (Ebner et al., 2014; Heinrich et al., 2013; Li & Singh, 2014; Nakamagoe, Tabuchi, Uemaetomari, Nishimura, & Hara, 2010; Wang, Simpkins, Dykens, & Cammarata, 2003; Yao & Brinton, 2012), reduced inflammation through suppressed transcription of the IL-6 gene (Manolagas, Jilka, Girasole, Passeri, & Bellido, 1993) and regulation of cholesterol (Malgrange et al., 2015; Yao & Brinton, 2012). Additionally, estrogen receptors are expressed in multiple regions of the brain, particularly the hippocampus, possibly explaining its larger size in women (Neufang et al., 2009). Estrogens promote neurogenesis, reduce formulation and accumulation of β-amyloid and are protective against ischemia-induced brain damage (Ebner et al., 2014; Li & Singh, 2014). Hormone therapy has been reported to have protective effects in menopausal women on cognition (Fischer, Gleason, & Asthana, 2014; Maki & Henderson, 2012) and hearing (Guimaraes et al., 2006) (although see Shumaker et al. (2004) who reported that estrogen therapy increased risk of MCI and dementia). Testosterone may also regulate function and have protective effects on the cochlea (Hasson, Theorell, Liljeholm-Johansson, & Canlon, 2009; Snihur & Hampson, 2012; Yang, Jin, et al., 2015; Yeo, Chang, Park, & Suh, 2003) and brain (Ebner et al., 2014; Holland, Bandelow, & Hogervorst, 2011; Maggio et al., 2012). Its mechanisms are unclear (Ebner et al., 2014) but research suggests that it may have a neuroprotective role on the CNS through androgen receptors (Fargo, Galbiati, Foecking, Poletti, & Jones, 2008; Sharma, Marzo, Jones, & Foecking, 2010) and particularly in cochlear hair cells (Yang, Jin, et al., 2015). It may also modulate the immune response in the cochlea (Yeo et al., 2003). Further research on the effects of this hormone is needed because results of its effects on cognition are mixed (Ebner et al., 2014) and there is very limited research of its effects on hearing.

Pro-angiogenic factors (particularly vascular endothelial growth factor-VEGF) maintain and promote vasculature and are upregulated in response to cytotoxic stimuli such as hypoxia,

excitotoxicity and oxidative stress (Ahluwalia, Jones, Szabo, & Tarnawski, 2014; Fetoni et al., 2011). Expression of VEGF declines with age leading to vascular deterioration and less prevention of neuronal apoptosis in the cochlea (Clinkard et al., 2013; Fetoni et al., 2011; London & Gurgel, 2014; Picciotti et al., 2004) and brain (Beazley-Long et al., 2013; Hohman, Bell, & Jefferson, 2015; Storkebaum & Carmeliet, 2004). In a longitudinal study, VEGF level correlated with hippocampal atrophy, executive function and memory and had protective effects against tau and amyloid-beta (Hohman et al., 2015).

Erythropoietin (Epo) is a glycoprotein hormone that functions as a cytokine and regulates red cell production but it is also cytoprotective possibly through its anti-apoptotic effects (Monge Naldi, Gassmann, & Bodmer, 2009). Its receptors are expressed in multiple areas of both the cochlea (Caye-Thomasen, Wagner, Lidegaard Frederiksen, Asal, & Thomsen, 2005; Monge Naldi et al., 2009) and brain (Maiese, Chong, Hou, & Shang, 2009). Its expression declines with age (Chung et al., 2004). It is upregulated in response to hypoxic–ischemic injury (Kumral et al., 2004; Monge Naldi et al., 2009). It mediates the regenerative effect of brain-derived neurotrophic factor (BDNF) on spiral ganglion neurons (Berkingali et al., 2008; Kaiser et al., 2013) and has a direct neuroprotective effect by promoting increased expression of BDNF against the action of Aβ on memory and synaptic plasticity volume (Esmaeili Tazangi, Moosavi, Shabani, & Haghani, 2015). In the cochlea, it has been demonstrated to have a protective effect on the hair cells (Han et al., 2013; Monge Naldi et al., 2009). It is associated with hippocampal neurogenesis (Osredkar, Sall, Bickler, & Ferriero, 2010), improvement of long-term potentiation (Esmaeili Tazangi et al., 2015) and protective effects on cognitive function (Hralova et al., 2014; Sargin et al., 2011). Epo treatment has been associated with improvement in memory and hippocampal volume (Miskowiak et al., 2014).

Insulin-like growth factor 1 (IGF-1) is a master regulator of function in multiple cellular types including those of the nervous system (Aleman & Torres-Aleman, 2009; Ashpole, Sanders, Hodges, Yan, & Sonntag, 2014). In the cochlea, IGF-1 is associated with the post-natal maintenance of hair cells and supporting cells possibly through its regulation of cellular pathways implicated in apoptosis, metabolism, response to oxidative stress and prevention of inflammation (Varela-Nieto, Murillo-Cuesta, Rodriguez-de la Rosa, Lassatetta, & Contreras, 2013; Yamahara, Yamamoto, Nakagawa, & Ito, 2015; Yamamoto, Nakagawa, & Ito, 2014). Its decline in the brain can lead to impaired plasticity, neurogenesis, synaptic function and neuronal apoptosis (Aleman & Torres-Aleman, 2009; Ashpole et al., 2014). Based on a review, Aleman and Torres-Aleman (2009) reported that decline in IGF-1 is associated with age-related cognitive decline in multiple cognitive functions.

Brain derived neurotropic factor (BDNF) has several well documented neuroprotective effects in the brain through its role in neuroprotection and neurogenesis (Allen, Watson, Shoemark, Barua, & Patel, 2013; Nagahara et al., 2009). Its role in the inner ear is less understood but it may have age-

related effects. With age, its expression in inner hair cells is down-regulated while in the spiral ganglion neurons and supporting cells (phalangeal or Deiter's cell) of inner hair synapses in the cochlea it is upregulated (Kaiser et al., 2013; Khalin, Alyautdin, Kocherga, & Bakar, 2015; Singer, Panford-Walsh, & Knipper, 2014).

Dopamine, implicated as having neuroprotective effects in the brain against multiple insults including glutamate excitotoxicity or ischemia (Morales, Sabate, & Rodriguez, 2013; Vaarmann, Kovac, Holmstrom, Gandhi, & Abramov, 2013) may also have the same function in the cochlea nervous system (Lendvai et al., 2011). Age-associated decline in dopamine expression may therefore lead to neural deterioration in both organs (Vaarmann et al., 2013).

3.3.5 Genetic factors

Genetic factors contribute significantly to both hearing and cognitive function in adults over 65 years of age (McGue & Johnson, 2011; Uchida, Sugiura, Sone, Ueda, & Nakashima, 2014). Based on a twin study, Wingfield et al. (2007) estimate that genetics accounts for one-half to two-thirds of the variance in hearing loss. An observational study on family history found that genetic association was stronger for moderate to severe hearing loss with differential risks for women (adjusted OR 3.0; 95% CI 1.6-5.6) and men (adjusted OR 2.0; CI 1.01-3.9) (McMahon et al., 2008). Using data from another twin study, Sachdev et al. (2013) reported significant genetic contributions to ageing in multiple cognitive functions, including processing speed (42-62%), working memory (59%), cognitive flexibility (31%), and episodic memory (41-51%). This was also significant for estimates of brain atrophy rates, including total brain volume (63%), total grey matter (68%), and total white matter (71%). Genetic markers may influence the ageing process in the cochlea and brain through multiple biochemical pathways including their direct influence on biological structure and function, timing and rate of late-life changes or indirectly through other age-related disorders such as inflammation (McGue & Johnson, 2011). Both ARHL (Fransen et al., 2015) and AD (Bird, 2008) are polygenic in nature with the phenotype depending on an aggregated effect of multiple genetic factors. However, several common genetic markers have emerged which may aid in risk assessment for age-related disorders and offer an opportunity for clinical therapy (Bu, 2009; Cacabelos, Cacabelos, Torrellas, Tellado, & Carril, 2014).

ApoE e4 (*apolipoprotein E-epsilon4*) is a key genetic risk factor strongly linked in isoform-dependent manner with sporadic AD (Risacher et al., 2015; Ward et al., 2012). It has also been associated with increased risk of both cognitive decline (Plassman, Williams, Burke, Holsinger, & Benjamin, 2010), vascular dementia (Rohn, 2014) and with ARHL (Kurniawan et al., 2012; Mener et al., 2014). The mechanisms by which it affects neurodegeneration are still obscure (Gamba et al., 2015). A key pathway may be its role in the brain in regulating the distribution and homeostasis of cholesterol which is vital for neuronal structure and function (Leoni & Caccia, 2013; Leoni, Solomon, & Kivipelto, 2010; Pfrieger & Ungerer, 2011; Vance, 2012). It is essential for the generation of Aβ and NFT and plays a role in their accumulation and effects (Bu, 2009; Gamba et

al., 2015; Leoni et al., 2010). It also modulates neuroinflammation (Tai et al., 2015) and induces mitochondrial dysfunction and oxidative stress (Chang et al., 2005; Shea, Rogers, Ashline, Ortiz, & Sheu, 2002) which may have interactive effects leading to rapid AD progression (Gamba et al., 2015). It may affect function in the cochlea through its effects on cholesterol homeostasis (Malgrange et al., 2015). Both the brain and the cochlea rely on *de novo* synthesis for cholesterol supply as their respective blood-barriers prevent recruitment from circulation (Malgrange et al., 2015). ApoE may also affect both structures indirectly through hypercholesterolemia in the main vasculature and associated atherosclerosis (Guo, Zhang, Du, Nair, & Yoo, 2005; Lathe, Sapronova, & Kotelevtsev, 2014; McNeill, Channon, & Greaves, 2010).

Other vascular-related genetic factors include EDN1 (*endothelin-1*), a potent vasoconstrictor that can induce hypoperfusion (Thomas, Miners, & Love, 2015; Uchida, Sugiura, Sone, et al., 2014). Elevated levels of EDN1 have been associated longitudinally with ARHL (Uchida, Sugiura, Nakashima, Ando, & Shimokata, 2009), and histopathologically in post-mortem assessment of cerebral cortex in AD (Palmer, Barker, Kehoe, & Love, 2012; Thomas et al., 2015) and vascular dementia (Thomas et al., 2015) and in multiple areas of the cochlea including the stria vascularis and spiral ganglion in animal studies (Xu, Tang, Liu, & Liu, 2008; Xu, Tang, Liu, & Liu, 2007). A meta-analysis reported that vascular endothelial growth factor (VEGF) gene promoter polymorphisms were associated with AD risk (Liu et al., 2013). Similar polymorphisms and consequent differential expression levels of VEGF may affect the cochlea (Picciotti et al., 2004). In a Japanese population-based cohort study, polymorphisms of TNF-α and TNF-receptor super family were significantly linked with hearing loss (Uchida, Sugiura, Ueda, et al., 2014). Polymorphisms of IL-1β, IL-6 and TNF-α are also predictive of AD (Michaud et al., 2013) and vascular dementia incidence (Mansoori et al., 2012).

Polymorphisms relating to oxidative stress may also play a role. UCP2 (*uncoupling protein 2*) reduces oxidative stress in the mitochondria through regulation of the generation of mitochondrial free radicals (Uchida, Sugiura, Sone, et al., 2014; Wang, Zhai, et al., 2014). It has been associated with hearing loss (Sugiura, Uchida, Nakashima, Ando, & Shimokata, 2010) and has a critical role in neurogenesis, dendritic growth, and synaptogenesis in the hippocampus, and with learning and memory (Wang, Zhai, et al., 2014). Glutathione S-transferases (GSTs) genes are involved in the detoxification of cytotoxic compounds such as ROS (Uchida, Sugiura, Ando, Nakashima, & Shimokata, 2011). One particular class, glutathione S-transferase theta 1 (GSTT1), has been linked to ARHL (Angeli et al., 2012; Bared et al., 2010) and to AD (Ghosh et al., 2012). Mitochondrial NAD-dependent deacetylase sirtuin-3 (SIRT3) has been linked to hearing loss (Someya et al., 2010) and brain health (Glatt et al., 2007) through its regulation of production of superoxide and antioxidants in the mitochondria. SIRT3 has been found to mediate the benefits of caloric restriction on prevention of oxidative damage in the cochlea (Someya et al., 2010). NAD-dependent deacetylase sirtuin-1 (SIRT1) has also been linked to hearing loss (Xiong et al., 2015)

and brain health (Ng, Wijaya, & Tang, 2015), possibly through its regulation of mitochondrial autophagy (Lee et al., 2008).

MTHFR (*methylenetetrahydrofolate reductase*) encodes critical enzymes in folate metabolism (Uchida, Sugiura, Sone, et al., 2014). The MTHFR C677T polymorphism has been associated in observational studies with hearing function (Pollak et al., 2012; Uchida, Sugiura, Sone, et al., 2014) and cognitive function (Tsai et al., 2011). Pollak et al. (2012) reported a dose-dependent correlation of MTHFR 677T with the degree of hearing loss in young (<40) Polish males. Another observational study associated this marker with a higher risk for vascular dementia and AD in combination with a genetic marker for inflammation (Mansoori et al., 2012). Additionally, a meta-analysis reported it to be significantly linked with vascular dementia (Sun et al., 2015). This may be due to impaired folate metabolism and consequent hyperhomocysteinemia (Kronenberg, Colla, & Endres, 2009; Martinez-Vega et al., 2014). In cross-sectional studies, Uchida, Sugiura, Sone, et al. (2014) and Mansoori et al. (2012) reported an effect for C677T on hearing and AD risk, respectively, that was independent of folate and plasma homocysteine levels. Indeed, Mansoori et al. (2012) found no difference in plasma homocysteine levels between AD, VaD and healthy controls. Uchida, Sugiura, Sone, et al. (2014) suggested that C677T may exert an independent affect by protection of DNA code during replication through preventing imbalances in the nucleotide pool.

ESRRγ (*estrogen-related receptor, gamma*) was linked to maintenance of hearing in three independent human cohorts (Nolan et al., 2013). This may occur through its effects on the supporting cells of the inner ear hair cells, the organ of Corti and Reissner's membrane (Nolan et al., 2013). It is also associated with a neuroprotective effect in neuron cell culture, possibly through regulation and protection of dopaminergic neuronal phenotype (Lim, Choi, & Choi, 2015).

GRM (*glutamate receptor, metabotropic*) 7, which regulates glutamate synaptic transmission, was linked to ARHL in an observational study (Friedman et al., 2009) and is a genetic risk for AD based on meta-analysis of observational studies (Perez-Palma et al., 2014). Glutamate is the primary excitatory neurotransmitter in the cochlea (Friedman et al., 2009) and the brain (Zhou & Danbolt, 2014) where it regulates multiple neuronal processes including neurogenesis and synaptic plasticity (Perez-Palma et al., 2014). It is highly expressed in the hippocampus and plays an important role in learning and memory (Perez-Palma et al., 2014). Alteration in its signalling can lead to excitotoxicity and apoptosis in the brain (Rudy, Hunsberger, Weitzner, & Reed, 2015) and cochlea (Friedman et al., 2009).

3.4 Mechanistic pathways

Loss of hearing due to age-related processes or an accumulation of insults to the cochlea may have negative long-term effects on cognitive function. There are several mechanistic pathways by which ARHL may lead to decline in cognitive function (Lin, Metter, et al., 2011; Lindenberger & Baltes, 1994). See Figure 3.3 for an outline of these pathways.

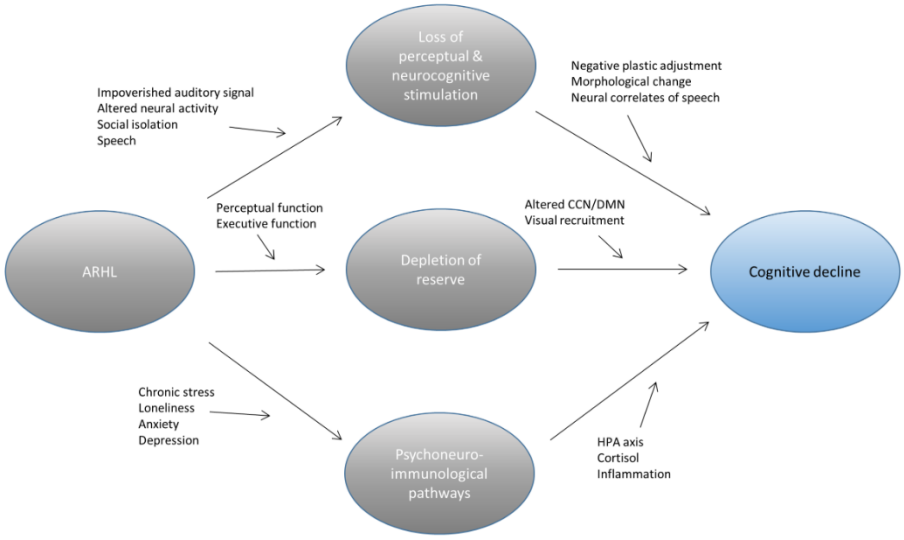

Figure 3.3: Map of mechanistic pathways between ARHL and cognitive decline.

3.4.1 Loss of perceptual and neurocognitive stimulation

ARHL may directly lead to cognitive decline through loss of perceptual and neurocognitive stimulation and consequent cortical reorganisation and disruption of neurocognitive function (Kuiper et al., 2015; Lin, Metter, et al., 2011; Lin et al., 2013). The adult brain, particularly the sensory cortices, is highly sensitive to changes in environment and re-adjusts its neural structures in response to input through associative or homeostatic plastic mechanisms (Whitt, Petrus, & Lee, 2014). Prolonged loss of auditory stimulation and subsequent altered neural activity may therefore lead to atrophy of the auditory cortex and other associated neuroanatomical regions (Fetoni et al., 2015; Gold & Bajo, 2014; Sergeyenko et al., 2013). Recent cross-sectional and longitudinal neuroimaging studies have linked ARHL to atrophy in regional areas in the brain involved in audio-perceptual and speech processes suggesting a mechanistic association (Eckert et al., 2012; Husain, Medina, et al., 2011; Lin, Ferrucci, et al., 2014; Wingfield & Peelle, 2015). ARHL may hypothetically have broader effects on neurocognitive processes not specific to speech-auditory tasks through handicap of higher-order cognitive perception of speech (Campbell & Sharma, 2013) and social function (Gopinath et al., 2012) leading to loss of social and cognitive stimulation. This loss of stimulation may extend decline resulting from ARHL to higher-order neurocognitive processes such as attention and memory (Husain, Medina, et al., 2011; Lin, Ferrucci, et al., 2014; Tun et al., 2009) and possibly contribute to the greater decline in whole brain volume observed in this population (Lin, Ferrucci, et al., 2014).

An impoverished auditory signal may lead to degeneration of synaptic function and neural circuits related to basic acoustic perception (Fetoni et al., 2015; Pozo & Goda, 2010; Sale, Berardi, & Maffei, 2014; Turrigiano, 2012; Whitt et al., 2014). Weaker encoding in the brainstem auditory pathways (Bidelman, Villafuerte, Moreno, & Alain, 2014; Peelle et al., 2011) may lead to their morphological degeneration through a demyelinating process (Chang et al., 2004; Lin et al., 2008; Peelle et al., 2011). Animal studies have found strong evidence of morphological alterations in neural correlates of auditory perception (Fetoni et al., 2015; Gold & Bajo, 2014) including altered synapses (Fetoni et al., 2013) and misalignment of tonotopic cortical maps in the primary auditory cortex (Cheung, Bonham, Schreiner, Godey, & Copenhaver, 2009; Kakigi, Hirakawa, Harel, Mount, & Harrison, 2000; Rajan, Irvine, Wise, & Heil, 1993; Robertson & Irvine, 1989; Schwaber, Garraghty, & Kaas, 1993; Seki & Eggermont, 2002).

Loss of auditory function can lead to cortical disinhibition as evidenced by increased excitability in response to speech (Bidelman et al., 2014), possibly due to overcompensation through mechanisms of homeostatic plasticity such as synaptic scaling or altered excitatory/inhibitory neural network activity (Fetoni et al., 2015; Kamal, Holman, & de Villers-Sidani, 2013; Pozo & Goda, 2010; Sale et al., 2014; Turrigiano, 2012; Whitt et al., 2014). This is supported by animal studies that have reported decreased activation and loss of inhibitory interneurons (Takesian, Kotak, Sharma, & Sanes, 2013) and increased activation of excitatory synapses in the auditory cortex (Kotak et al., 2005) consistent with theories of homeostatic plasticity (Gold & Bajo, 2014). Additionally, loss of sensory stimulation may lead to less activation of the stimuli responsive regions including the locus coeruleus and basal forebrain with consequences for production of neurotransmitters such as dopamine (Daulatzai, 2016). This may have cascading consequences through upregulation of neuroinflammation and increased production of amyloid beta and tau (see Daulatzai, 2016 for a review). Furthermore, alterations in neural transmission, particularly related to dopaminergic decline, may contribute to a poorer signal-to-noise ratio observed with ageing, and consequently to degraded neural representations (Backman, Nyberg, Lindenberger, Li, & Farde, 2006; Li, Lindenberger, & Sikstrom, 2001).

Language is processed both in the primary auditory cortex in the temporal lobe and in other cortices via ventral and dorsal pathways (Friederici, 2012; Hickok & Poeppel, 2007; Poeppel, Emmorey, Hickok, & Pylkkanen, 2012). The classic view is that the bilateral ventral pathway is involved in sound-to-meaning mapping and syntactic processes and the left lateral dorsal pathway in mapping sounds onto articulatory motor representations (Hickok & Poeppel, 2007; Poeppel, 2014). On auditory tasks, ARHL was associated with down-regulation of neural activity and reduced connectivity within these pathways (Campbell & Sharma, 2013; Husain et al., 2014; Lazard, Lee, Truy, & Giraud, 2013; Peelle et al., 2011), the occurrence of which has been linked with duration of hearing loss (Lazard et al., 2013). Reduced connectivity in the bilateral ventral pathway was also linked with language skill (Li, Booth, et al., 2013) possibly due to disrupted

mapping of acoustic speech to semantic representations (Binder, Desai, Graves, & Conant, 2009; Hickok & Poeppel, 2007; McClelland & Rogers, 2003) with related decline of phonological processing skills and phonological memory (Andersson, 2002; Classon, Rudner, Johansson, & Ronnberg, 2013). Additionally, multiple neuroimaging studies have found that pure-tone thresholds were linked with increased neurological atrophy in regions associated with these pathways (Eckert et al., 2012; Husain, Medina, et al., 2011; Lin, Ferrucci, et al., 2014; Peelle et al., 2011). Husain, Medina, et al. (2011) also reported alterations in multiple white matter tracts such as the superior longitudinal fasciculus which are implicated in the speech processing pathways (Friederici, 2012). Eckert et al. (2012) found that atrophy of the primary auditory cortex was preferentially affected by high but not low frequency hearing loss. High frequency thresholds are vital for speech perception (Barrenas & Wikstrom, 2000) and are the first to be affected in the process of ARHL (Gates & Mills, 2005) suggesting that atrophy in these regions is driven by loss of speech function, further supporting a mechanistic association.

Speech perception and comprehension involves a hierarchy of perceptual-cognitive processes extending from basic perceptual processing of sounds to higher level cognitive processing such as attention, emotional perception and working memory (Davis & Johnsrude, 2007; Friederici, 2012; Hickok & Poeppel, 2007; Lemke & Scherpiet, 2015; Poeppel, 2014). Degraded auditory input may therefore have a cascade effect extending to these higher neurocognitive systems in a bottom-up fashion (Peelle et al., 2011). On auditory tasks, neuroimaging studies of auditory tasks report less activation of neural regions external to the primary auditory system (Husain et al., 2014; Husain, Pajor, et al., 2011). This includes the left superior frontal gyrus, left inferior parietal lobe, left superior occipital gyrus, and limbic regions including the amygdala, posterior cingulate cortex and parahippocampus. Studies examining neurodegeneration have found hearing loss to be associated with deterioration in the anterior cingulate, left superior and bilateral medial frontal gyri (Husain, Medina, et al., 2011), left primary somatosensory cortex (Eckert et al., 2012) and right parahippocampal gyrus (Lin, Ferrucci, et al., 2014). Additionally, decline was observed in connectivity of white matter tracts sub-serving these pathways and in networks facilitating higher cognitive processing (Husain et al., 2014; Husain, Medina, et al., 2011). Apart from the superior temporal cortices, Lee et al. (2003) found decreased glucose metabolism in the anterior cingulate gyri and in the right parahippocampal gyrus. Additionally, in animal models, noise-induced hearing loss was associated with impaired hippocampal neurogenesis (Kraus et al., 2010; Yu, Zhai, Dai, & Hu, 2011). These regions are independently associated with memory encoding (Browndyke et al., 2013; Preston & Eichenbaum, 2013), semantic memory (Binder et al., 2009), verbal and semantic fluency (Clark et al., 2014) and attention and executive functions (Gasquoine, 2013). An fMRI study found that greater grey matter loss in some of these regions, including the parahippocampus, inferior and middle temporal gyrus and posterior cingulate, predicted greater risk of conversion from MCI to AD (Chetelat et al., 2005). Another study found that these regions were associated

with dysregulation of emotional contagion and poorer appraisal of socioemotional stimuli in patients with MCI and AD (Sturm et al., 2013).

Hearing loss may lead to reallocation of higher cognitive processes to compensate for perceptual degradation in a top-down fashion, resulting in explicit, effortful processing of speech (Campbell & Sharma, 2014; Pichora-Fuller, 2003; Ronnberg et al., 2013; Wingfield & Grossman, 2006). This may lead to less cognitive resources for higher processing of speech (Mishra, Stenfelt, Lunner, Ronnberg, & Rudner, 2014) or for encoding information (Craik et al., 1983; Tun et al., 2009) with longer term decline in memory function (Gallacher et al., 2012; Ronnberg et al., 2011; Valentijn et al., 2005). Increased recruitment of higher cognitive functions could hypothetically lead to their maintenance (Ronnberg et al., 2013). Behavioural studies have reported preservation of immediate and working memory but decline in delayed episodic, phonological and semantic memory (Lyxell, Andersson, Borg, & Ohlsson, 2003; Ronnberg et al., 2011). However, progressive age-associated decline in cognitive and hearing capacity and also sustained perceptual effort may overwhelm or exhaust the individual's capacity to compensate (McGarrigle et al., 2014) and thus affect even these functions (Anstey, Luszcz, et al., 2001b; Bush et al., 2015). In older adults with hearing loss, Erb and Obleser (2013) found increased activation of the anterior insula, thought to be part of a cognitive control network (Eckert et al., 2009) in response to clear speech stimuli but decreased activation with degraded stimuli.

Hearing loss is associated with greater perceived social isolation (loneliness) independently of objective social participation (Weinstein & Ventry, 1982) possibly due to direct impairment of social function. This may directly lead to loss of neurocognitive stimulation of higher-order cognitive functions independently of speech stimulation (Lin, Metter, et al., 2011; Lindenberger & Baltes, 1994). Epidemiological studies have found strong links between social or cognitive activity and neurocognitive health suggesting that social disengagement is a risk factor for cognitive decline (Barnes, Mendes de Leon, Wilson, Bienias, & Evans, 2004; Brown et al., 2012; Lovden, Ghisletta, & Lindenberger, 2005). Cognitive and social stimulation may promote neurogenesis and synaptic density (Sale et al., 2014) giving greater protection against incidence of cerebrovascular disease (Valenzuela et al., 2012) and AD (Bennett et al., 2006; Wilson, Scherr, Schneider, Tang, & Bennett, 2007).

ARHL cannot be reversed and the causes remain to be elucidated (Yamasoba et al., 2013). Assistive technology (hearing aid or cochlear implant) has been demonstrated to have some benefit for cognitive (Acar et al., 2011; Deal et al., 2015) and psychosocial function (Acar et al., 2011; Miller et al., 2015; Mosnier et al., 2015). Hearing aids can be adjusted to improve speech perception and minimise cognitive load (Ives et al., 2014). This may be supplemented by cognitive (Anderson, White-Schwoch, Choi, & Kraus, 2014; Henshaw & Ferguson, 2013), perceptual (Woods et al., 2015) or communication training (Oberg, Bohn, & Larsson, 2014) to improve the benefit provided by these aids.

3.4.2 Neurocognitive compensation and depletion of reserve

Epidemiological, observational and neuroimaging studies suggest that there are beneficial neurocognitive processes which adaptively maintain or support cognitive function concomitant with degradation in neural structures and networks due to age-associated or pathological changes (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014; Stern, 2009, 2012). These compensatory processes may be determined by genetic, environmental and lifestyle factors which impart a reserve against neurodegenerative processes (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014; Sachdev et al., 2013; Stern, 2009, 2012). Factors such as education, social network size and pre-morbid IQ can predict clinical cognitive outcomes in dose-response fashion, independent of neuropathologic burden (Bennett et al., 2006; Mortimer et al., 2003; Stern, 2009, 2012; Stern, Alexander, Prohovnik, & Mayeux, 1992; Valenzuela & Sachdev, 2006). It is hypothesised that such factors may determine inter-individual differences in neurocognitive function and raise the threshold at which age-associated or pathological burden affects function (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014; Stern, 2009, 2012). Indices of reserve have been demonstrated to be associated with cognitive outcomes in numerous brain-related conditions including AD (Roe et al., 2008; Roe et al., 2010), stroke (Ojala-Oksala et al., 2012), traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003) and penetrating brain injury (Grafman, Salazar, Weingartner, Vance, & Amin, 1986). ARHL may hypothetically place a burden additional to other age-associated declines, having a cumulative burden or it may deplete reserve and lower the threshold for symptomatic manifestation of neuropathologies and age-related neural changes (Lin, Metter, et al., 2011).

There are multiple hypothetical markers, such as neurological substrates, neurocognitive processes and neurochemical systems which potentially contribute to and constitute reserve (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014; Robertson, 2013, 2014; Stern, 2009, 2012; Yoshizawa, Gazes, Stern, Miyata, & Uchiyama, 2014). Brain size and neuronal density may provide a bulwark against neuropathology or injury (‘brain reserve’) (Mori et al., 1997; Mortimer et al., 2003; Stern, 2009, 2012). Individual differences in efficiencies of task-related neural networks and capacity to recruit additional neural resources to compensate for declines may also alter clinical outcomes (‘cognitive reserve’) (Holtzer et al., 2009; Reuter-Lorenz & Park, 2014; Robertson, 2014; Stern, 2009; Zarahn et al., 2007). Neuroplastic mechanisms (Robertson, 2013; Whitt et al., 2014) and noradrenergic systems (Robertson, 2013, 2014) may facilitate positive plastic adjustments to promote neurocognitive functioning. Cerebral glucose metabolism may also underlie differences in neural efficiencies (Yoshizawa et al., 2014).

There are multiple hypothetical processes through which ARHL may lead to a depletion of this reserve (Campbell & Sharma, 2014; Lin, Ferrucci, et al., 2014; Lin, Metter, et al., 2011; Lin et al., 2013). Most simply, loss of stimulation may lead to deterioration in brain reserve indicated by regional (Eckert et al., 2012; Husain, Medina, et al., 2011; Lin, Ferrucci, et al., 2014) and global

brain atrophy (Lin, Ferrucci, et al., 2014) inducing a direct depletion of a source of reserve which may provide a bulwark against trauma (Mori et al., 1997; Mortimer et al., 2003; Stern, 2009, 2012). Hearing loss may deplete neural reserve specific to the auditory system. There is evidence of such a reserve which buffers the effects of acquired hearing loss and age on cognitive-perceptual function (Skoe & Kraus, 2014) and which may be acquired through environmental enrichment, consistent with theories of cognitive reserve (Reuter-Lorenz & Park, 2014; Stern, 2012). Musical training is associated with better central auditory processes including speech processing (Smayda, Chandrasekaran, & Maddox, 2015) and working memory in older adults (Slevc, Davey, Buschkuehl, & Jaeggi, 2016) possibly through efficiencies in excitatory-inhibitory subcortical neural networks enabling finer auditory signal processing (Smayda et al., 2015).

At the subcortical level, prior to conscious processing of speech, individual differences due to lifelong experiences such as musicianship and bilingualism enabled a more comprehensible speech signal (Weiss & Bidelman, 2015; White-Schwoch, Carr, Anderson, Strait, & Kraus, 2013) that is resilient to age-related peripheral hearing loss (Skoe & Kraus, 2014; Zendel & Alain, 2012), and improved multi-modal working memory (Slevc et al., 2016). Additionally, in animal studies, decline in hearing acuity leads to realignment of associated topographic cortical maps to become responsive to remaining auditory input (Cheung et al., 2009; Kakigi et al., 2000; Schwaber et al., 1993). ARHL may place a burden on these capacities (Bidelman et al., 2014) lowering the threshold for age-associated perceptual-cognitive decline.

Concomitant with decline in neural systems in the primary auditory cortex due to hearing loss, neural ageing studies have reported increased activity in regions associated with explicit speech processing or cognitive control systems to support auditory function within a perceptible threshold (Campbell & Sharma, 2013; Erb & Obleser, 2013; Peelle et al., 2011; Wong et al., 2009). Deterioration in phonological memory subsequent to hearing loss (Andersson, 2002; Andersson & Lyxell, 1998; Lyxell et al., 2003) also appears to drive this increased recruitment (Classon, Rudner, & Ronnberg, 2013). Similar findings have been reported in the visual domain where older adults compensated for visual processing deficits by recruiting frontal neural systems related to higher order neurocognitive functions as evidenced by slower reaction times but equally accurate performance compared to young controls (Dennis & Cabeza, 2011; Grady et al., 1994). Neuroimaging studies have also reported increased activation of multiple nodes in frontal and parietal regions (Campbell & Sharma, 2013; Husain et al., 2014; Husain, Pajor, et al., 2011; Lazard et al., 2013) and the anterior insula (Erb & Obleser, 2013) which are associated with the frontoparietal control network (FPCN) (Andrews-Hanna et al., 2014; Niendam et al., 2012). This network has been hypothesised as partially mediating cognitive reserve by facilitating top-down regulation of cognitive functions including attention, working memory, conscious visual perception and episodic memory retrieval (Robertson, 2014).

Increased cognitive effort on speech tasks may have several functions (Wong, Ettlinger, Sheppard, Gunasekera, & Dhar, 2010). It may enhance perception by either reallocating greater attentional resources to aid perceptual function (Craik & Byrd, 1982; Wild et al., 2012; Wong et al., 2010) or by inhibiting competing answers or interference from noise (Hasher & Zacks, 1988; Jonides et al., 2000; Wong et al., 2010). On auditory tasks in the hearing loss population, behavioural and pupillometry studies report increased recruitment of attention or working memory to maintain performance (McGarrigle et al., 2014; Rudner & Lunner, 2014; Tun et al., 2009). Adults with hearing loss may rely further on alternate environmental cues to aid perceptual processing such as speech-reading, or contextual or phonological cues (Ronnberg et al., 2013; Wingfield & Grossman, 2006). Behavioural studies have demonstrated that visual cues improve speech perception (Bernstein & Grant, 2009; Grant & Seitz, 2000; Grant, Walden, & Seitz, 1998) and higher level cognitive processing (Mishra et al., 2014). On visual rhyme judgement tasks, participants with acquired hearing loss are more susceptible to interference from orthographically similar but non-rhyming word pairs (Andersson, 2002; Andersson & Lyxell, 1998; Classon, Rudner, Johansson, et al., 2013; Classon, Rudner, & Ronnberg, 2013; Lyxell et al., 2003). In an EEG study, hearing loss patients demonstrated increased P2 CAEP amplitude and latency, a possible marker of perceptual effort which significantly correlated with pure-tone thresholds and speech-in-noise perception (Campbell & Sharma, 2013). Another EEG study by Classon, Rudner, Johansson, et al. (2013) reported that behavioural performance only matched controls when given enough time for explicit processing, similar to findings by Grady et al. (1994) in the visual domain. Behavioural performance was also associated with an amplified N2-like response in the right centroparietal region (Classon, Rudner, Johansson, et al., 2013), thought to be a marker of increased cognitive control (Folstein & Van Petten, 2008).

Higher order functions may also aid speech interpretation by facilitating increased recruitment in working memory of the motor and phonological processing systems (Ronnberg et al., 2013; Wong et al., 2010). Hearing loss studies using auditory and phonological tasks have found increased activity and functional connectivity in specific regions in the frontal (Campbell & Sharma, 2013; Husain, Pajor, et al., 2011; Wong et al., 2009) and parietal (Classon, Rudner, Johansson, et al., 2013; Husain et al., 2014; Lazard et al., 2013; Wang, Fan, et al., 2014) lobes which have been associated with phonological and semantic decision making (Friederici, 2012; Hartwigsen et al., 2015). This suggests explicit mapping of acoustic signals onto lexical and articulatory motor representations in working memory (Ronnberg et al., 2013). This compensatory mechanism may involve a temporary recruitment of these systems (Wild et al., 2012; Wong et al., 2009) and may lead to suboptimal performance in cognitive functions usually compensated for by these neural resources or networks during ageing (Robertson, 2014; Stern, 2009) or AD (Boyle, Wilson, Schneider, Bienias, & Bennett, 2008) consistent with the “information-degradation” hypothesis (Pichora-Fuller, 2003; Wayne & Johnsrude, 2015). Longer-term auditory deprivation may lead to neural remodelling and neuroplastic adjustments to facilitate increased recruitment of cognitive

control mechanisms to support perceptual function (Campbell & Sharma, 2014; Lin, Metter, et al., 2011) possibly leading to a more permanent depletion of reserve (Lin, Metter, et al., 2011).

Several neuroimaging studies have reported increased connectivity within the default mode network (DMN) (Husain et al., 2014; Li, Booth, et al., 2013; Wang, Fan, et al., 2014). This may be due to mental fatigue associated with increased perceptual effort (McGarrigle et al., 2014) as similar results, which correlated with levels of fatigue, were observed in a sample with cancer-related fatigue (Hampson, Zick, Khabir, Wright, & Harris, 2015). Increased connectivity between nodes of the DMN with nodes of cognitive control networks (CCNs), including the FPCN was also reported (Husain et al., 2014; Wang, Fan, et al., 2014). The DMN typically deactivates with increasing task difficulty or cognitive load and consequent increased activity in CCNs (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003; McKiernan, D'Angelo, Kaufman, & Binder, 2006; Sonuga-Barke & Castellanos, 2007). Segregation between these networks has been viewed as favourable for optimal cognitive performance (Anticevic et al., 2012; Fox et al., 2005; Sonuga-Barke & Castellanos, 2007). However, recent research suggests that selective integration between the DMN and CCNs may support performance on tasks with a higher cognitive load (Hearne, Cocchi, Zalesky, & Mattingley, 2015) such as complex cognitive tests (Hearne et al., 2015; Leech et al., 2011; Liang, Zou, He, & Yang, 2015) or in social cognition (Li, Mai, et al., 2014; Mars et al., 2012; Meyer & Lieberman, 2012; Meyer, Spunt, Berkman, Taylor, & Lieberman, 2012). Increased perceptual effort or cognitive load as a consequence of ARHL may therefore drive integration between networks. However, it may be maladaptive for longer-term cognition as it has been associated with increased variability in cognitive performance (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008) and with semantic memory deficits in a MCI sample (Gardini et al., 2015).

Increased reliance on visual stimuli to maintain function and communication (Bernstein & Grant, 2009; Grant & Seitz, 2000; Grant et al., 1998; Mishra et al., 2014) may result in cross-modal cortical reorganisation (Campbell & Sharma, 2014). Campbell and Sharma (2014) assessed visual evoked potentials (VEP) in mild-moderate acquired hearing loss adults and reported increased activation of ventral stream processing in auditory temporal regions (inferior, medial and superior temporal gyri). The ventral steam is implicated in facial processing (Nasr & Tootell, 2012) indicating recruitment of auditory cortical areas to aid speech perception (Campbell & Sharma, 2014). The N1 VEP latency was negatively correlated with both pure-tone thresholds and speech-in-noise perception, suggesting that loss of hearing function triggered this neural adaption.

Future randomised controlled trials (RCTs) should examine, along with cognitive benefits (Acar et al., 2011; Deal et al., 2015) if treatment of hearing loss impacts on task-related neural networks and attenuates neuroplastic changes. Minimising cognitive load and improving speech perception (Ives et al., 2014) may provide a key pathway for treatment of age-related cognitive decline through protecting reserve (Lin, Metter, et al., 2011).

3.4.3 Psychoneuroimmunological pathways

Psychosocial stress due to social difficulties and isolation associated with ARHL may cause neurodegeneration and cognitive decline through psychoneuroimmunological pathways which respond maladaptively to these stressors (Juster, McEwen, & Lupien, 2010; Lin, Ferrucci, et al., 2014; Reader et al., 2015). ARHL is associated with chronic stress (Hasson, Theorell, Wallen, Leineweber, & Canlon, 2011) possibly through multiple psychosocial stressors, including social-related frustration and emotional distress (Gopinath et al., 2012), loneliness (Weinstein & Ventry, 1982) or cognitive fatigue due to increased listening effort or cognitive load (Hornsby, 2013; McGarrigle et al., 2014). There is support for a mechanistic association because treatment of acquired hearing loss through assistive technology (Acar et al., 2011; Mosnier et al., 2015), education on communication (Hickson, Worrall, & Scarinci, 2007) and coping strategies (Garnefski & Kraaij, 2012) have been demonstrated to improve psychosocial outcomes in older adults with hearing loss. Factors such as depression (Wilson, Capuano, et al., 2014), loneliness (Wilson, Krueger, et al., 2007), stress and anxiety (Wilson, Begeny, et al., 2011) have been associated with cognitive decline independently of neuropathologic hallmarks of dementia. A recent meta-analysis of major depressive disorder studies reported that depression was associated with atrophy of the hippocampus and the amygdala (Schmaal et al., 2015). This suggests that these pathways and social factors contribute to clinical outcomes (Bennett et al., 2006).

Environmental stressors trigger a psychoneuroimmunological response, termed ‘allostasis’, the purpose of which is to maintain physiological stability or homeostasis by adapting to the environmental challenge (Juster et al., 2010; McEwen & Gianaros, 2011). Specifically, stressors trigger the hypothalamic-pituitary-adrenal (HPA) axis to release glucocorticoids (GCs) and the sympathetic-adrenal-medullary (SAM) axis to release catecholamines (epinephrine and norepinephrine) to alter physiological systems in the body and enable a fight-or-flight response (Ebner et al., 2014; Juster et al., 2010; McEwen & Gianaros, 2011; McEwen & Morrison, 2013). These pathways are particularly responsive to social factors (Wirth, 2015). These biomediators of the stress response interact with other factors such as genetic make-up and current psychological state to affect these physiological systems in a non-linear, dynamic and interactive way (McEwen & Gianaros, 2011). When stressors are chronic, the cumulative burden of homeostatic adaption to stress has a deteriorative effect on the body and the brain and leads to metabolic, cardiovascular and immunological dysfunction and decline - a state termed ‘allostatic load’ (Garrido, 2011; Juster et al., 2010).

GCs (primarily cortisol) are steroid hormones produced by the adrenal gland that alter cellular metabolic processes and suppress the immune system to meet the energetic demands of the behavioural response to the challenge (Garrido, 2011). GCs can pass through the blood-brain barrier (BBB) to cortisol receptors located in several sites including the hippocampus, amygdala and frontal lobe (Ebner et al., 2014; McEwen & Morrison, 2013; Wirth, 2015). These regions also

modulate HPA axis activity in response to GCs providing a feedback loop to regulate their levels (Ulrich-Lai & Herman, 2009). Disruption of this loop through excessive stress can cause disinhibition of the HPA axis, having a cascade effect and lead to increased brain ageing, the 'glucocorticoid cascade hypothesis' (Garrido, 2011; McEwen & Morrison, 2013). GCs have rapid effects on neuronal excitability and metabolism and consequently on cognitive and affective processes (Ebner et al., 2014; McEwen & Morrison, 2013; Wirth, 2015). They can induce neuroplastic changes (McEwen & Gianaros, 2011), and cause grey matter atrophy (Kremen et al., 2010; Lupien et al., 1998; MacLullich et al., 2006), and white matter hyperintensities (Cox et al., 2015). Hypercortisolemia is associated with decline in multiple cognitive functions including episodic memory (Lee et al., 2007; Li et al., 2006; Lupien et al., 1998; Pulopulos et al., 2014), processing speed (Franz et al., 2011; Lee et al., 2007) and executive functions (Franz et al., 2011; Lee et al., 2007; Pulopulos et al., 2014) in middle-aged to older adults. It is also associated with incident cognitive impairment (Karlamangla, Singer, Chodosh, McEwen, & Seeman, 2005) and increased rate of decline in MCI (Popp et al., 2015) and AD (Csernansky et al., 2006; Popp et al., 2015). Stress is possibly linked to the pathogenesis of AD (Catania et al., 2009; Dong & Csernansky, 2009; Green, Billings, Roozendaal, McGaugh, & LaFerla, 2006; Sotiropoulos et al., 2011; Wang et al., 2011). Stimulation of the HPA axis is mechanistically linked to production of amyloid-beta through secretion of corticotrophin releasing factor by the hypothalamus (Park et al., 2015). Stress may also accelerate the ageing process itself. Stress induced depression was associated with alterations in quantity of mtDNA and telomere length possibly due to altered metabolic function induced by GCs (Cai et al., 2015).

Repeated release of epinephrine and norepinephrine through the SAM axis can cause upregulation of pro-inflammatory genes through adrenergic receptors and granulocyte-macrophage colony-stimulating factor (GM-CSF) with subsequent production in the bone marrow of monocytes which are unresponsive to the regulatory action of GCs (Powell et al., 2013; Reader et al., 2015). Furthermore, neuronal activation in stress responsive brain regions is associated with microglial activation, possibly through the release of norepinephrine and subsequent activation of a signalling pathway associated with stress responses (Juster et al., 2010; Reader et al., 2015). This brain-region specific inflammatory response can lead to recruitment to these regions of monocytes from peripheral circulation contributing further to neuroinflammation (D'Mello et al., 2009; Reader et al., 2015). This state is a possible mechanistic pathway through which chronic stress leads to clinical depression and anxiety (Reader et al., 2015). ARHL is a significant risk factor for both (Bernabei et al., 2011; Li, Zhang, et al., 2014).

The nature, intensity and duration of the stressor can have differential effects on immunological function and can alter the inflammatory state (Reader et al., 2015). When the response is acute, cortisol has an immunosuppressive function through apoptotic action on immune cells to allow re-routing of metabolic resources to stress response functions (Barnes & Adcock, 2009; Reader et al.,

2015). With chronic and unremitting stress, cortisol can lead to immunosuppression and a reduced inflammatory state in the longer-term, increasing susceptibility to disease (Cohen et al., 2012). Conversely, chronic and intermittent stress can lead to a pro-inflammatory state of GC-insensitive immune cells (Barnes & Adcock, 2009; Chrousos et al., 1996). Perhaps the key stressor associated with hearing loss is loneliness independently of social isolation (Weinstein & Ventry, 1982). This specific trigger in the older adult population has been demonstrated to lead to multiple pathological outcomes (Hawkley & Capitanio, 2015). This includes upregulation of inflammatory genes and consequent pro-inflammatory state (Cole, Hawkley, Arevalo, & Cacioppo, 2011; Cole et al., 2007) and higher risk of dementia (Holwerda et al., 2014).

Interestingly, chronic stress and subsequent dysregulation of the HPA and SAM axes may provide an additional common aetiological cause of both ARHL and cognitive decline (Canlon, Theorell, & Hasson, 2013; Horner, 2003). Activation of the immune system subsequent to stress may rapidly lead to a pro-inflammatory state in the inner ear with consequent loss of hearing function (Horner, 2003). Cortisol may also affect hearing via steroid hormone receptors in the inner ear altering hearing function rapidly through non-genomic pathways or slowly through altering genetic expression (Horner, 2003). Chronic stress also leads to a higher risk of other pathophysiological conditions (including diabetes, hypertension and atherosclerosis) which are potential common causative factors for both ARHL and pathological cognitive ageing (Horner, 2003). Interventions which focus on cognitive coping and goal adjustment may modify symptoms of depression and anxiety in people with acquired hearing loss (Garnefski & Kraaij, 2012) and may provide an additional avenue for treatment along with assistive devices.

3.5 Conclusions

The systemic effects of age-associated pathophysiologies such as atherosclerosis, inflammation and oxidative stress and the vulnerability of the cochlea and brain to their effects provides strong support for a common cause hypothesis (Lindenberger & Baltes, 1994). Statistical analysis of epidemiological data has offered strong evidence that the observed relationship between ARHL and cognitive function has a common aetiological origin (Wayne & Johnsrude, 2015). They may be linked as part of a frailty syndrome (Panza, Solfrizzi, & Logroscino, 2015). ARHL has been linked with multiple indicators of functional decline and is a biomarker for frailty syndrome which has been causally linked to dementia (Panza, Solfrizzi, & Logroscino, 2015; Panza, Solfrizzi, Seripa, et al., 2015). However, several epidemiological studies have found significant correlation between ARHL and pathological cognitive ageing independent of possible aetiological factors such as vascular dysfunction (Deal et al., 2015; Lin, Metter, et al., 2011; Lin et al., 2013). In the meta-analysis (reported in Chapter 2), the pooled effect size of studies controlling for VRFs remained significant, suggesting other contributing factors. Furthermore, findings of alterations in neural activation and structure in hearing loss samples suggest that hearing loss can contribute directly to neurocognitive changes (Campbell & Sharma, 2013, 2014; Husain et al., 2014; Peelle et al., 2011).

This suggests that ARHL also has a mechanistic association with cognitive function and thus contributes to cognitive ageing. Most likely, the relationship underpinning ARHL and cognitive function is multifactorial.

Currently, there are no pharmaceutical options available to treat the aetiological causes of ARHL (Yamasoba et al., 2013) or dementias such as AD (Feldman et al., 2014; Folch et al., 2015; Karran et al., 2011; Thies & Bleiler, 2013). Epidemiological and experimental studies have found attenuation of cognitive decline with use of hearing aids (Acar et al., 2011; Deal et al., 2015) although others have found no such benefit (Lin, Ferrucci, et al., 2011; Lin et al., 2013). Treatment with hearing aids is a rehabilitative process requiring follow-up and adherence (Barker, Mackenzie, Elliott, Jones, & de Lusignan, 2014). Older adults may be reluctant to use hearings aids due to expense, social stigma or rehabilitative effort (McCormack & Fortnum, 2013). Additionally, the complex effects of ARHL on functioning, including cognition and depression, suggest that it may impact individuals differently and therefore may require different treatment strategies. Key areas for future research include the RCTs to test the efficacy of different treatment strategies (Lin & Albert, 2014). These strategies may range from treatment with hearing aids to psychosocial interventions for depression, anxiety or impaired social function which may accompany hearing loss. Additionally, intervention studies which explore approaches to encourage participants in the community-dwelling population to adhere to hearing aid use would be useful. Furthermore, additional studies which explore the benefits of later clinical intervention through hearing aid use for improved cognitive and psychosocial outcomes in those with cognitive impairment and dementia would be informative.

Chapter 4 Methods

4.1 Introduction

The purpose of this thesis was to examine the association of age-related hearing loss (ARHL) with cognitive ageing with a view to explicating the possible causal basis for this association. This chapter gives an overview of the theoretical framework for the thesis, research issues, the methods used to conduct testing and the aims of the thesis. The reviews reported in Chapters 2 and 3 indicated support for a mechanistic association. Therefore, it was decided to examine possible neuropsychological markers indicating a mechanistic pathway through which hearing loss causes cognitive decline.

4.2 NIEAD model: a hypothetical framework

Previous research has suggested a small but consistent link between ARHL and cognitive decline, cognitive impairment and dementia (Lin, Ferrucci, et al., 2014; Lin, Ferrucci, et al., 2011; Lin, Metter, et al., 2011; Lin et al., 2013) , a finding support by the meta-analysis reported in Chapter 2. The underlying aetiological basis for this association is uncertain. As reviewed in Chapter 3, the association is most likely due to multi-causal factors. However, there is consistent support from behavioural and neuro-imaging studies for a mechanistic basis linking ARHL with cognitive decline. Based on the previous review work, a hypothetical model termed Neurocognitive Implicit-Explicit Asymmetric Decline (NIEAD) is posited and outlined here. This model describes a hypothetical mechanistic pathway whereby ARHL causes cognitive decline through decline in implicit, semi-automatic processes but maintained explicit, executive functioning.

Following hearing loss, there is decreased activation of neural regions in subcortical structures (Daulatzai, 2016) and the primary auditory cortex and increased activation of attentional resources to compensate to promote perception of auditory input through various mechanisms (Campbell & Sharma, 2013; Peelle et al., 2011; Peelle & Wingfield, 2016; Ronnberg et al., 2013). This may cause decline in implicit cognitive processes through two main complementary pathways.

Firstly, loss of sensory stimulation may lead to less activation of neural regions, including the locus coeruleus and basal forebrain and may disrupt production of neurotransmitters such as dopamine and acetylcholine (Daulatzai, 2016). Disruption in these processes, particularly dopamine production, may contribute to a poorer neural signal-to-noise ratio impacting cognitive function (Backman et al., 2006; Li et al., 2001). Interestingly, altered dopamine neurotransmission can have dissociable effects depending on the brain region involved (Cools, Miyakawa, Sheridan, & D'Esposito, 2010) supporting theoretical models that make a distinction between implicit and explicit cognitive processes. In frontal cortex regions, dopamine can modulate executive cognitive processes and in striatal structures it can modulate implicit learning and information integration (Cools & M., 2010; Cools et al., 2010; Milton & Pothos, 2011). As there is a reallocation of

cortical resources to support executive processes (Campbell & Sharma, 2013), these functions may be preferentially maintained (Ronnberg et al., 2013).

Secondly, reallocation of cognitive resources to demanding tasks draws resources from implicit, automatic neurocognitive processes and suppresses them, even when they are beneficial to task completion (Stock, Steenbergen, Colzato, & Beste, 2016). Higher auditory working memory load impairs visual ventral stream processing and causes a reduction in processing of task-irrelevant stimuli (Klemen, Buchel, Buhler, Menz, & Rose, 2010). Working memory load can lead to decreased pre-cortical processing of task-irrelevant stimuli, even in other modalities, and subsequently increased cross-modal connectivity to support to brain regions processing primary tasks when attentional resources are challenged (Regenbogen et al., 2012). Increased explicit processing may directly interfere with implicit processing such as encoding of stimuli, apart from the integrity of the stimuli (Cousins, Dar, Wingfield, & Miller, 2014). When attentional resources are limited (Tun et al., 2009), prolonged reliance on these resources to support perceptual function may have costs for implicit cognitive processes through neuroplastic adjustment. Certain implicit processes which may be normally maintained through functional reorganisation of relevant neural regions with age (Logie et al., 2015; Stern, 2009, 2012) may decline due to reallocation of cognitive reserve to maintain auditory perception. This would suggest a possible mechanism through which hearing loss affects cognitive decline through a cascade effect. Subsequent to hearing loss, executive processes compensate not just for diminished auditory input but also for decline in implicit processes, contributing to further disruption in implicit processing, thereby creating a vicious cycle.

Theory development in cognitive psychology has often outlined binary cognitive processes or a distinction between implicit and explicit processes (Wingfield et al., 2015). The cognitive neuroimaging literature supports a differentiation between explicit and implicit cognitive processes in learning and memory and has described dissociable neural correlates of both (Ramponi, Barnard, Kherif, & Henson, 2011; Yang & Li, 2012). Such a distinction has been described under challenging listening conditions in the Ease of Language Understanding (ELU) model (Ronnberg et al., 2013). This model describes how, when implicit speech processing is disrupted due to degraded auditory input, there is increased reliance on explicit processes to perceive speech. It was predicted by the ELU that there would be maintained executive function but decline in long-term episodic and semantic memory systems due to lack of recruitment in speech processes and a disuse effect (Ronnberg et al., 2011; Ronnberg et al., 2014). The NIEAD model posits that decline in implicit function occurs prior to decline in the main cognitive domains including memory systems and that this is the pathway through which ARHL affects this decline. Additionally, it posits that decline occurs not through a disuse effect but through direct lack of stimulation and compensatory efforts by explicit functions which suppress automated cognitive processing of stimuli (Klemen et al., 2010; Regenbogen et al., 2012).

As decline in implicit processes may be compensated for by maintained executive functions, this would suggest that on standard tests of cognitive domains there would be a small but consistent association between ARHL and cognitive decline (Lin et al., 2013). As ARHL progresses and with further decline in implicit cognitive processes, the cumulative burden over time would become more apparent in main cognitive domains. However, tests assessing implicit function would be sensitive to such decline and could identify it prior to any tests of main cognitive domains such as executive function, episodic memory or lexico-semantic processing tests which recruit both implicit and explicit processes. Furthermore, as decline occurs through both loss of sensory stimulation to polysensory neural structures and suppression of automated processes by executive function, this effect will be observed independent of test modality.

This explicit-implicit asymmetry in decline is in contradiction to other models of cognitive ageing which typically posit cognitive decline as being mediated by a global decline such as a general slowing (Albinet, Boucard, Bouquet, & Audiffren, 2012; Salthouse, 1996) or a specific decline in executive resources (Albinet et al., 2012; Buckner, 2004; Salthouse et al., 2003). Conversely, it complements theories of cognitive ageing which describe compensatory efforts by executive resources for decline in posterior regions (Grady et al., 1994), decreased hemispheric lateralisation (Cabeza, 2002) or neuropathology (Stern, 2012). If ARHL contributes to cognitive ageing through a decline in implicit processes, it may account for some variance in findings between these models, particularly given the wide prevalence of ARHL (World Health Organisation, 2015).

To the best of the author's knowledge, this is the first model outlining implicit and explicit function with ARHL. This hypothetical model represents a synthesis of epidemiological findings of the association between hearing loss and cognitive decline (Lin, Ferrucci, et al., 2014; Lin, Ferrucci, et al., 2011; Lin, Metter, et al., 2011; Lin et al., 2013), research on speech function under challenging listening conditions (Peelle & Wingfield, 2016; Ronnberg et al., 2013) and theories of cognitive ageing (Dennis & Cabeza, 2011; Reuter-Lorenz & Park, 2010). As such, this model is complementary to these previous research paradigmatic approaches. This thesis aimed to explore cognitive decline in a sample with probable ARHL using this model as a hypothetical framework to inform analysis. Specifically, three studies were designed with the *a priori* hypothesis that hearing loss would be associated with decline in implicit, semi-automatic cognitive functions but maintained explicit executive processes. In the three studies, a hearing loss group was compared to a control group on markers of implicit and explicit function. These three studies are reported in Chapters 5, 6 and 7.

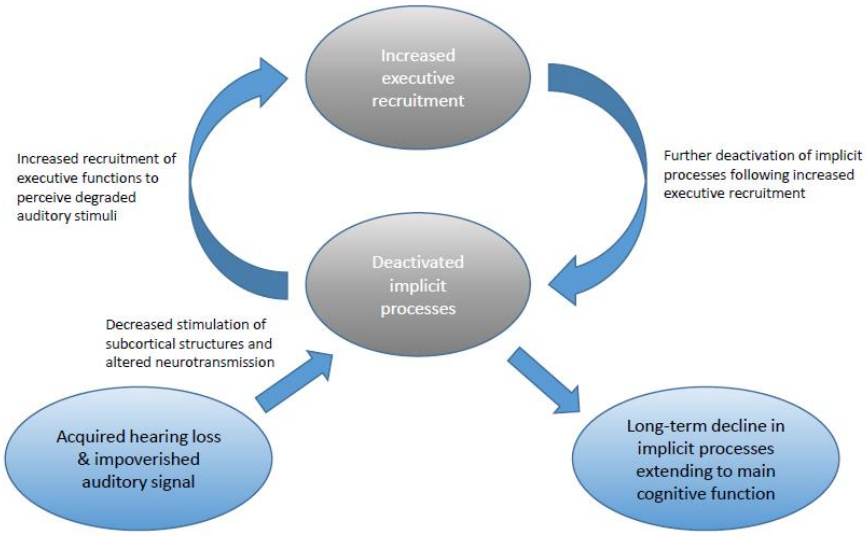

Figure 4.1: The NIEAD model.

4.3 Methodological considerations

The primary methodological issue in this thesis was to select tests to assess age-related cognitive changes as commonly reported in the literature but that would also be appropriate for use with a sample of older adults with hearing loss. In the literature, there are concerns that poorer performance on batteries of cognitive tests in ARHL samples may be due to poorer perceptual acuity and increased mental effort to perceive auditory stimuli rather than any impairment in cognitive function. Tests were based on the battery from the NEIL MRU (Neuro Enhancement for Independent Lives Memory Resaerch Unit) and TILDA (The Irish Longitudinal Study on Ageing) studies. Several tests from this battery using auditory stimuli were replaced with other tests using non-auditory stimuli which are more appropriate for a hearing loss sample. The only exception was the MoCA. This was retained as there were no other adequate tests of general cognitive function or cognitive impairment screening instruments that did not use auditory stimuli. The normal score and a score that adjusted for auditory items were calculated (discussed further below). According to the author's hypothesis, the effects of ARHL on cognitive function should generalise across modality. In other words, the pattern of decline should be observed in visual based tests of cognitive function.

Construct validity of neuropsychological tests is open to question. These tests are not process pure measures but rather are tests of different cognitive processes which may overlap to varying degrees. For example, a test of executive function may assess a multitude of executive processes such as inhibition, updating, task-switching, etc. Similarly, sub-optimal performance on a test of episodic memory may reflect difficulties with either storage or retrieval processes. Furthermore, performance on a test may represent interactions between multiple domains such as executive function and processing speed and both executive and non-executive processes. Each neuropsychological test selected will be discussed below.

There are multiple factors that may affect performance on neuropsychological tests, including but not limited to health factors, demographic factors or bias due to the presence in samples of individuals with cognitive impairment. To control and account for these factors, several approaches were taken. Inclusion/exclusion criteria were applied using a health screen measure. This screening (described below) was designed to exclude those with health factors that may confound results. Additionally, following completion of the testing phase, groups were matched for age, gender and pre-morbid IQ to ensure a representative comparative control group. As there were concerns that using screening tools such as the MoCA would lead to a biased assessment of global cognitive function, a screening criterion based on the global cognitive function z-score was used instead. While an adjusted MoCA score was calculated, adaption of screening tools such as the MoCA through deleting auditory items have a negative impact on the psychometric properties of the test (Pye, Charalambous, Leroi, Thodi, & Dawes, 2017). Z-scores from tests that assessed the same domain were combined into a single score. These domain scores were further collapsed to give a score for general cognitive function. Any participant included in the analytic sample (after matching) who was found to have a score <-1.5 SD on this outcome was subsequently excluded. Additionally, an extensive background questionnaire assessing a range of factors was administered to assess for differences between groups in factors that might affect performance.

Pure-tone audiometry was selected as the measure of hearing loss. No issues were foreseen with this measure in terms of confound between accurate assessment of hearing and poor cognitive function. It requires the participant to depress a button on a hand-held device in response to an auditory stimulus. This measure of peripheral hearing acuity does not require significant higher auditory cortical processing (Pickles, 2008). AD substrate has been found in the auditory neural regions but not in the peripheral auditory structures (Sinha et al., 1993). Additionally, this assessment has been conducted reliably with older adults in the early stages of dementia (Uhlmann, Larson, Rees, Koepsell, & Duckert, 1989). Furthermore, all audiometric testing for this study was conducted by experienced audiologists.

4.4 Participants

4.4.1 Recruitment

Participants for the main study ‘Hearing ability, Cognitive Function and Lifestyle in Older Adults’ were recruited from multiple organisations and communities including Active Retirement Ireland, Age Action Ireland, DeafHear, the Irish Countrywomen's Association and from local parishes and community groups throughout Ireland. Recruitment began in October 2015 and testing was conducted between January 2016 and January 2017. Advertisements seeking volunteers aged 50 years of age or over were placed in newsletters of these organisations and on local noticeboards.

Recruitment for a sub-study assessing temporary memory binding is reported in Chapter 7. Participants for this sub-study were recruited from the sample of participants who had taken part in

the main study ‘Hearing ability, Cognitive Function and Lifestyle in Older Adults’ and had completed all the assessments for this study. Recruitment for this study began in October 2016 and testing began October 2016 and was completed January 2017.

4.4.2 Screening and inclusion/exclusion criteria

The exclusion/inclusion criteria for the main study were adapted from the criteria used in the NEIL MRU and from the Christensen, Moye, Armson, and Kern (1992) Health Screening Questionnaire (Appendix B). Participants who had previously taken part in the NEIL MRU or TILDA studies were excluded to avoid practice effects due to overlap in testing batteries. Others excluded were:

- anyone with a history of brain injury or illness that caused a permanent decrease in cognitive or mental functions or who had been diagnosed as having a brain tumour;
- anyone with epilepsy, stroke, or neurological conditions (e.g. Parkinson’s disease, multiple sclerosis, cerebral palsy, or Huntington's disease);
- anyone who had a history of drug/medication/alcohol abuse;
- anyone who had been hospitalised for mental or emotional problems in the previous five years or who was taking certain medications for a psychiatric condition;
- anyone with an injury, swelling, inflammation or pain in the hands or wrists;
- anyone who reported congenital or pre-lingual hearing loss, or hearing loss due to injury or disease.

The health screening questionnaire included questions on factors such as visual impairment, diabetes, hypertension and history of dementia among immediate biological relatives (Appendix B). Participants were not excluded based on these factors.

4.4.3 Study process

Please see Figure 4.2 for a timeline of the study process from recruitment to analysis. A total of 244 people expressed an interest in taking part in the main study ‘Hearing ability, Cognitive Function and Lifestyle in Older Adults.’ Sixty-five discontinued contact after being sent an information pack informing them of the study or withdrew subsequently. Fifty-five were excluded based on the above criteria. Of the 124 invited for testing, two withdrew during testing due to time constraints or discomfort. One was unavailable for audiological assessment. Nine did not return questionnaires. Four of these could not complete all measures during assessment and their data was withdrawn. One participant was excluded due to being a native Irish speaker and six were excluded due to revealing a hearing loss as a result of disease, medication or injury. Therefore, 101 participants were left that had completed all of the assessments. Fifty of these participants met the WHO criteria for hearing loss (see WHO criteria in section 4.5.2.3) and the remaining 51 participants were below this threshold and were designated as controls.

The demographic data for this sample are listed in Table 4.1. The hearing loss group was older whereas the control group had a higher proportion of females. This may reflect different

recruitment strategies (general public versus audiometric clinic). Alternatively, in the case of age, it may be due a higher prevalence of hearing loss in older samples (Lin, Niparko, et al., 2011) and among males (Lin, Thorpe, et al., 2011).

Table 4.1: Demographic data for the 101 participants prior to matching

	Hearing loss *M (SD)*	**Control** *M (SD)*	**Total sample** *M (SD)*
Demographic			
N	50	51	101
Age	74.84 (7.86)	64.84 (7.43)	69.79 (9.12)
Gender (*female/male)*	28/22	39/12	67/34
Education *(years)*	13.05 (3.71)	14.13 (3.02)	13.59 (3.40)
Education *(level)*	2.68 (0.89)	2.94 (0.79)	2.81 (0.85)

Participants with hearing loss were matched with controls for age (within five years), gender and pre-morbid IQ (within 0.5 SDs/7.5 IQ points). Where more than three matches for a participant were found using this criteria, the criteria were narrowed first by age and then by pre-morbid IQ until there were three or fewer matches. This left 33 hearing loss participants matched with 34 control participants. Matching of the two groups was conducted and completed prior to any statistical analysis of the data. Due to insufficient data to extract implicit and explicit indices, one hearing loss participant was removed from the sample in Study 1 (reported in Chapter 5). For the same reason, one control and one hearing loss participant (a different participant to the one removed from Study 1) were removed from the sample in Study 2 (reported in Chapter 6).

This left 32 hearing loss participants and 34 controls in Study 1 and 32 hearing loss participants and 33 controls in Study 2. The study process for the temporary memory binding sub-study (Study 3) is reported in full in Chapter 7. The participants for this sub-study were recruited from the sample of 101 participants that had completed the main study 'Hearing ability, Cognitive Function and Lifestyle in Older Adults.' No participants were removed from any of the three study samples on the basis of their general cognitive function Z-score. Ethical approval was given by the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin for both the main study and the sub-study. All participants gave written informed consent (Appendices D and G) before participating in both the main study and the sub-study.

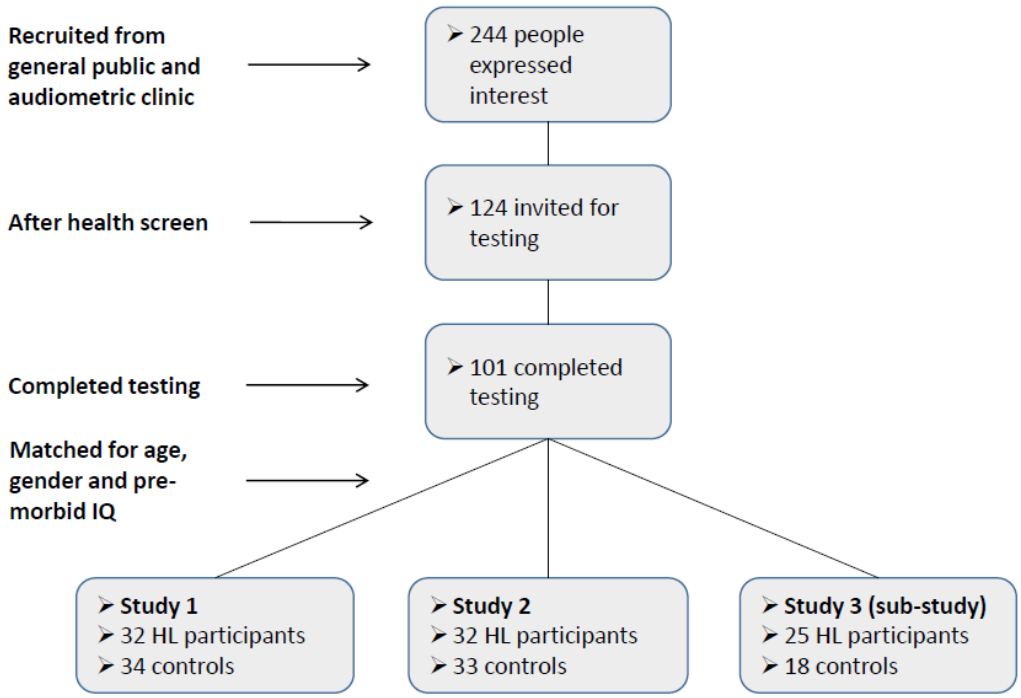

Figure 4.2: Timeline of study process

4.5 .Assessment

The study assessment consisted of a background assessment covering various demographic, clinical, health and psychosocial factors. These were selected based on the test battery from the NEIL MRU and TILDA studies.

4.5.1 Background assessment

4.5.1.1 Demographic factors

Participants were given a questionnaire assessing relevant sociodemographic data including: age, gender, education (both years and highest attainment) and marital status. Educational attainment was assessed according to a scale of eight different possible levels of attainment which were categorised as four levels where level 1 = primary, level 2 = secondary, level 3 = third level/undergraduate and level 4 = fourth level/post graduate. Marital status was assessed according to different possible relationship statuses and participants were categorised as either having a partner or not.

4.5.1.2 Health factors

Self-rated physical health and mental and emotional health were assessed using five point self-report questions from TILDA where 1 = poor, 2 = fair, 3 = good, 4 = very good and 5 = excellent. Participants were asked whether they consumed alcohol or not and how many units they consumed on average per week. They were also asked if they smoked or were former smokers. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman,

& Kupfer, 1989). This test has 19 questions which give seven component scores that are added to yield a global score ranging from 0-21, where 0 indicates no sleep difficulties and 21 indicates great sleep difficulties.

4.5.1.3 Clinical factors

Pre-morbid IQ was assessed using the National Adult Reading Test (NART) (Nelson, 1982). The NART is a widely used test that contains a list of words presented visually which the participant is asked to read and say out loud. It contains fifty words which become progressively more difficult to pronounce. The participant's score is based on the number of words pronounced correctly and is used to estimate their IQ. This test was administered as part of the main neuropsychological battery. As reading is an overlearned skill, it is thought that previous familiarity with words may index intelligence prior to any decline in other cognitive functions (Nelson & McKenna, 1975). This test has previously used with an ARHL population and no significant difference was found in performance compared to those without hearing loss (Lin, Ferrucci, et al., 2011).

Participants were asked to rate their memory using a TILDA test item with the same answer scale as for the physical, and mental and emotional health items. Frailty was assessed using the Survey of Health, Ageing and Retirement in Europe (SHARE) Frailty Instrument (Romero-Ortuno, Walsh, Lawlor, & Kenny, 2010). This instrument calculates a frailty score based on responses to questions and handgrip strength. The questions were administered as part of the questionnaire and consisted of items assessing exhaustion, weight loss, slowness and low physical activity. Handgrip strength, a biomarker of cognitive decline (Fritz, McCarthy, & Adamo, 2017), was assessed using a grip strength dynamometer administered during the neuropsychological assessment.

Depression was assessed using the Center for Epidemiologic Studies Depression Scale – 10 item (CESD-10) (Radloff, 1977). The scores range from 0 to 30 where 0 reflects better mood and 30 reflects more depressed mood. Anxiety was assessed using the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) (Zigmond & Snaith, 1983). This contains seven items with a sum score ranging from 0 to 21, where 0 means no distress and 21 means great distress. Apathy was assessed using the Apathy Evaluation Scale – Self-rated (AES-S) (Marin, Biedrzycki, & Firinciogullari, 1991). This instrument contains 18 items with a range of 18-72, where higher scores indicate greater apathy.

4.5.1.4 Psychosocial factors

Several background psychosocial factors were assessed in the questionnaire. Social network was assessed using the Lubben Social Network Scale (LSNS) (Lubben et al., 2006). This contains six items, with scores ranging from 0 to 30, where higher scores indicate greater social connectivity. Loneliness was assessed using the six-item De Jong Gierveld Loneliness Scale (De Jong Gierveld & Van Tilburg, 2006). Scores on this six-item measure range from 0 to 11, where higher scores indicate greater loneliness. Boredom proneness was assessed with a single self-report question with

a four-point scale (Conroy, Golden, Jeffares, O'Neill, & McGee, 2010) where higher scores indicate greater boredom. Perceived stress was assessed using the Perceived Stress Scale-4 item (PSS-4) (Cohen, Kamarck, & Mermelstein, 1983). Scores on this four-item questionnaire range from 0 to 16, where higher scores indicate greater stress.

4.5.2 Hearing loss assessment

4.5.2.1 Self-reported hearing loss and background

The Hearing Handicap Inventory for the Elderly Screening Version (HHIE-S) (Ventry & Weinstein, 1983) is a ten-item questionnaire used to assess perceived emotional and social difficulties in activities of daily function due to hearing loss. Scores range from 0 to 40. During the neuropsychological assessment, a questionnaire assessing the participant's background audiological factors was administered along with the HHIE-S (Appendix E – does not include HHIE-S). This questionnaire assessed factors such as when participants first noticed hearing loss, use of hearing aids, whether or not they experienced tinnitus and whether or not any family members had hearing loss. These factors were measured in case of future interest of examining the link between them and cognitive outcomes. In the empirical chapters of this thesis, the number of participants with tinnitus and the number of participants using hearing aids are identified as it has been reported previously that these factors may have implications for neurocognitive outcomes (Acar et al., 2011; Husain, Medina, et al., 2011).

4.5.2.2 Audiometric assessment

Pure-tone air conduction audiometry was selected as the measure of hearing loss on the basis that it is considered to be the criterion standard of peripheral hearing loss. All audiometric testing was conducted during the study time frame. Prior to testing, participants' ears were checked by otoscope for wax, infection, perforations or any other abnormalities and participants were asked a series of questions to collect information on their background. Air conduction thresholds in each ear were obtained with calibrated audiometers, (Grayson Sadler GSI 61 or Interacoustics Callisto) and TDH 39 supra-aural earphones (Telephonics, Huntington, New York). Audiometers were calibrated once a year. Audiometric testing followed guidelines based on the British Society of Audiology Guidelines (BSA, 2011) and was completed in a sound-attenuating booth meeting ANSI (American National Standards Institute) standards.

Pure-tone air conduction audiometry was conducted starting with the participant's perceived better hearing ear. Thresholds were measured in decibels (dB) hearing level. Measurement began at 0.5 kHz and 40/50 dB descending by 10 dB incrementally until the signal could no longer be heard, and then increasing and decreasing by 5 dB steps until a threshold was established. If the signal could not be heard at 50 dB, volume was increased by 10 dB steps until detected. This procedure was repeated for each frequency in turn, in order of pitch, up to 8 kHz. Frequencies 0.5, 1, 2, 3, 4,

and 8 kHz were tested. All testing was conducted by qualified audiologists who are registered with ISHAA (Irish Society of Hearing Aid Audiologists).

4.5.2.3 Criteria for audiometric hearing loss

The WHO (World Health Organisation) guidelines for calculating pure-tone average (PTA) hearing loss were followed (PTA of frequencies 0.5, 1, 2 & 4 kHz in the better ear). PTA was also calculated at these frequencies for the worse ear. The PTA for both ears was also calculated at low frequencies (0.25, 0.5 & 1 kHz) (Frederiksen et al., 2014) and at high frequencies (3, 4, & 6 kHz) (Agrawal et al., 2008) to provide an estimate of low and high frequency loss. Following WHO guidelines, participants with a hearing loss ≥26 dB at frequencies 0.5, 1, 2 & 4 kHz in the better ear were allocated to the hearing loss group. Participants below this threshold were allocated to the control group.

4.5.3 Neuropsychological assessment

A neuropsychological battery assessing several broad domains of cognition was used. A combination of computerised and pen-and-paper tests was used. Tests were based on the test battery from the NEIL MRU and TILDA. Several tests from this battery using auditory stimuli were replaced with tests using visual stimuli which are more appropriate for a hearing loss sample. Multiple tests were used for the episodic memory and executive function domains as these domains were of specific interest. Prior to beginning the cognitive assessment, participants were administered the Stanford Sleepiness Scale in order to assess current alertness. The temporary memory binding test, administered in a sub-study, will be described in Chapter 7.

4.5.3.1 Episodic memory

To assess episodic memory, the Free and Cued Selective Reminding Test (FCSRT) (Grober, Buschke, Crystal, Bang, & Dresner, 1988) and the Wechsler Memory Scale-III (WMS-III) spatial span forward subset (Wechsler, 1997) were used.

4.5.3.1.1 FCSRT

The Free and Cued Selective Reminding Test (FCSRT) was used to assess immediate and delayed recall. It uses a different paradigm to other tests of episodic memory by asking the subject to identify each of the words to be remembered by pointing and reading aloud in response to its semantic category. This controls for attention during the encoding phase and thus any confound in attention deficits or initiation of memory strategies due to ageing (Buckner, 2004). The semantic categories are then used during the recall phase to differentiate between poorer performances due to impaired retrieval processes compared to impaired encoding processes (Lemos, Simoes, Santiago, & Santana, 2014). The FCSRT is often used in clinical settings due to its efficacy in differentiating between MCI subgroups, predicting the conversion from MCI to AD and differentiating AD patients from individuals affected by other forms of dementia (Bastin & Salmon, 2014; Carlesimo, Perri, & Caltagirone, 2011; Derby et al., 2013; Dubois et al., 2007; Lemos et al., 2014). It has been

associated with hippocampal volume (Sanchez-Benavides et al., 2010; Sarazin et al., 2010), parahippocampal glucose metabolism (Lekeu et al., 2003) and with biomarkers for AD in cerebrospinal fluid (Rami et al., 2011; Wagner et al., 2012). It has demonstrated good reliability and validity (Grober, Ocepek-Welikson, & Teresi, 2009; Lemos et al., 2014).

In the FCSRT test, there are 16 items in total. The subject is prompted to recall each item by category in an immediate recall phase. The subject is then asked to recall each item from memory within two minutes. Any items not recalled during this 'free recall' phase are prompted using the category cue for that item. This procedure is conducted three times in total. Prior to each trial, the participant is asked to count back from a number by three seconds as an interference. The participant is then asked to recall the items 30 minutes later in a delayed recall phase. As with the immediate recall phase, any items not recalled are prompted using the category cue. The scores used for this study were the immediate and delayed free recall scores. The total possible score is 48 for the immediate recall phase (the sum of the scores for three free recall trials) and 16 for the delayed recall phase. Several cognitive tests were administered in between the immediate and delayed recall phases, none of which involved memory or any items similar to those used in the FCSRT. The same form of the FCSRT was administered to all participants.

4.5.3.1.2 WMS-III spatial span forward subset

The Wechsler Memory Scale-III (WMS-III) spatial span forward subset was used to assess individual capacity to temporarily store information in working memory. It has good reliability (see Lezak, 2004 for a discussion of the WMS-III and its psychometric properties). The forward subset of the WMS-III spatial span and other similar tests has been demonstrated to differentiate dementia (including AD) patients from healthy counterparts (Carlesimo, Fadda, Lorusso, & Caltagirone, 1994; Foxe et al., 2016; Huntley & Howard, 2010). While typically used to assess working memory, the forward and back subsets are thought to correspond to dissociable components of temporary storage of information and manipulation of this information in accordance with models of working memory (Baddeley, 1986; Baddeley, 2000). This is supported by neuro-imaging evidence which reports both components as relying on posterior parietal regions and prefrontal systems with greater reliance on prefrontal regions as manipulation is required (Foxe et al., 2016; Owen et al., 1999; Smith & Jonides, 1997; Toepper et al., 2010). For this reason, the forward subset was allocated to the episodic memory domain and the backward subset was allocated to the executive function domain. Performance on the forward subset has been related to thinning in the bilateral precentral sulcus and parieto-occipital thinning in AD patients (Foxe et al., 2016). The examiner taps a sequence of cubes and the participant is instructed to tap the same cubes in the same order. The first item consists of two cubes and the last item consists of nine cubes. There are two trials per item. The test is discontinued when the participant fails to accurately recall both trials of one item. One point is allocated for every trial accurately completed with a total possible score of 16.

4.5.3.2 Executive function

To assess executive function, the Visual Reasoning subtest of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) battery (Roth et al., 1986), Sustained Attention to Response task (SART) (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997), semantic (animals) fluency (Vaughan, Coen, Kenny, & Lawlor, 2016), the phonological fluency test from the MoCA (Montreal Cognitive Assessment) (Nasreddine et al., 2005) and the WMS-III spatial span backward subset were used (Wechsler, 1997).

4.5.3.2.1 CAMDEX Visual Reasoning

The Visual Reasoning test is a subtest from the Cambridge Cognitive Examination (CAMCOG) which is the objective test portion of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX). The CAMCOG has a high test-retest reliability in Alzheimer patients and healthy controls (Lindeboom, Ter Horst, Hooyer, Dinkgreve, & Jonker, 1993). It requires the participant to view a grid of four boxes, one of which is empty and to select one coloured shape from six which best completes the visual pattern. There were six trials and one point was awarded for each correct answer.

4.5.3.2.2 SART

The Sustained Attention to Response (fixed) task (SART) is a measure of executive control of behaviour. It has good validity and reliability (Manly et al., 2003; Robertson et al., 1997). The SART was administered on a computer screen. Participants were shown a sequence of numbers from 1 to 9 and were instructed to press a computer key in response to every number except 3. Each digit appeared for 300 milliseconds (ms), with an interval of 800 ms before the next digit appeared. The cycle of digits, 1 to 9, was repeated 23 times, giving a total of 207 trials. There are two versions of this task: the $SART_{fixed}$ and the $SART_{random}$. In the 'fixed' version, numbers are presented sequentially. In the 'random' version, numbers are presented at random. For this thesis, the $SART_{fixed}$ was used because this is the version used in the TILDA and NEIL MRU batteries. Outliers were defined as response times that were more than three standard deviations outside the participant's mean reaction time and were removed. The outcome scores of interest were the number of commission errors (pressing the key in response to the digit 3) and the number of omission errors (not pressing the key in response to digits 1, 2, 4-9). A total number of 184 omission errors and 23 commission errors were possible.

4.5.3.2.3 Semantic and phonological fluency

Two tests of verbal fluency were used to assess executive function; the phonological and semantic fluency tasks (Crawford, Bryan, Luszcz, Obonsawin, & Stewart, 2000; Crawford & Henry, 2005; Salthouse et al., 2003). Results from neuroanatomical and neuroimaging studies suggest that semantic fluency tasks are modulated more by the temporal lobe whereas the phonological fluency task is modulated by the frontal lobe (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Birn et al., 2010; Henry & Crawford, 2004b). Performance on fluency tasks have also been related to

structural and functional changes in AD patients (Rodriguez-Aranda et al., 2016). Fluency tasks have demonstrated good reliability (Ruff, Light, Parker, & Levin, 1996). The semantic fluency test requires the participants to name as many animals as they can in under a minute. The phonological fluency test from the MoCA uses a similar paradigm with participants instructed to say as many words beginning with the letter 'f' as they can in under a minute. Participants are told that they can say any kind of word except for people's names, places or numbers. Both fluency tasks were recorded using audio recorders and transcribed.

4.5.3.2.4 WMS-III spatial span backward subset

The WMS-III spatial span backward subset (Wechsler, 1997) assesses working memory and was administered in the same fashion as the spatial span forward with the exception that the participant was asked to tap the cubes in the backward order in which the test administrator tapped them. As with the forward subset, the backward subset has differentiated dementia groups from healthy controls (Carlesimo et al., 1994; Foxe et al., 2016; Huntley & Howard, 2010). This subset is supported by both posterior parietal regions and prefrontal systems with greater reliance on prefrontal regions as task demand increases (Foxe et al., 2016; Owen et al., 1999; Smith & Jonides, 1997; Toepper et al., 2010).

4.5.3.3 Processing speed

Processing speed was assessed using a computer based choice reaction time test (CRT) (Brennan, 2011) and the mean response time (RT) from the SART (Robertson et al., 1997). The CRT is a two-choice response task which provides a pure measure of processing speed in the elderly compared to other measures of processing speed (Albinet et al., 2012).

For the CRT, a customised Ergodex keyboard was attached to the computer and placed in front of the participant. There were four buttons on this board. One button, on the top right corner, was for administrative use only. Another button was in the lower, middle part of the board and had a 'START' logo written underneath. There were two other buttons in the upper middle part of the keyboard above the 'START' button that were spaced apart from each other. The words 'YES' (button on left-hand side) and 'NO' (button on the right-hand side) were written underneath. The participant was instructed to hold down the START button on the keyboard and wait for a stimulus to appear ('YES' or 'NO') on the computer screen. The participant was instructed to then press the corresponding button (using the same finger) as fast as they could following appearance of the stimulus i.e. to press 'YES' if YES appeared and 'NO' if NO appeared. They were then instructed to return their finger to the initial position of holding down the 'START' button. As a safeguard against pre-emptive responding, target offset cannot be achieved if the 'START' key is released before the target appears on screen. The task consists of 100 trials with an equal number of 'NO' and 'YES' trials presented in random order.

The CRT is a self-paced task. The next trial did not begin until the participant returned to depressing the 'START' button. It provides a measure of two components: a cognitive component, which is a measure of the time to perceive the stimulus and make a decision to initiate a response and a motor component which is a measure of the time to execute the response (Roberts & Pallier, 2001). The cognitive component was a measure of the time from stimulus onset to releasing the 'START' button. The motor component was a measure of the time from releasing the 'START' button to depressing the corresponding stimulus button. The SART mean RT was the mean time (ms) for response on all go-trials (1, 2, 4-9).

Age-related cognitive slowing is thought to be mediated by decline in white matter integrity (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Penke et al., 2010; Salami, Eriksson, Nilsson, & Nyberg, 2012).

4.5.3.4 Semantic memory

Semantic memory was assessed using the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001). There are multiple versions - the full 60 item version and various shorter 30- or 15-item versions. For this study, the 60-item version which has demonstrated good reliability (Katsumata et al., 2015) was used. Accuracy in lexical retrieval on this task is related to changes in the integrity of a neural network in the left lateral temporal lobe (Baldo, Arevalo, Patterson, & Dronkers, 2013; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Grossman et al., 2004). This test contains line drawn pictures of everyday objects which the participant was asked to name. The test begins with familiar, well-known items and progresses to less familiar, more difficult to name items. If the participant could not spontaneously name the item within 20 seconds, they were given a stimulus cue (e.g. musical instrument for harmonica). The test was started at item 30 and progressed from there unless the participant made an error before item 38. Where such an error was made, item 29 was presented and the test was administered backwards from there until the participant gave eight consecutive correct answers or reached item 1, at which point the participant was brought back to the item between items 30-37 at which they had made an error. The test was administered until participants reached the final item or until the participant had eight consecutive failures even with stimulus cues. One point was awarded for each item named correctly, including for those named after being prompted with the stimulus cue.

4.5.3.5 Visuospatial ability

The Medical College of Georgia (MCG) Complex Figure test was administered to assess visuospatial ability (Loring & Meador, 2003; Meador et al., 1993). This test is comparable to other complex figures copy tests such as the Rey-Osterrieth test which typically demonstrate high reliability (Lezak, 2004). They are often used in clinical neuropsychology as they are effective in discriminating AD in its earliest stages (Fujimori et al., 1998). Performance is related to frontal and posterior temporal-parietal cortex functioning in AD patients (Forstl, Burns, Levy, & Cairns, 1993; Melrose, Harwood, Khoo, Mandelkern, & Sultzer, 2013; Salmon et al., 2009; Teipel et al., 2006;

Tippett & Black, 2008) possibly reflecting recruitment of both visual perceptual skills and executive functions (Melrose et al., 2013). A complex line-drawing figure was placed in the front of the participant with its length along the participant's horizontal plane. The figure was on the top half of an A4 size sheet of white paper. The participant was instructed to copy the figure to the bottom half of the sheet in the same size and shape. The reproduced drawing is scored according to an 18 item scoring sheet with a possible range of 0-36 points (two points per item).

4.5.3.6 Global cognition

General cognitive function was assessed using the MoCA (Nasreddine et al., 2005). The MoCA has a higher sensitivity and similar specificity compared to the Mini-Mental State Examination (MMSE) for cognitive decline (Nasreddine et al., 2005). MoCA scores have been correlated with biomarkers for AD (Dao et al., 2015; Meng et al., 2015) and with abnormality in white matter tracts (Meng et al., 2012). It has been associated with grey matter volume abnormalities in frontal and temporal lobes in a sample of patients with silent cerebral infarction (Yang, Zhang, et al., 2015) and with white matter abnormalities in older adults with probable MCI (Cooley et al., 2015). The MoCA was reported to be significantly associated with hippocampal atrophy (O'Shea, Cohen, Porges, Nissim, & Woods, 2016; Ritter, Hawley, Banks, & Miller, 2017) and individual domain scores have correlated with several neuroimaging indices (Paul et al., 2011). The MoCA assesses eight broad cognitive domains – visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall and orientation. Scores range from 0-30. A point was added to the final score if the participant had 12 years of education or less. As individuals with hearing loss may underperform on auditory items, an additional score on this test was calculated following the scoring procedures of Dupuis et al. (2015). This procedure involves removing all four auditory items when calculating the total score and gives a potential range of scores from 0-20.

4.5.4 Procedure

As this battery was based on the neuropsychological battery used in the NEIL MRU, a similar procedure was followed with a few adaptations to allow for amendments. Piloting of the testing battery was conducted to assess logistical problems, the ordering of the tests, and the viability of using these tests with a hearing loss population. The order in which the tests were administered was carefully considered (listed in Figure 4.3). The tests administered between the FCSRT immediate and delayed recall phases were selected on the basis that they involved no recall aspect or any items similar to those in the FCSRT. They were also selected as together they took roughly 30 minutes to complete, the required time to have passed before administering the FCSRT delayed phase. The grip strength was administered after completing all neuropsychological tests. An instruction manual outlining the standard operating procedures was written based on the MRU testing manual to ensure consistency in testing. All testing was conducted by the principal researcher or by research assistants who were either studying for a master's degree in psychology or had completed one.

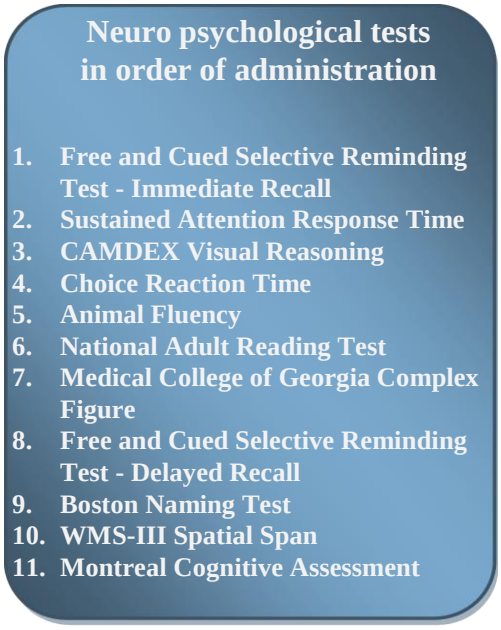

Figure 4.3: List of neuropsychological tests in order of administration.

Participants underwent neuropsychological and audiometric assessment independently. Participants completed both assessments in one appointment session or in separate appointments depending on convenience for the participant and availability of the audiologist. Neuropsychological assessment took approximately 1.3 hours to complete and audiological assessment took approximately 25 minutes. Participants completed the background questionnaire at home. Participants were contacted if any items in the questionnaire were not completed.

The temporary memory binding test and testing procedure are outlined in Chapter 7.

4.5.5 Statistical analysis

The statistical methods to assess differences between the hearing loss and control group on the background and main neuropsychological assessments are reported here. The results of the methods performed on this data are reported in each study chapter to provide a description of the background and neuropsychological characteristics of the samples and their respective differences and similarities. The methods used to extract the indices of implicit and explicit function and the statistical methods particular to each of the three studies are reported in their respective chapters. The statistical tests conducted on the implicit and explicit markers were to test the primary hypothesis of implicit-explicit asymmetry as outlined previously. Further exploratory analysis on these data was conducted to assess possible future avenues for research.

For both groups, the means and standard deviations for background factors and neuropsychological performance were calculated. All scores for neuropsychological tests and the variability indices were converted to standardised z-scores using the means and standard deviations for the whole

sample on each task. As some tests assessed the same general cognitive domain, each test was allocated to a cognitive domain. A composite score for each cognitive domain was then calculated by calculating the average z-score across tests for each participant prior to calculating the z-score means and standard deviations for both groups. A global z-score was also calculated for each individual by calculating the average z-score across cognitive domains.

Normality of continuous data was examined using the Kolmogorov-Smirnov test and by analysing the Q-Q plots and the data distribution in the histograms. Non-normal data was either transformed or analysed using non-parametric tests as appropriate. For comparison of background and neuropsychological data, independent samples t-tests (two-tailed) were used for continuous variables and Chi-square tests for independence were used for categorical variables. Levene's Test for Equality of Variances was used to assess homogeneity of variances between groups for t-tests. The non-parametric alternative tests, Mann-Whitney *U* and Fisher's exact tests, were used where appropriate.

Cohen's *d* was selected as the measure of the effect size in differences between groups for all tests. Effect sizes were calculated using an online calculator (Wilson, 2017) following the formulas published in Lipsey and Wilson (2001). For outcomes assessed using Fisher's exact test, Cohen's *d* was calculated based on outcome frequency (odds ratio). Effect sizes for Mann-Whitney *U* were converted from *r* to Cohen's *d* (Borenstein et al., 2011). The effect sizes were considered as either "small = 0.2," "medium = 0.5," or "large = 0.8" (Cohen, 1988). No power calculation was conducted *a priori* to these three studies as they were considered exploratory in design and analysis (Hertzog, 2008; Isaac & Michael, 1995; Jones, Carley, & Harrison, 2003). An alpha level of 0.05 was used as a significance criterion for all statistical tests. Tests were carried out with the software Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL, U.S.A.) for Windows (Microsoft Corporation, Redmond, WA, USA).

4.6 Overall Summary and Objectives

The search for biomarkers and modifiable risk factors for cognitive decline and dementia is of primary importance. While ARHL has emerged as a possible risk factor, the epidemiological evidence suggests a small association. However, there is some variance in epidemiological findings examining ARHL and cognitive decline (Gallacher et al., 2012; Lin, Ferrucci, et al., 2011; Wayne & Johnsrude, 2015). This is possibly due to variances in audiometric criteria of hearing loss (e.g. self-report or low vs. high frequencies) or suboptimal audiometric methodology (e.g. no sound treated room or booth) (Gallacher et al., 2012; Lin, Ferrucci, et al., 2011; Lindenberger & Baltes, 1994). Biases in cognitive testing due to loss of hearing acuity may lead to poorer cognitive outcomes that do not accurately reflect the cognitive status of the patient (Dupuis et al., 2015; Gallacher et al., 2012).

The objective in Chapters 5, 6 and 7 is to assess the viability of a new theoretical model of the association between ARHL and cognitive decline. The studies reported in these chapters were designed to assess how ARHL may lead to deterioration in implicit, automatic processes across several domains. These domains: executive function, processing speed, lexical-semantic and episodic memory are of great importance in research on cognitive ageing and in clinical diagnosis of dementia. The testing battery used to assess these domains was selected on the basis that the tests use purely visual stimuli (with the exception of the MoCA). This thesis will outline how ARHL may specifically contribute to decline in these domains.

Chapter 5 ARHL & processing speed, intra-individual variability and top-down executive control

5.1 Introduction

Decline in processing speed is observed consistently in older adults, is considered an important marker of cognitive ageing (Salthouse, 1996; Verhaeghen & Salthouse, 1997) and is a predictor of daily function (Wahl, Schmitt, Danner, & Coppin, 2010).

Based on behavioural evidence, the processing-speed theory of cognitive ageing posits that age-related cognitive decline can be accounted for by a single or global mechanism of cognitive slowing (Salthouse, 1996). This general slowing affects higher-order cognitive operations due to consequent inefficiency. Age-related slowing in cognitive performance has been observed in a wide range of tasks across different cognitive domains and at different levels of task difficulty (see Verhaeghen & Cerella, 2008 for a meta-analytic review). Most cognitive tasks reveal a similar ratio of slowing in performance to that observed in simple reaction tasks consistent with the generalised slowing hypothesis (Cerella, 1985, 1994). A similar ratio of slowing has also been observed in the motor domain suggesting a broad systemic effect (Sleimen-Malkoun, Temprado, & Berton, 2013) possibly due to dedifferentiation of neural processes within different neurocognitive domains (Sleimen-Malkoun et al., 2013), decline in the central nervous system (CNS) (Eckert, 2011; Salthouse, 1996, 2000) or deterioration of white matter integrity in the brain (Eckert, 2011; Head et al., 2004; Madden et al., 2004; Penke et al., 2010; Persson et al., 2006; Vernooij et al., 2009; Wen & Sachdev, 2004).

In contrast, prefrontal-executive theories such as the Frontal Ageing (West, 1996, 2000), Resources Deficit (Craik, 1986; Craik et al., 1983; Craik & Byrd, 1982), and Inhibition Deficit hypotheses (Hasher & Zacks, 1988; Hasher, Zacks, & May, 1999) posit that general age-related cognitive decline is mediated by executive resources - primarily localised in frontal cortex areas - which are most sensitive to ageing (Dennis & Cabeza, 2011). This view has also accounted for significant variance in cognitive ageing suggesting that executive function is a potential mediator of cognitive deficits due to ageing (Clarys, Bugaiska, Tapia, & Baudouin, 2009; Dennis & Cabeza, 2011) and daily function (Cahn-Weiner, Boyle, & Malloy, 2002; Royall et al., 2007; Vaughan & Giovanello, 2010).

See (Albinet et al., 2012) & Eckert (2011) for a discussion of these two theories and their empirical application.

Studies examining empirical evidence for these two theories have reported mixed findings (Baudouin, Clarys, Vanneste, & Isingrini, 2009; Bugaiska et al., 2007; Fisk & Sharp, 2004; Fisk & Warr, 1996), not least due to difficulties in partitioning their independent effects when assessing

processing speed and executive functions (Salthouse, 2005; Salthouse et al., 2003). Furthermore, neurocognitive evidence suggests that both central executive resources and efficiency in neural connectivity underlie cognitive performance (Bucur et al., 2008; Eckert, 2011; Haasz et al., 2013). This has led to more nuanced interpretations that suggest that general processing speed and central executive processes overlap in variance and make unique contributions to the cognitive ageing process (Albinet et al., 2012). More recent hypotheses such as cognitive reserve (Stern, 2009), PASA (Posterior-Anterior Shift in Ageing) (Grady et al., 1994) and the compensation account of HAROLD (Hemispheric Asymmetry Reduction in OLDer Adults) (Cabeza, 2002) describe neurocognitive ageing as a dynamic process in which top-down processes compensate for ageing deficits. Executive resources may compensate for deficits in specific cognitive processing and promote processing speed (Reuter-Lorenz et al., 2000) or episodic memory (Gutchess et al., 2005). Conversely, increased recruitment of prefrontal cortex regions to promote accuracy on cognitive tests may lead to slower performance (Grady, 2012; Grady et al., 1994). Executive resources can also compensate for peripheral sensory deficits and reduced sensory processing in central neural regions helping to maintain perceptual function (Cabeza & Dennis, 2007; Campbell & Sharma, 2013; Park et al., 2004; Ronnberg et al., 2013). This may have immediate costs for implicit cognitive functions (Tun et al., 2009) such as encoding in episodic memory (Daselaar et al., 2003; Gutchess et al., 2005; Rosen et al., 2002) which would otherwise be supported by these executive processes. This reallocation of executive resources may contribute to the deficits associated with ageing including those in processing speed (Lin et al., 2013).

Speech perception involves a nuanced trade-off between higher order attentional control processes and stimulus driven automatic processes with the ratio altering depending on contextual demands (Heald & Nusbaum, 2014; Peelle & Wingfield, 2016; Ronnberg et al., 2013). Under optimal conditions, perception of speech is fast, automatic and conducted with minimal cognitive effort. With hearing loss, there is a shift to controlled, top-down processing to support processing of the auditory signal which would otherwise be processed in automatic fashion. This shift in processing strategy is measured on different time scales (from a scale of milliseconds to seconds) (Ronnberg, Rudner, Foo, & Lunner, 2008). Even among hearing aid users and under optimal listening conditions, there is a tax on cognitive resources (Humes, 2007; McCoy et al., 2005). In the longer-term, increased recruitment of executive functions may maintain them (Ronnberg et al., 2013) but, along with loss of stimulation, may cause decline in automatic cognitive processes. Cognitive processing speed is typically assessed using mean reaction time (RT) to simple stimuli measures that involve executive functions, decision-making and motor function (Eckert, 2011). When tasks require more executive processing, response latency typically increases with more effort to maintain accuracy (Grady et al., 1994). A decline in automatic cognitive processes due to hearing loss as predicted by the proposed model (NIEAD) (Chapter 4) would suggest slower response times but maintained accuracy on tasks that require more explicit processing compared to simple reaction time tasks where there would be no differences. According to the proposed model, this effect is due

to recruitment of executive resources both for accuracy and to compensate for inefficiencies in automatic processes.

Apart from mean reaction time, a growing body of research suggests that fluctuations in trial-to-trial response times or accuracy scores on cognitive tests do not purely reflect error but also constitute a meaningful indicator of neurocognitive function (Dykiert, Der, Starr, & Deary, 2012; Haynes, Bauermeister, & Bunce, 2017; Hultsch, MacDonald, & Dixon, 2002; Hultsch, Strauss, Hunter, & MacDonald, 2011; MacDonald, Li, & Backman, 2009; MacDonald, Nyberg, & Backman, 2006). Intra-individual variability (IIV) is a possible marker of CNS efficiencies in frontal-cortex mediated executive processes rather than general brain dysfunction (Bellgrove, Hester, & Garavan, 2004; Stuss, Murphy, Binns, & Alexander, 2003). Increased IIV is associated with neurological deterioration in frontal regions (Sowell et al., 2003; Stuss et al., 2003), in white matter (Anstey et al., 2007; Bunce et al., 2007) as well as decreased integrity in functional brain networks (Kelly et al., 2008; Walhovd & Fjell, 2007).

IIV has been demonstrated to have predictive power for neurocognitive outcomes greater than measures of mean response times (Hultsch et al., 2011; Lovden, Li, Shing, & Lindenberger, 2007) including incident cognitive impairment up to ten years later (Bielak, Hultsch, Strauss, Macdonald, & Hunter, 2010; Koscik et al., 2016) and conversion to clinical dementia from the pre-clinical stage (Holtzer, Verghese, Wang, Hall, & Lipton, 2008; Tales et al., 2012). It has also been linked with asymptomatic ApoE e4 (*apolipoprotein E-epsilon4*) (Duchek et al., 2009), AD (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Jackson, Balota, Duchek, & Head, 2012) and with mortality (Batterham, Bunce, Mackinnon, & Christensen, 2014; Shipley, Der, Taylor, & Deary, 2006). Therefore, it is considered to be a potential clinical marker for dementia apart from measures of speed and accuracy (Haynes et al., 2017).

The most common indicators of IIV are individual standard deviation (ISD) and the coefficient of variation (CV) which is the ISD divided by the participant mean reaction time (i.e. adjusted for processing speed) (Dykiert et al., 2012; Haynes et al., 2017). IIV increases in most populations with task difficulty (McLaughlin, Borrie, & Murtha, 2010; Stuss & Binns, 2008) but in the elderly it is reduced in untimed tests (Hofland, Willis, & Baltes, 1981). The NIEAD hypothesis would predict that if IIV is due to inefficiencies in automated processing speed rather than executive processes, with hearing loss there would be less decline in the CV than the ISD. There is some support from neuro-imaging studies for altered IIV with hearing loss due to increased reliance on executive function in speech processing. On a speech task, increased connectivity between the default mode network (DMN) and dorsal attention network (DAN) was observed in a hearing loss sample (Husain et al., 2014). Such connectivity has been hypothesised to support performance on tasks with a higher cognitive load (Hearne et al., 2015) such as complex cognitive tests (Hearne et al., 2015; Leech et al., 2011; Liang et al., 2015) or in social cognition (Li, Mai, et al., 2014; Mars et al., 2012; Meyer & Lieberman, 2012; Meyer et al., 2012). However, segregation between the DMN

and executive control networks is viewed as favourable for optimal cognitive performance (Anticevic et al., 2012; Chand et al., 2017; Fox et al., 2005; Sonuga-Barke & Castellanos, 2007) and integration may be maladaptive for longer-term cognition as it has been associated with increased IIV (Kelly et al., 2008).

Sustained attention is the ability to endogenously process stimuli with non-arousing or repetitive qualities (Robertson et al., 1997) and is thought to be due to the workings of two interacting subsystems: vigilance and arousal (Biederman & Spencer, 1999; Paus, 2001; Paus et al., 1997). Interestingly, IIV in response latencies can be disaggregated into temporal components of fast (FFV - moment-to-moment) and slow variability (SFV - change over task length) using a Fast Fourier Transformation (FFT) (Castellanos et al., 2005; Johnson, Kelly, et al., 2007; Johnson, Robertson, et al., 2007). The former is thought to reflect fluctuations in top-down executive control of vigilant attention which relies on a right lateralised network of cortical areas including the cingulate gyrus, prefrontal cortex and inferior parietal lobule (Fassbender et al., 2004; Langner & Eickhoff, 2013; O'Connor, Robertson, & Levine, 2011). The latter is thought to reflect alterations in arousal (Johnson, Kelly, et al., 2007; Johnson, Robertson, et al., 2007) - a bottom-up, subcortical system mediated through the thalamus and noradrenergic brainstem structures, including the locus coeruleus (Coull, 1998; Langner & Eickhoff, 2013; Sturm et al., 1999; Van der Werf, Witter, & Groenewegen, 2002). This technique has previously been employed to uncover interesting measures of neurocognitive function apart from traditional measures of reaction time mean and standard deviation. Greater variability on both of these markers was observed in children with attention deficit hyperactivity disorder (ADHD) (Johnson, Lui, & Yaffe, 2007; Johnson, Kelly, et al., 2007). In older adults, FFV (associated with top-down control processes) on the SART was associated with pre-frailty and frailty syndrome (O'Halloran, Finucane, Savva, Robertson, & Kenny, 2014) and was also a retrospective predictor of falling (O'Halloran et al., 2011). However, in ARHL samples, the proposed NIEAD model would predict that top-down levels would be maintained but that arousal levels would be poorer. If this were so, then it would appear to contradict findings of poorer top-down control with frailty, an age-related syndrome (O'Halloran et al., 2014) and suggest that ARHL makes a unique contribution to cognitive decline above physiological health or its association with frailty (Panza, Solfrizzi, & Logroscino, 2015; Panza, Solfrizzi, Seripa, et al., 2015).

The purpose of this chapter was to examine differences in indices of processing speed and IIV between a group of older adults with and without hearing loss. These indices were extracted from participant performance on two subcomponents (motor and cognitive) of the choice reaction time task (CRT) and the Sustained Attention to Response Task ($SART_{fixed}$). These indices allow analysis of whether there is a difference in IIV across task complexity and whether this difference may be attributed to higher-order cognitive processes or due to deterioration of efficiencies in processing speed and arousal levels. It was predicted that on the $SART_{fixed}$ those with hearing loss

would have the same level of accuracy but greater mean RTs compared to controls. Also, there would be a greater difference in mean RT on the SART$_{fixed}$ due to the explicit processing demands of this task than for the CRT. It was predicted that there would be a greater difference between groups on ISD measures of IIV than for CV measures (which control for processing speed) on both the SART$_{fixed}$ and CRT. It was predicted that on the SART$_{fixed}$ the hearing loss group would have significantly greater SFV compared to controls but that there would be no significant difference in FFV.

5.2 Methods

A summary of the methods is outlined below. See Chapter 4 for full details of the methods for this study.

5.2.1 Participants

There were 32 hearing loss participants and 34 controls after matching participants for age ($\pm$ 5 years), gender and pre-morbid IQ (+ 0.5 SDs/7.5 points) and excluding one participant due to insufficient data on the SART to calculate the FV indices.

5.2.1.1 Background assessment

Background information was collected from all participants using questionnaires that assessed demographic, audiological, health and clinical factors. All measures were completed by included participants.

5.2.1.2 Audiological assessment

Objective and self-report measures of hearing loss were completed by all included participants.

5.2.1.3 Neuropsychological assessment

All neuropsychological measures were completed by included participants.

5.2.1.4 Processing speed and intra-individual variability

Plaese see Chapter 4 for a description of the CRT and the SART$_{fixed}$. Both the CRT and the SART$_{fixed}$ are visual tests and are therefore appropriate for use with a hearing loss sample. Instructions were given verbally by the examiner and were also presented visually as part of the testing software. Both tests involved practice trials to ensure that the participant understood the instructions. For both tasks, processing speed was assessed using the mean RTs. IIV was measured using individual standard deviation (ISD) and the coefficient of variation (CV) which is the ISD divided by the participant mean reaction time (Dykiert et al., 2012; Haynes et al., 2017). ISD measures the spread of observations whereas CV is a normalised measure of variability that reflects the ratio of the standard deviation to the mean. The Fast Fourier Transform (FFT) was used to distinguish two components of RT variability, fast- and slow-frequency variability (FFV and SFV respectively) (Castellanos et al., 2005; Johnson, Kelly, et al., 2007; Johnson, Robertson, et al., 2007).

5.2.2 Procedure

After recruitment, participants underwent neuropsychological and audiometric assessment independently and completed the background questionnaire at home. Participants were contacted if any items were not completed.

5.2.3 Statistical analysis

The statistical methods particular to this study are reported here. Please see Section 4.4.3 in Chapter 4 for a description of how the background and main neuropsychological data were treated, and how normality and group differences in effect sizes were assessed.

The distribution of each individual's raw latency scores on both the CRT and SART were examined for outliers, which were defined as responses that occurred more than 3SDs outside the participant's own mean RT. These single trial outliers were removed before mean reaction times, ISD and CVs were calculated. Analyses were conducted on data from all CRT trials irrespective of response accuracy as previous research indicates little difference in results of analysis conducted with data from all trials (correct plus incorrect) when compared to data from only correct trials (Burton, Strauss, Hultsch, Moll, & Hunter, 2006). For the SART, ISD and CV outcomes were based on all 'go-trials'.

Variance in mean RT can be made up of different sources of variance occurring on different time scales. This can be either a continuous slowing down of the reaction time over the length of the task (*slow frequency variability*), and the quick changes occurring on a moment to moment basis (*fast frequency variability*). The FFT procedure was used to decompose the variance of the RT into these two additive components and was conducted on the raw data following the procedure as outlined previously (Castellanos et al., 2005; Johnson, Kelly, et al., 2007; Johnson, Robertson, et al., 2007; O'Halloran et al., 2014; O'Halloran et al., 2011). To prepare the data for the FFT, RTs for trials with no response (correct no-go trails and omission errors) were interpolated from the preceding and following trials. It was planned to remove data from participants with more than six consecutive zero answers. One participant was excluded from the dataset for this reason. The RT data was analysed according to Welch's averaged, modified periodogram method. The full time-series was first divided into seven segments. Each segment was Hamming-windowed and zero-padded to length. The FFT was then calculated for each segment and was averaged across segments to provide a spectrum per individual. The first three segments and the last four segments were also averaged separately to analyse change in variability over the two halves of the test. The slow frequency measure encompassed all sources of variability slower than once per SART cycle and captured any gradual changes in response time over the course of the task. The fast frequency measure encompassed all sources of variability faster than once per SART cycle and captured any trial-to-trial variability. Preparation of the SART data and the FFT was conducted using MatLab (Version R2016b).

Several exploratory analyses were conducted. Correlation analyses between processing speed and executive function measures were conducted using Spearman's Rho. Hierarchical multiple regression was used to assess hearing loss as a moderator for the relationship between SART RT and SART total errors scores. As a matter of interest, differences between groups on ISD and CVs were explored using analysis of covariance (ANCOVA) in which age, gender and years of education were included as covariates. The non-parametric alternative test, rank analysis of covariance (Quade, 1967) was used where appropriate.

The primary analysis examining the difference between groups on SFV and FFV was conducted using ANCOVA in which age, gender and years of education were included as covariates. The relationship between groups on SFV and FFV was further explored using hierarchical multiple regression to assess hearing loss as a moderator for the relationship between the ratio of SFV and FFV. Linear mixed models were performed to further explore the relationship between hearing group and change in frequency variability over time.

5.3 Results

5.3.1 Participant characteristics

Using Student's t-tests (two-tailed), Mann-Whitney U and Chi-square, there were no significant differences between groups in age, gender, pre-morbid IQ or education (years and level) (Table 5.1). The difference in age between groups approached significance. There were no significant differences on any other background or on demographic, health, clinical and psychosocial factors. No further analysis was conducted on these factors as they were descriptive.

Table 5.1: Background data for the hearing loss and control groups					
	Hearing loss group *M (SD)*	**Control group** *M (SD)*	**Significance test**		
			Est.	*p*	*Cohen's d*
Demographic					
N	32	34	-	-	-
Age	71.38 (6.96)	68.41 (6.05)	*t*; -1.85	0.07	0.46
Gender (*female/male*)	19/13	26/8	χ^2; 2.22	0.14	0.37
Education *(years)*	13.7 (3.52)	13.62 (3.23)	*t*; -0.1	0.91	0.02
Education *(level)*	2.56 (0.84)	2.76 (0.82)	*U*; 462	0.26	0.28
Marital status *(partner/none)*	22/10	21/13	χ^2; 0.35	0.55	0.15
Audiological					
WHO better ear PTA	47.77 (16.6)	13.79 (6.71)	*U*; 0	**<0.001**	3.37
WHO worse ear PTA	60.74 (25.78)	19.6 (8.9)	*U*; 22	**<0.001**	2.92
Low freq. better ear PTA	38.85 (19.05)	8.24 (5.35)	*U*; 72	**<0.001**	2.24
Low freq. worse ear PTA	51.56 (26.01)	13.87 (7.87)	*U*; 64	**<0.001**	2.33
High freq. better ear PTA	60.16 (19.82)	22.79 (10.89)	*U*; 49.5	**<0.001**	2.51
High freq. worse ear PTA	71.93 (26.61)	31.57 (13.1)	*U*; 86	**<0.001**	2.1
Self-rated hearing *(HHIE-S)*	18.94 (9.85)	4.35 (6.26)	*U*; 126	**<0.001**	1.78
Health					
Self-rated physical health	3.66 (0.9)	3.71 (0.91)	*U*; 534.5	0.9	0.03
Self-rated mental health	4 (0.8)	3.94 (1.04)	*U*; 542	0.98	0.01
Alcohol consumption *(yes/no)*	25/7	27/7	χ^2; 0.02	0.9	0.03
Alcohol units *(per wk)*	9.29 (7.62)	9.41 (9.61)	*U*; 320	0.75	0.08
Smoker current *(yes/no)*	1/31	1/33	χ^2; 0.002	0.97	0.01
Smoker former *(yes/no)*	15/17	12/22	χ^2; 0.92	0.34	0.24
Sleep quality *(PSQI)*	5.28 (2.99)	4.82 (2.63)	*U*; 492.5	0.51	0.16
Clinical					
Pre-morbid IQ *(NART)*	111.46 (7.01)	111.28 (7.97)	*U*; 533.5	0.89	0.03
Self-rated memory	3.44 (0.88)	3.26 (0.67)	*U*; 481	0.38	0.22
Frailty *(SHARE score)*	0.31 (0.82)	0.19 (0.91)	*U*; 484	0.44	0.19
Depression *(CESD-10)*	5.19 (3.49)	5.32 (4.95)	*U*; 502.5	0.59	0.13
Anxiety *(HADS-A)*	3.66 (2.81)	4.26 (3.54)	*U*; 509.5	0.66	0.11
Apathy *(AES-S)*	27.41 (5.7)	27.68 (6.98)	*U*; 521.5	0.77	0.07
Psychosocial					
Social network *(LSNS)*	20.53 (5.14)	19.41 (6.15)	*U*; 494	0.52	0.16
Loneliness *(De Jong Gierveld)*	0.47 (0.72)	0.76 (1.28)	*U*; 501.5	0.53	0.15
Boredom proneness *(Conroy)*	1.47 (0.57)	1.5 (0.66)	*U*; 544	>0.99	0
Perceived stress *(PSS-4)*	3.34 (2.42)	3.15 (3.18)	*U*; 482	0.42	0.2

AES-S; Apathy Evaluation Scale – Self-rated (Marin et al., 1991); CESD-10; Center for Epidemiologic Studies Depression Scale – 10 item (Radloff, 1977); Conroy; Conroy Boredom proneness (Conroy et al., 2010); De Jong Gierveld; 6-item De Jong Gierveld Loneliness Scale (De Jong Gierveld & Van Tilburg, 2006); HADS-A; Hospital Anxiety and Depression Scale-Anxiety subscale (Zigmond & Snaith, 1983); HHIE-S; Hearing Handicap Inventory for the Elderly Screening Version (Ventry & Weinstein, 1983); LSNS; Lubben Social Network Scale (Lubben et al., 2006); NART; National Adult Reading Test (Nelson, 1982); PSQI; Pittsburgh Sleep Quality Index (Buysse et al., 1989); PSS-4; Perceived Stress Scale-4 item (Cohen et al., 1983); PTA; Pure-tone average; SHARE; Survey of Health, Ageing and Retirement in Europe Frailty Instrument (Romero-Ortuno et al., 2010); WHO; World Health Organisation;

There was a significant difference between groups on all audiological measures ($p < 0.001$). This included the WHO pure-tone average in better and worse ear, averages for low and high frequencies and the HHIE-S score. Twenty-two (68.75%) of the participants in the hearing loss group wore hearing aids. None of the participants in the control group wore hearing aids. Fourteen (43.75%) participants in the hearing loss and six (17.65%) in the control group reported having previously experienced tinnitus. One participant in the control group reported difficulty with vision. No participant was excluded based on global cognitive domain score.

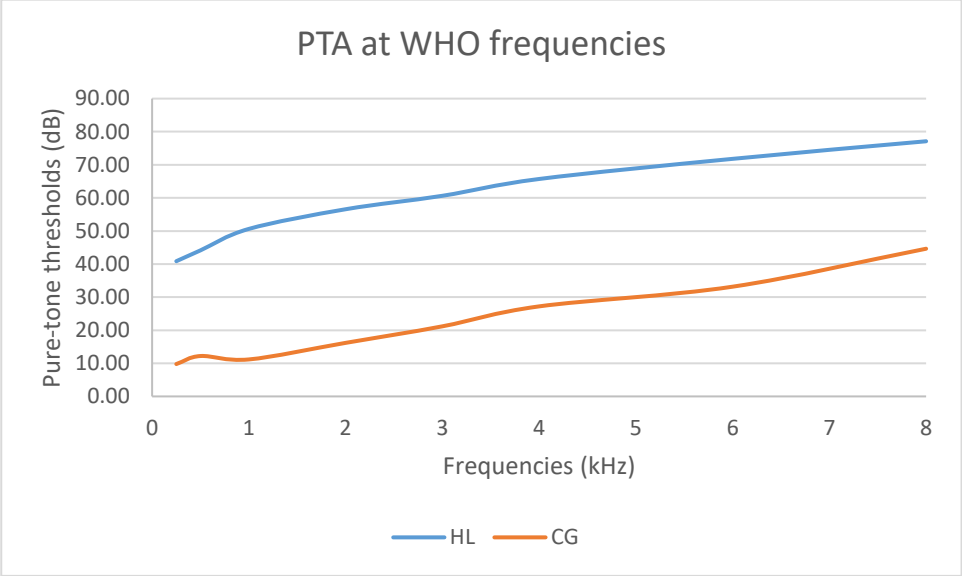

Figure 5.1: Difference in pure-tone threshold between the two groups at each frequency.

Table 5.2: Neuropsychological data for the hearing loss and control groups				
	HLG *M (SD)*	**CG** *M (SD)*	**HLG** *Z (SD)*	**CG** *Z (SD)*
Current sleepiness				
Stanford Sleepiness Scale	1.81 (1.15)	1.79 (0.91)	-0.01 (1.12)	0.01 (0.89)
Episodic memory				
FCSRT immediate free recall	33.97 (6.36)	33.62 (5.71)	0.03 (1.06)	-0.03 (0.95)
FCSRT immediate total	48.03 (0.6)	47.88 (0.54)	0.14 (1.05)	-0.13 (0.95)
FCSRT delayed free recall	12.38 (2.78)	12.56 (2.4)	-0.04 (1.08)	0.03 (0.93)
FCSRT delayed total recall	15.91 (0.39)	15.94 (0.24)	-0.06 (1.22)	0.05 (0.75)
WMS-III SS forward	7 (1.85)	6.76 (2.09)	0.06 (0.94)	-0.06 (1.06)
Composite z-score			0.02 (0.82)	-0.02 (0.66)
Executive function				
CAMDEX visual reasoning	3.53 (1.5)	3.85 (1.21)	-0.12 (1.11)	0.11 (0.89)
SART commission errors	3.34 (2.5)	3.74 (2.83)	0.08 (0.94)	-0.07 (1.06)
SART omission errors	6.5 (4.79)	6.94 (7.11)	0.04 (0.79)	-0.04 (1.17)
SART total errors	9.84 (6.51)	10.68 (8.67)	0.06 (0.85)	-0.05 (1.13)
Phon. fluency *(MoCA)*	14.09 (5.11)	14.94 (4.05)	-0.1 (1.12)	0.09 (0.88)
Sematic fluency *(animals)*	21.78 (5.82)	22.24 (5.34)	-0.04 (1.05)	0.04 (0.96)
WMS-III SS backward	6.25 (1.69)	5.97 (2.1)	0.08 (0.89)	-0.07 (1.1)
WMS-III SS total	13.25 (3.02)	12.74 (3.64)	0.08 (0.9)	-0.07 (1.09)
Composite z-score			-0.01 (0.61)	0.01 (0.62)
Processing speed				
CRT mot. mean RT (*ms*)	352.44 (150.71)	302.62 (81.83)	-0.21 (1.24)	0.2 (0.67)
CRT cog. mean RT (*ms*)	526.94 (198.04)	495.4 (76.32)	-0.11 (1.34)	0.1 (0.52)
CRT total mean RT (*ms*)	875.3 (313.85)	795.69 (117.61)	-0.17 (1.33)	0.16 (0.5)
SART mean RT (*ms*)	347.98 (78.84)	308.17 (43.89)	-0.31 (1.2)	0.29 (0.67)
Semantic memory				
BNT	54.84 (4.05)	55.38 (3.23)	-0.08 (1.12)	0.07 (0.89)
Visuospatial ability				
MCG Complex Figure	24.08 (4.17)	27.06 (4.99)	-0.32 (0.87)	0.3 (1.04)
Global cognition				
MoCA	25.59 (2.86)	25.76 (3.26)	-0.03 (0.94)	0.03 (1.07)
MoCA adj.*	17.47 (1.72)	17.32 (2.29)	0.04 (0.85)	-0.03 (1.13)
Composite global z-score [+]			-0.11 (0.57)	0.11 (0.48)

[*] Equal variances not assumed

+ Composite z-score calculated from the mean of the composite scores for episodic memory (except FCSRT and Spatial Span total scores), executive functions and from the scores for processing speed (CRT total mean RT), semantic memory and visuospatial ability.

All CRT reaction times and SART mean RT transformed to inverse scores to account for non-normality. SART commission and total errors were transformed to square root and omission errors to $\log_{10}(+1)$. For SART commission and omission errors, arithmetic signs on z-scores set so that higher scores indicated better performance

Table 5.2 (Continued): Neuropsychological data for the hearing loss and control groups

	Significance test		
	Est.	*p*	*Cohen's d*
Current sleepiness			
Stanford Sleepiness Scale	*U*; 522.5	0.76	0.07
Episodic memory			
FCSRT immediate free recall	*t*; -0.24	0.81	0.06
FCSRT immediate total	*U*; 529	0.68	0.10
FCSRT delayed free recall	*t*; 0.29	0.77	0.07
FCSRT delayed total recall	*U*; 541	0.93	0.02
WMS-III SS forward	*t*; -0.48	0.63	0.12
Composite z-score	*t*; -0.19	0.85	0.05
Executive function			
CAMDEX visual reasoning	*t*; 0.96	0.34	0.24
SART commission errors	*t*; 0.44	0.67	0.11
SART omission errors	*t*; -0.09	0.93	0.02
SART total errors	*t*; 0.18	0.86	0.04
Phon. fluency *(MoCA)*	*t*; 0.75	0.46	0.18
Sematic fluency *(animals)*	*t*; 0.33	0.74	0.08
WMS-III SS backward	*t*; -0.6	0.55	0.15
WMS-III SS total	*t*; -0.62	0.54	0.15
Composite z-score	*t*; 0.15	0.88	0.04
Processing speed			
CRT mot. mean RT (*ms*)	*t*; 1.6	0.12	0.39
CRT cog. mean RT (*ms*)	*t*; 0.49	0.63	0.12
CRT total mean RT (*ms*)	*t*; 1.42	0.16	0.35
SART mean RT (*ms*)	*t*; 2.15	**0.04**	0.53
Semantic memory			
BNT	*U*; 523	0.79	0.07
Visuospatial ability			
MCG Complex Figure	*t*; 2.62	**0.01**	0.65
Global cognition			
MoCA	*U*; 502	0.59	0.13
MoCA adj.*	*U*; 523	0.79	0.07
Composite global z-score [+]	*t*; 1.69	0.1	0.42

[*] Equal variances not assumed

+ Composite z-score calculated from the mean of the composite scores for episodic memory (except FCSRT and Spatial Span total scores), executive functions and from the scores for processing speed (CRT total mean RT), semantic memory and visuospatial ability.

All CRT reaction times and SART mean RT transformed to inverse scores to account for non-normality. SART commission and total errors were transformed to square root and omission errors to $\log_{10}(+1)$. For SART commission and omission errors, arithmetic signs on z-scores set so that higher scores indicated better performance

5.3.2 Neuropsychological performance

There was no significant difference between groups on the Stanford Sleepiness Scale (Table 5.2). There were no differences in episodic memory and executive function measures or composite scores. This included the SART error scores. There were no significant differences in semantic memory or global cognition. There was a significant difference in the MCG Complex Figure Copy Test. This will be explored and discussed further in Chapter 7. As regards processing speed, there was no significant difference between groups on any of the CRT scores. However, there was a significant difference between groups on SART RT (t (64) = 2.15 p = 0.04, Cohen's d = 0.53).

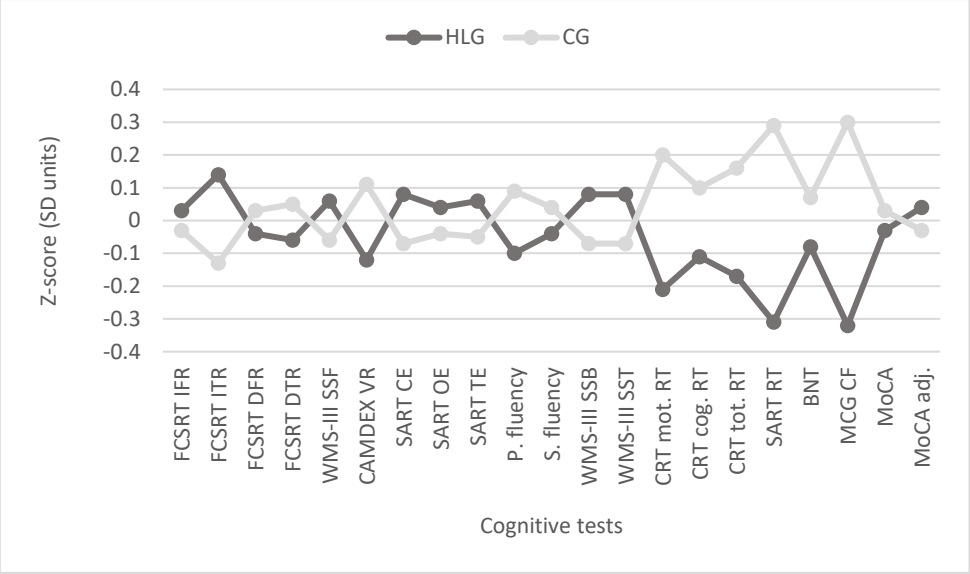

Figure 5.2: Difference in mean performance between the two groups on each cognitive test (based on z-scores).

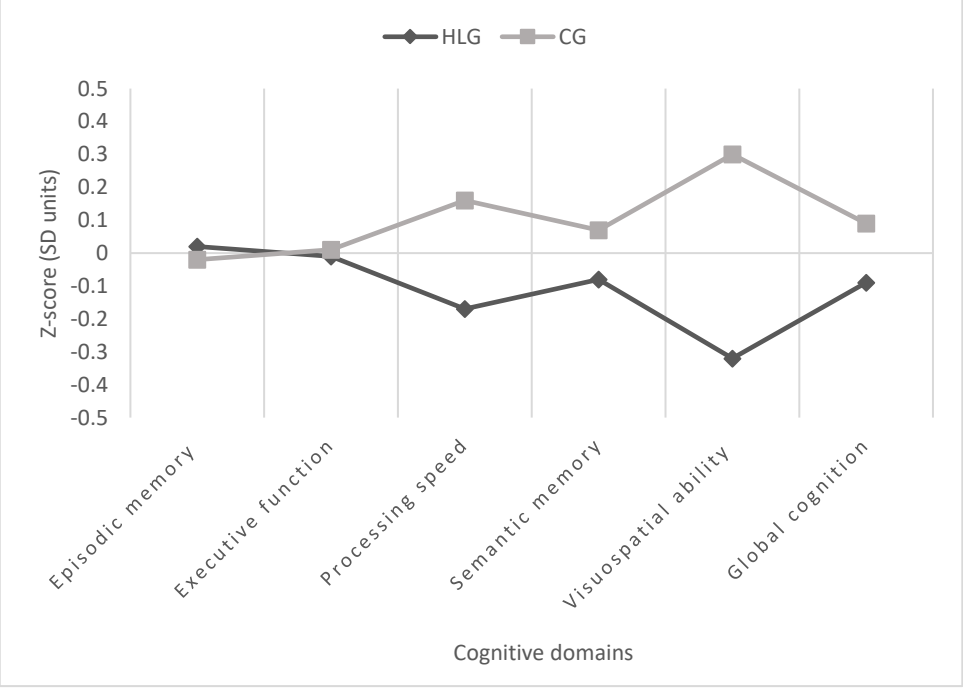

Figure 5.3: Difference in mean performance between the two groups on each cognitive domain (based on z-scores).

5.3.3 Processing speed & executive function

Correlations between executive function and processing speed measures are shown in Table 5.3. When processing speed measures were correlated with each other for both groups, the SART RT was significantly correlated with all CRT RT outcomes in the control group. In contrast, none of the correlations between the SART RT and the CRT RT outcomes was significant in the hearing loss group. For both groups, the CRT motor and cognitive RTs were significantly correlated with the CRT total RT but not with each other. For the control group, the composite executive function score was correlated with the SART RT, the CRT motor and total RTs but not the cognitive RT.

Table 5.3: Spearman's rho correlations for processing speed and executive function for the hearing loss and control groups

	CRT motor RT		CRT cognitive RT		CRT total RT	
	HL	CG	HL	CG	HL	CG
Executive functions						
SART Com. errs	0.15 (0.4)	**0.35 (0.04)**	**-0.4 (0.03)**	0.22 (0.22)	-0.2 (0.27)	**0.43 (0.01)**
SART Om. errs	0.14 (0.45)	0.31 (0.08)	**-0.5 (0.004)**	0.27 (0.13)	-0.33 (0.07)	**0.42 (0.01)**
SART Tot. errs	0.18 (0.33)	0.31 (0.07)	**-0.52 (0.002)**	0.28 (0.11)	-0.31 (0.09)	**0.42 (0.01)**
CAMDEX VR	0.07 (0.72)	0.23 (0.19)	-0.15 (0.43)	-0.04 (0.84)	-0.13 (0.47)	0.17 (0.34)
Let. fluency	0.02 (0.91)	**0.57 (<0.001)**	0.15 (0.41)	0.05 (0.79)	0.09 (0.64)	**0.42 (0.01)**
Cat. Fluency	0.3 (0.1)	0.2 (0.25)	0.21 (0.25)	0.17 (0.35)	0.31 (0.08)	0.21 (0.22)
WAIS SS Back	0.2 (0.26)	0.15 (0.39)	0.05 (0.8)	0.23 (0.19)	0.18 (0.32)	0.3 (0.08)
Exec. function	0.24 (0.18)	**0.41 (0.02)**	-0.22 (0.22)	0.24 (0.17)	-0.07 (0.7)	**0.47 (0.01)**
Processing speed						
CRT motor RT	.	.	.	.	.	.
CRT cognitive RT	0.08 (0.66)	0.21 (0.24)	.	.	.	.
CRT total RT	**0.7 (<0.001)**	**0.77 (<0.001)**	**0.68 (<0.001)**	**0.72 (<0.001)**	.	.
SART RT	0.31 (0.09)	**0.44 (0.01)**	0.14 (0.43)	**0.35 (0.04)**	0.28 (0.12)	**0.55 (0.001)**

Table 5.3 (Continued): Spearman's rho correlations for processing speed and executive function for the hearing loss and control groups

	SART RT	
	HL	CG
Executive functions		
SART Com. errs	-0.16 (0.4)	0.26 (0.14)
SART Om. errs	0.02 (0.9)	0.3 (0.08)
SART Tot. errs	-0.03 (0.88)	0.3 (0.08)
CAMDEX VR	-0.08 (0.68)	0.32 (0.07)
Let. fluency	0.31 (0.08)	0.18 (0.32)
Cat. Fluency	**0.38 (0.04)**	0.11 (0.55)
WAIS SS Back	0.31 (0.09)	0.31 (0.08)
Exec. function	0.22 (0.22)	**0.41 (0.02)**
Processing speed		
CRT motor RT	.	.
CRT cognitive RT	.	.
CRT total RT	.	.
SART RT	.	.

Prior to conducting analysis, the scores on all tests were set so that higher score indicated better performance.

The direction of the correlation was positive, indicating that better executive function in the control group was associated with faster response latencies. For the hearing loss group, the executive function measure was not correlated with any of the RT outcomes. The SART error scores had no significant correlations with SART RT for either group (although correlations were larger for controls). For the control group, correlations for SART error scores were stronger with CRT motor

and total RT than with CRT cognitive score. For the hearing loss group, associations were stronger with CRT cognitive RT. Furthermore, the correlations for the controls were generally positive, indicating that better executive function was associated with faster response latencies. In the hearing loss group, better executive function indicated slower response latencies.

This relationship between processing speed and executive function was explored further using hierarchical multiple regression analysis. An assessment was conducted as to whether hearing loss moderated the ability of the SART mean RT to predict SART accuracy scores. An interaction term between SART RT and hearing group was added to the main effects model. SART RT was mean centred prior to inputting into the regression model. Age, gender and years of education were entered as covariates. Preliminary analyses were conducted to ensure that there was no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. One outlier was identified and reviewed to assess leverage and Cook's Distance. Based on these values, it was kept in the model. Hearing group membership moderated the predictive effect of SART mean RT on SART total error score as evidenced by a significant increase in total variation explained of 7.8%, ($F(1, 62) = 5.566$, $p = 0.022$). Simple slopes analysis revealed that there was a statistically significant positive linear relationship between SART mean RT and SART error score in normally hearing participants (beta = 0.072, std. err. 0.029, $p = 0.017$, d = 0.31) but not in hearing loss participants (beta = -0.008, std. err. = 0.017, $p = 0.641$, d = 0.06).

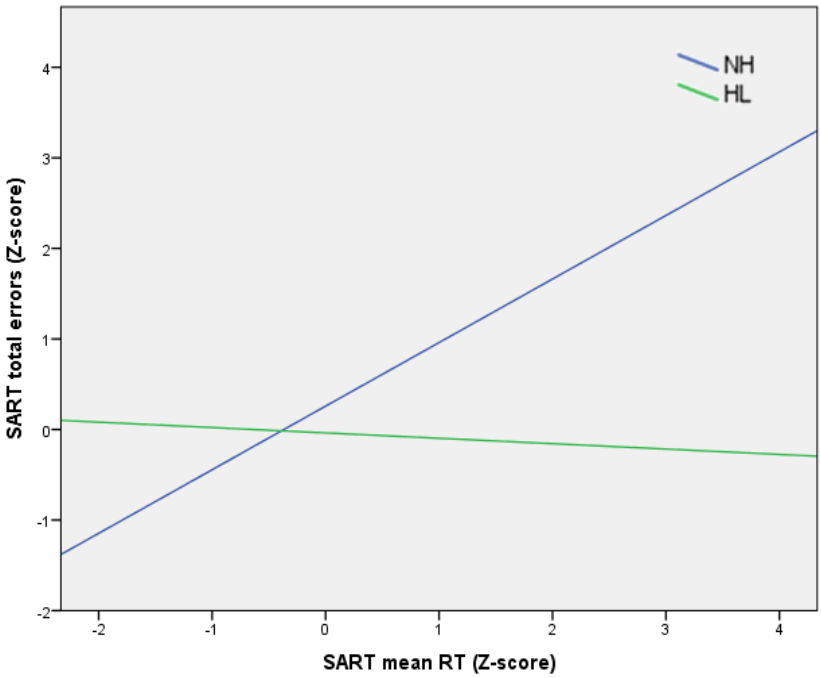

Figure 5.4: Brinley plot of SART error score and SART mean reaction time (RT).

The Graph in Figure 5.4 plots the relationship between SART mean RT and SART total error score for the two groups. The increase in error score was linearly associated with an increase in SART mean RT for the control group but in the hearing loss group an increase in SART mean RT was associated with a reduction in SART error score.

5.3.4 ISD and CV Variability outcomes

Table 5.4: Neuropsychological data for the hearing loss and control groups

	HLG	CG	HLG	CG	Significance test		
	M (SD)	*M (SD)*	*Z (SD)*	*Z (SD)*	*Est.*	*p*	*Cohen's d*
Variability measures							
CRT Mot. ISD	94.42 (49.51)	74.19 (35.31)	-0.12 (1.37)	0.11 (0.41)	*F*; 0.52*	0.47	0.18
CRT Mot. CV	0.27 (0.11)	0.23 (0.09)	-0.05 (1.21)	0.05 (0.77)	*F*; 0.06*	0.82	0.06
CRT Cog. ISD	106.73 (176.33)	77.51 (52.62)	-0.16 (1.39)	0.15 (0.34)	*F*; 2.62*	0.11	0.4
CRT Cog. CV	0.26 (0.2)	0.24 (0.12)	-0.18 (1.32)	0.17 (0.53)	*F*; 2.55*	0.12	0.39
CRT Tot. ISD	163.29 (314.95)	91.68 (77.49)	-0.14 (1.41)	0.14 (0.24)	*F*; 0.51*	0.48	0.18
CRT Tot. CV	0.25 (0.27)	0.18 (0.11)	-0.13 (1.34)	0.12 (0.5)	*F*; 0.13*	0.72	0.09
SART ISD	200.84 (445.66)	112.99 (74.19)	-0.24 (1.13)	0.22 (0.81)	*F*; 2.01	0.16	0.35
SART CV	0.17 (0.19)	0.14 (0.07)	-0.16 (1.09)	0.15 (0.9)	*F*; 0.66	0.42	0.2

SART data log10 transformed.

* Assessed using rank analysis of covariance (Quade, 1967).

Age, gender and years of education included in analyses as covariates. Arithmetic signs on z-scores set so that higher scores indicated better performance.

The ISD and CV outcomes of the CRT motor, cognitive, and total scores, and the SART for the hearing loss and control groups were compared using ANCOVA (Table 5.4). Age, gender and years of education were included in analyses as covariates. There were no significant differences between groups on any of these measures. However, across all outcomes, the effect sizes (Cohen's d) were much lower for CV than for ISD (i.e. when controlling for processing speed) with the exception of CRT cognitive CV and ISD which nearly had the same effect size.

5.3.5 FFT-based model of variability

Linear multiple regression was used to test the ability of the variability components derived from the FFT analysis (SFV and FFV) to predict the SD of the SART RT. A significant association was found [$R^2 = 0.76$ (adjusted $R^2 = 0.75$); $F(2,63) = 100.88$, $p < 0.001$] suggesting that the two components accounted for roughly 75% of the predicted value of the SD of the SART RT supporting the validity of the FFT model of variability (Johnson, Kelly, et al., 2007).

Table 5.5: Neuropsychological data for the hearing loss and control groups				
	HLG *M (SD)*	**CG** *M (SD)*	**HLG** *Z (SD)*	**CG** *Z (SD)*
Frequency variability				
SART FFV	146,123.68 (120,437.67)	123,393.02 (92,094.22)	-0.11 (1.13)	0.10 (0.86)
SART SFV	943.67 (1173.85)	544.59 (610.78)	-0.22 (1.25)	0.21 (0.65)

Table 5.5 (Continued): Neuropsychological data for the hearing loss and control groups			
	Significance test		
	Est.	*p*	*Cohen's d*
Frequency variability			
SART FFV	*F*; 0.17	0.68	0.1
SART SFV	*F*; 2.20	0.14	0.37

SART frequency variability measures log10 transformed.

Age, gender and years of education included as covariates.

There was no significant difference between groups on either SART FFV or SFV as assessed using ANCOVA (Table 5.5). However, the difference between groups on the slow variability outcome was larger compared to that for the fast frequency variability outcome with the hearing loss group demonstrating greater variability.

5.3.6 Moderator analysis

Hierarchical multiple regression was run to assess the increase in FFV explained by SFV and the addition of an interaction term between SFV and hearing group to a main effects model. Age, gender and years of education were entered as covariates. Preliminary analyses were conducted to ensure that there was no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Outliers were identified based on values of studentised deleted residuals, leverage and Cook's Distance. Three outliers were identified. The regression model was run with and without these outliers. As there was little difference in statistical significance or confidence intervals of the coefficients of interest, they were kept in.

Hearing group moderated the increase in FFV observed with change in SFV as evidenced by the addition of the interaction term which explained an additional 7.5% of the total variance, ($F(1, 59) = 6.448$, beta = 77.34, std err. = 30.36, $p = 0.013$). Simple slopes analysis demonstrated that the linear relationship between SFV and FFV was significant for the control group (beta = 112.121, std. err. = 26.624, $p < 0.001$, d = 0.54) and for the hearing loss group (beta = 34.78, std. err. = 14.78, $p = 0.022$, d = 0.3). Compared to the control group, an increase in SFV predicted a significantly lesser degree of increase in FFV for the hearing loss group.

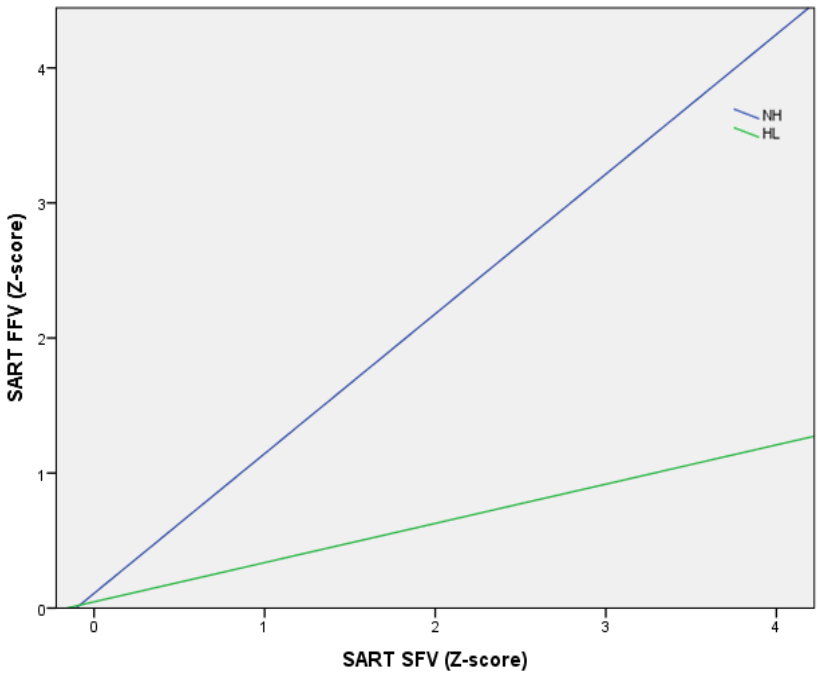

Figure 5.5: Brinley plot of SART slow and fast frequency variability (total test).

The Graph in Figure 5.5 plots the relationship between FFV and SFV (z-scores) for the two groups. For the control group, SFV and FFV were more evenly matched in degree of variability, whereas for the hearing loss group SFV contributed more to the overall variability than FFV. This relationship was also plotted for the first and second halves of the test as shown below:

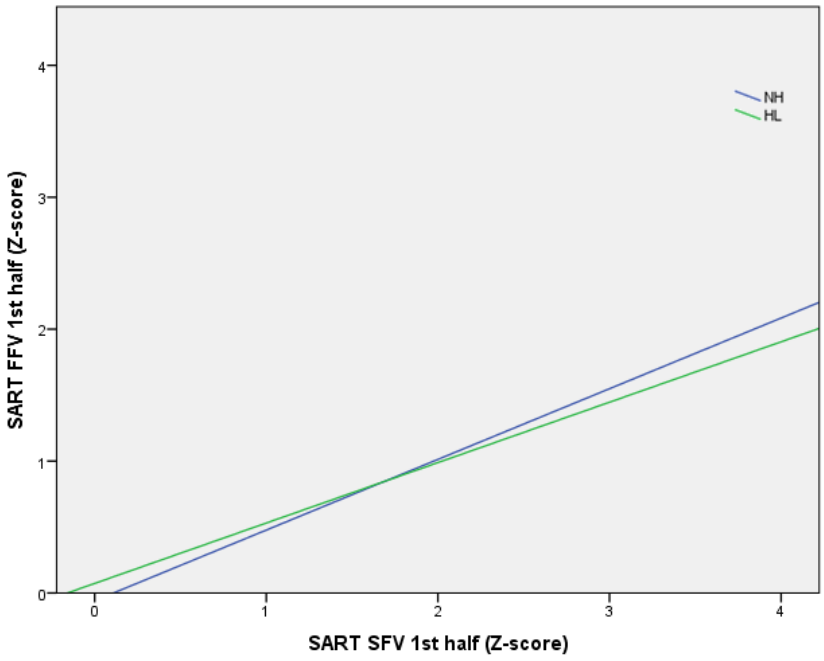

Figure 5.6: Brinley plot of SART slow and fast frequency variability (first half).

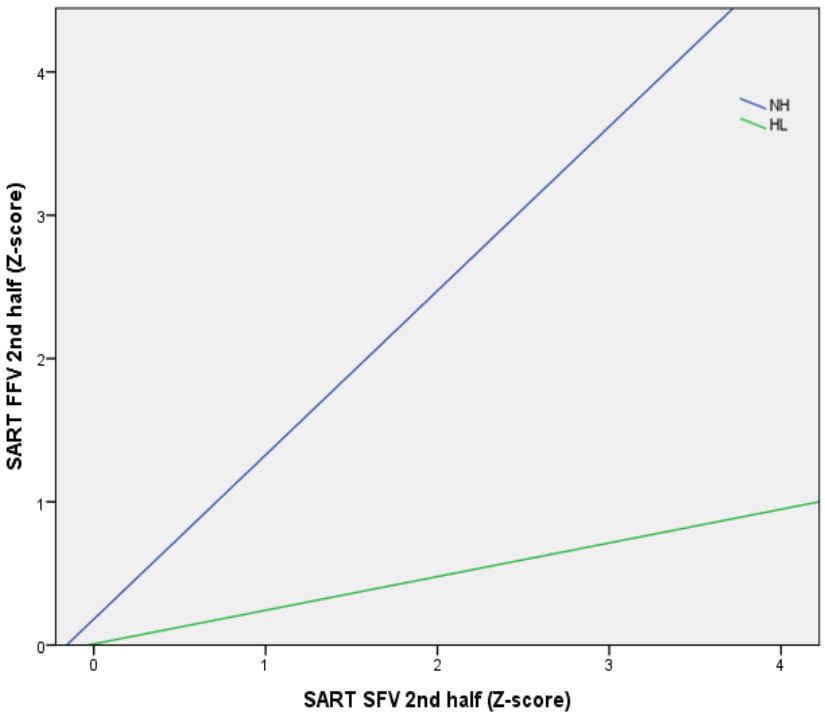

Figure 5.7: Brinley plot of SART slow and fast frequency variability (second half).

Linear mixed models were performed to conduct further analysis of the relationship between hearing group and change in FFV as predicted by SFV over time. These values for the two halves were log-transform$_{10}$ for normality. As fixed effects, the elements entered were time, SFV and hearing group with a time by hearing group by SFV interaction term. Age, gender and education (years) were entered as covariates (fixed effects). As a random effect, subject was entered. Prior to entering any interaction term, there was no significant main effect for any variable. When all terms were entered, there was no significant effect for any of the two-way interaction terms between each of the main predictor variables (group, time and SFV) or the three way interaction term. When the three-way interaction term was dropped from the model, there was no significant effect for any of the two-way interaction terms. When the two-way interaction terms were removed from the model and the three-way term added, there was a significant effect. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality.

Another model was conducted with the slope added as a random factor. Based on the -2 Restricted Log Likelihood and Akaike's Information Criterion, the first model was deemed the better fit. The covariance structure selected for the error terms based on the above criteria for all analyses reported here was scaled identity (which assumes a constant variance across occasions and no correlation between time sections). The main effect for time was significant (beta = 1.41, p = 0.032, d =0.56). The main effect of group was not significant (beta = 1.35, p = 0.11, d = 0.4). There was a significant effect for the interaction between group, time and SFV (beta = -0.9, p = 0.007, d =0.73). There was no significant effect for any of the included covariates ($p > 0.1$). As seen in Figure 5.6, for the first half of the task, variability accounted for a similar proportion of FFV and SFV in the

two groups. However, as seen in Figure 5.7, in the second half, variability accounted for an increasing proportion of FFV for the controls but of SFV for the hearing loss group. This indicates decline in neural arousal levels across task for the hearing loss group.

5.4 Discussion

This chapter examined the relationship between indices of processing speed, intra-individual variability and executive functioning with the purpose of exploring how ARHL may contribute to changes in patterns typically observed in cognitive ageing. Results indicated a qualitatively different relationship between executive function and processing speed for those with hearing loss compared to those with normal hearing. Furthermore, the results indicated that this was due to deterioration in bottom-up, implicit processes in those with hearing loss. As predicted, there was no significant difference between the hearing loss and control groups on any of the CRT processing speed (mean RT) measures but there was a significant difference between groups on SART RT ($p = 0.04$, Cohen's $d = 0.53$). The hearing loss group demonstrated increased SART response latency whereas there was no significant difference between groups in SART error scores.

Correlational analysis found that, for the control group, there were significant associations between the composite executive function score and three of the four processing speed measures, including SART RT, whereas there was none for the hearing loss group. This was further explored by hierarchical multiple regression which found that hearing loss moderated the relationship between SART response latency and accuracy. In the control group, more SART errors were found in conjunction with slower mean RT whereas in the hearing loss group, fewer SART errors were accompanied by slower mean reaction. In contrast to predictions, there were no significant differences in ISD or CV scores between groups on the CRT or the SART. However, there was a decrease in difference between groups when processing speed was controlled for (in CV compared to ISD).

When variance in SART response latency was separated into slow and fast frequency components using the Fast Fourier Transform method there was a greater difference between groups in slow frequency variability (SFV) than in fast frequency variability (FFV). As predicted, the hearing loss group had increased SFV (indicative of deteriorating brain arousal levels), although this was not significant ($p = 0.1$, Cohen's $d = 0.41$). When this was explored further using hierarchical multiple regression, it was found that increase in SFV was associated with significantly less increase in FFV in the hearing loss group. This was interpreted as being due to the larger SFV value for the hearing loss group. In other words, for the control group, both SFV and FFV values contributed roughly equally to the total variance but for the hearing loss group, the majority of the variance was accounted for by SFV. This finding was further supported when explored over time using linear mixed models. The two groups were similar in trajectory for the first half of the test but for the second half the hearing loss group had much greater SFV indicating a deterioration in neural arousal.

Multiple studies of cognitive ageing have highlighted the importance of processing speed and executive function as predictors and possible mediators of age-related cognitive decline (Bouazzaoui et al., 2010; Clarys et al., 2009; Eckert, 2011; Salthouse, 1996, 2010b) with both functions making a unique contribution to the cognitive ageing process (Albinet et al., 2012) and operating in a dynamic relationship (Cabeza & Dennis, 2007). As cognitive performance involves dynamic interactions between multiple domains of cognition (Keller, 2006) and on neural networks between distinct neuroanatomic regions (Andrews-Hanna et al., 2014; Andrews-Hanna et al., 2007; Buckner et al., 2011; Raichle, 2010; Yeo et al., 2011), decline within specific neural systems can have an effect on the aggregate speed of cognitive processes (Eckert, 2011) apart from any global slowing in neural processes i.e. due to loss of myelination and consequent slowing conduction rates (Fjell & Walhovd, 2010; Morris & McManus, 1991). Studies have suggested that ARHL is associated with an accelerated decline in processing speed independent of demographic and cardiovascular risk factors (Lin et al., 2013) but less pronounced decline in executive function (Ronnberg et al., 2014), findings that were supported by the meta-analysis conducted in Chapter 2. However, the mechanistic basis for this association has not been explicated (Wayne & Johnsrude, 2015). The pattern emerging from the findings of this study lends support to the proposed NIEAD hypothesis that ARHL mechanistically disrupts bottom-up automated processes with cascading consequences for efficiency in cognitive functioning.

Hearing loss was associated with a different pattern of performance on the SART task reflecting an altered cognitive strategy. In the control group, an increase in SART errors was associated with slower mean RT reflecting reduced cognitive processing speed or decline in attention or both (Carriere, Cheyne, Solman, & Smilek, 2010; Greene, Bellgrove, Gill, & Robertson, 2009). However, in the hearing loss group, fewer SART errors were accompanied by slower mean RT suggesting that these participants maintained accuracy at the expense of increased response latency (Carriere et al., 2010; Greene et al., 2009). As both groups had the same level of accuracy as measured by commission and omission error scores, this suggests that the hearing loss group was compensating for additional inefficiencies in neural processing. This is in line with previous findings that indicate that older adults increasingly rely on executive functions to promote accuracy, leading to slower performance (Cabeza & Dennis, 2007; Grady, 2012; Grady et al., 1994). However, these findings are typically in comparison to young adults or less successfully ageing older adults (i.e. those who perform poorly in terms of accuracy). Furthermore, this pattern has also been observed when compensating for peripheral sensory deficits and reduced sensory processing such as in the primary auditory and visual cortices (Cabeza & Dennis, 2007; Campbell & Sharma, 2013; Grady, 2012; Grady et al., 1994; Park et al., 2004; Ronnberg et al., 2013). However, such studies examining speed-accuracy trade-offs examine such effects within the modality affected (Cabeza & Dennis, 2007). The tests used in this study to assess processing speed, the CRT and SART, use only visual stimuli. Increased SART response latency in the hearing loss sample cannot be attributed to increased cognitive load induced by peripheral sensory deficits as

observed on tests using auditory stimuli (Tun et al., 2009). This indicates that ARHL has broader effects on cognition beyond neural auditory processes.

This relationship between executive function and processing speed was explored further in this chapter by investigating differences in IIV. It was expected that the hearing loss group would have significantly increased IIV due to the loss of integrity between functional brain networks previously observed (Husain et al., 2014) which has been associated with increased IIV in other populations (Kelly et al., 2008). However, the non-significant finding is consistent with research indicating that IIV is a marker of efficiencies in cognitive control processes (Bellgrove et al., 2004; Stuss et al., 2003) which are hypothesised to be maintained with hearing loss (Ronnberg et al., 2013). This is supported perhaps by the decrease in difference in IIV between groups when processing speed was controlled for, indicating that the discrepancy between groups on SART response latency was due to processes other than decline in executive control processes.

In this study, regression analysis suggested that in normal cognitive ageing, as exemplified here by the control group, there is a similar rate of decline in both FFV and SFV possibly reflecting a broader decline in neural processing efficiency. Previous analyses of variability in older adults using this technique support this finding (O'Halloran et al., 2014; O'Halloran et al., 2011). This was consistent with the findings in the control group where the trajectory of decline shifted toward greater FFV across time on the task indicating that top-down executive processes contributed marginally more to increased IIV. While decline in FFV was similar in the hearing loss group to that observed in the controls, in the hearing loss group there was a greater discrepancy in SFV scores indicating deterioration in brain arousal levels but maintained executive function. This pattern complements neuro-imaging studies that report decreased activity in the primary auditory cortex under challenging listening conditions in conjunction with increased recruitment of executive processes modulated by frontal regions to perceive auditory stimuli (Campbell & Sharma, 2013; Erb & Obleser, 2013; Peelle et al., 2011; Wong et al., 2009). Such studies have reported increased activation of multiple nodes in frontal and parietal regions (Campbell & Sharma, 2013; Husain et al., 2014; Husain, Pajor, et al., 2011) and the anterior insula (Erb & Obleser, 2013) which are associated with the frontoparietal control network (Andrews-Hanna et al., 2014; Niendam et al., 2012) that modulates sustained vigilant attention (Coull, 1998; Coull, Frith, Frackowiak, & Grasby, 1996; Fassbender et al., 2004; O'Connor, Manly, Robertson, Hevenor, & Levine, 2004; Pardo, Fox, & Raichle, 1991).

It is not clear exactly how hearing loss would affect neural arousal response on a visual task. It may possibly be through altered functioning in the locus coeruleus and in the thalamus which processes sensory input (Cappe, Rouiller, & Barone, 2009; Daulatzai, 2016; Van der Werf et al., 2002) and supports arousal in sustained attention (Coull, 1998; Sturm et al., 1999; Van der Werf et al., 2002). Sensory stimulation activates the locus coeruleus and enhances cortical norepinephrine which mediates neural arousal levels. Therefore, sensory decline may lead to down-regulation in function

(see Daulatzai, 2016 for a review). The locus coeruleus innervates the thalamus and cerebral cortex and releases norepinephrine into thalamic and cortical circuits. Therefore, loss of auditory input may disrupt efficient signal processing (Bidelman et al., 2014; Peelle & Wingfield, 2016) in multimodal sensory subcortical networks such as in the thalamus (Van der Werf et al., 2002). Regions thought to be specific to the auditory modality in the thalamus have been demonstrated to integrate visual information to influence behaviour suggesting their interconnection (Budinger & Scheich, 2009; Cappe et al., 2009; Komura, Tamura, Uwano, Nishijo, & Ono, 2005; Noesselt et al., 2010).

Alternatively, higher order executive functions may support perception of auditory stimuli by inhibiting subcortical processing of visual information. The neocortex can contribute to selective attention via corticofugal pathways by inhibiting the sensory information that reaches the thalamus (Nunez & Malmierca, 2007). Diverting resources to one function may accelerate the reduction of neural specialisation in the ventral visual cortex with ageing (Park et al., 2004). An additional pathway is increased cross-modal connectivity and rewiring to support subcortical processing of auditory stimulus when attentional resources are challenged (Horng & Sur, 2006; Komura et al., 2005; Regenbogen et al., 2012), or alternatively, cross-modal re-wiring of the auditory thalamus following loss of auditory input to redirect visual information to the primary auditory cortex (Campbell & Sharma, 2014; Horng & Sur, 2006). Neural reorganisation of the thalamus following hearing loss may disrupt efficiencies in arousal response to visual stimuli. These three pathways: bottom-up loss of sensory input, top-down inhibition of visual input processing and cross-modal integration, may be complementary.

In summary, this chapter has provided evidence that ARHL contributes to an altered trajectory in cognitive ageing and lends support to previous hypotheses that posit that ARHL makes a mechanistic contribution through altered neural activity in bottom-up perceptual-cognitive processes (Campbell & Sharma, 2013; Lin, Ferrucci, et al., 2011; Ronnberg et al., 2013). The ARHL sample demonstrated a qualitatively different pattern on the SART to controls. This suggests that the association of ARHL with cognitive decline is not reflective of advanced physiological ageing but rather that ARHL makes a unique contribution to an altered cognitive trajectory that cumulatively appears as accelerated age-related cognitive decline (Lin et al., 2013). This study is of clinical interest as executive processing may conceal this decline in bottom-up processes in patients with ARHL. ARHL participants demonstrated no difference to controls on the CRT, SART accuracy scores or in any other neuropsychological test included in the assessment battery apart from the MCG Complex Figure Copy Test (explored further in Chapter 7). Therefore, more sensitive cognitive tests which directly assess potentially affected cognitive processes may be required to detect these changes during earlier stages of decline. Further research is required to explore other processes mediated by subcortical regions that may be affected by ARHL and compensatory processes such as motor function. ARHL has been associated with increased risk of

falls (Kamil et al., 2015; Lin & Ferrucci, 2012; Viljanen, Kaprio, Pyykko, Sorri, Pajala, et al., 2009) and poorer mobility (Viljanen, Kaprio, Pyykko, Sorri, Koskenvuo, et al., 2009). The results of this chapter support further exploration of ARHL as a modifiable risk factor for cognitive decline.

Chapter 6 **ARHL & Fluency**

6.1 Introduction

The aim of this thesis is to explore how age-related hearing loss (ARHL) may contribute to cognitive ageing. In the previous chapter, this was examined through its association with processing speed and executive function. In this chapter, the association between ARHL and functioning in the executive and lexical domains is explored. Previous research has suggested that in the ARHL population, semantic and phonological representations in longer-term memory systems undergo decline due to disuse whereas decline in executive function is less pronounced due to its increased recruitment to process speech stimuli (Ronnberg et al., 2013). This was supported by the meta-analysis reported in Chapter 2. Several executive functions, including fluency, had a weaker association with ARHL in cohort studies compared to cross-sectional studies whereas effect sizes for delayed recall and semantic memory were similar across designs. Additionally, there was some evidence of decline in semantic memory, a function normally preserved in older age (Christensen, 2001; Nilsson, 2003; Ofen & Shing, 2013; Salthouse, 2010b; Schaie, 2005). In this chapter, the association of ARHL with performance on verbal fluency tasks was examined as well as how implicit and explicit cognitive processes and the integrity of semantic and phonological representations stored in memory may contribute to variance in performance.

Fluency is a key measure of general executive functioning and semantic memory in normal cognitive ageing (Crawford et al., 2000; Crawford & Henry, 2005; Kemper & McDowd, 2008; Salthouse et al., 2003). The participant is typically required to generate as many words as possible using either categorical (e.g. 'animals') or phonological rules (e.g. letter 'f') within a time limit (usually one minute) (Benton, 1968; Borkowski, Benton, & Spreen, 1967; Kemper & McDowd, 2008). In discourse, older adults often demonstrate difficulties in accessing and retrieving complete stored lexical information (Burke, MacKay, Worthley, & Wade, 1991) resulting in dysfluencies such as pauses, substitution errors and tip-of-the-tongue experiences (Burke, Worthley, & Martin, 1988; Obler, 1980; Ulatowska, Cannito, Hayashi, & Fleming, 1985). Performance on these tasks is assumed to correspond with such general discourse fluency reflecting efficiencies in multiple cognitive processes including semantic access and retrieval (Kemper & McDowd, 2008) as well as attention, inhibition and processing efficiency (Kemper & Sumner, 2001).

Fluency tests are one of the most commonly used neuropsychological assessments of cognitive function in healthy and clinical populations and are sensitive to a wide range of neurological disorders (Kemper & McDowd, 2008; Schmidt et al., 2017). Research suggests that both phonological and semantic fluency are based on clearly distinct and shared sets of neurocognitive processes (Schmidt et al., 2017) with phonological fluency more associated with frontal neural areas which mediate executive processes and semantic fluency more associated with the integrity

of the conceptual knowledge storage in temporal regions (Birn et al., 2010; Demonet et al., 1992; Gourovitch et al., 2000; Henry, Crawford, & Phillips, 2004; Meinzer et al., 2009; Schlosser et al., 1998). This has aided clinical profiling of neurocognitive disorders such as traumatic brain injury (Henry & Crawford, 2004a, 2004b, 2004c). For example, frontal cortical lesions are associated with a greater deficit in phonological fluency whereas in contrast, temporal damage is associated with a larger deficit in semantic fluency (Baldo et al., 2006; Biesbroek et al., 2016; Borkowski et al., 1967; Henry & Crawford, 2004a; Jurado, Mataro, Verger, Bartumeus, & Junque, 2000; Szatkowska, Grabowska, & Szymanska, 2000; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998).

Studies comparing semantic to phonological fluency with normal ageing suggest an advantage for semantic tasks into older age, up into the eighth decade (Cerhan et al., 2002; Kozora & Cullum, 1995; Vaughan et al., 2016). This is possibly due to the increased demands of phonological tasks on working memory to retrieve appropriate words and inhibit task-irrelevant semantic associations (Shao, Janse, Visser, & Meyer, 2014). This advantage appears to be slightly reduced with increasing age (Brickman et al., 2005; Crossley, D'Arcy, & Rawson, 1997; Herrmann, Walter, Ehlis, & Fallgatter, 2006; Kozora & Cullum, 1995; Mathuranath et al., 2003; Tomer & Levin, 1993; Vaughan et al., 2016) and may be insignificant in oldest age (Ravdin, Katzen, Agrawal, & Relkin, 2003). This is of clinical interest as, in a meta-analytic study, AD has been observed to be associated with greater impairment in semantic fluency relative to phonological fluency compared to healthy controls (Henry et al., 2004). This is thought to be due to loss of semantic knowledge in AD (Salmon, 2012) and mild cognitive impairment (MCI) (Clark et al., 2014) reflecting medial temporal lobe damage that is the signature of AD neuropathology (Mirandez, Aprahamian, Talib, Forlenza, & Radanovic, 2017; Rascovsky, Salmon, Hansen, Thal, & Galasko, 2007). This discrepancy, combined with reduced episodic memory, has widespread clinical utility in diagnosing AD (Masur, Sliwinski, Lipton, Blau, & Crystal, 1994; Papp et al., 2016) and has been a predictive marker of conversion to AD in MCI samples (Brandt & Manning, 2009; Nutter-Upham et al., 2008).

However, the literature has provided inconsistent results in respect of this discrepancy in the healthy and clinical populations which has been attributed to differences between studies in the type of letter and semantic category used (Henry et al., 2004; Laws, Duncan, & Gale, 2010; Teng et al., 2013; Vaughan et al., 2016). This variance in findings may also be explained by cognitive reserve having a protective effect on phonological fluency and neuropathology such as β-amyloid (Aβ) having a deteriorative effect on semantic fluency performance in cognitively normal older adults. Neuroimaging studies report that, along with decreased frontal activation with ageing, there appears to be increased fronto-parietal processing to compensate and support performance on fluency tasks (Ansado, Marsolais, Methqal, Alary, & Joanette, 2013; Baciu et al., 2016; Heinzel et al., 2013; Heinzel et al., 2015). Numerous studies report that preserved crystallised intelligence,

indicating no temporal lobe damage due to AD neuropathology (Buckner, 2004), was associated with a semantic advantage for older adults (Christensen, 2001; Nilsson, 2003; Ofen & Shing, 2013; Salthouse, 2010b; Schaie, 2005). A study examining fluency discrepancy in clinically normal older adults with abnormal β-amyloid (Aβ) deposition reported a greater longitudinal decline in semantic scores compared to controls but not for phonological scores (Papp et al., 2016). Atrophy of grey matter in the temporal lobe in older adults with no dementia was also associated with reduced performance in semantic fluency (Pelletier et al., 2017). Furthermore, education (a proxy for reserve) has been reported to be a better predictor of phonological scores than age, which is more closely correlated with semantic fluency (Heinzel et al., 2015; Mathuranath et al., 2003). Education was also associated with maintained activation in the frontal lobe (normally declining with age) during phonological tasks (Heinzel et al., 2013). This is perhaps supported by the finding that, in a mixed AD and control sample, high amyloid burden was associated with poorer semantic fluency but not with phonological fluency and pre-morbid IQ, another proxy for reserve, was associated with letter but not semantic fluency (Rentz et al., 2010).

Another consideration with cognitive tests is the extent to which they assess lower-order semi-automatic, discrete functions (Fodor, 1983; Rosen & Engle, 1997; Waters & Caplan, 1996) or involve executive processes (Just & Carpenter, 1992; Rosen & Engle, 1997). Fluency tasks, in particular, appear to have a multidimensional character whereby various cognitive functions such as verbal ability and executive control contribute to verbal fluency performance (Pakhomov, Jones, & Knopman, 2015; Shao et al., 2014). Research on fluency tests suggest that apart from total scores on phonological/semantic tasks, further markers of differential decline in cognitive functions can be extracted from this data. Speakers may rely on categorical strategies to extract related exemplars from memory such as geographical locations of animals (e.g. animals that live in the jungle or on farms) or words that are homonyms (e.g. fare and fair). This is evidenced by the finding that words are not produced randomly but rather in clusters which index the underlying integrity of semantic and phonological stores (Troyer, Moscovitch, & Winocur, 1997). This model has suggested that clustering relies more on automated cognitive processes whereas switching indicates successful retrieval of new clusters and indexes stronger top-down executive processes (Troyer et al., 1997). Such clusters, usually extracted manually, have been linked with cognitive ageing whereby age was associated with slightly larger clusters and smaller number of switches (Troyer, 2000).

These two components exhibit a similar pattern with frontal vs temporal lobe injury as observed in semantic/phonological discrepancy (Troyer et al., 1998). In phonological and semantic fluency tasks, patients with frontal lesions switch less frequently but produce normal cluster sizes. In contrast, patients with temporal lesions were unimpaired in both switching and clustering on phonological fluency but impaired in switching on semantic fluency tasks. Studies examining these markers in AD have reported smaller clusters (Gomez & White, 2006; Mueller et al., 2015; Ober, Dronkers, Koss, Delis, & Friedland, 1986; Rosen, 1980) and fewer switches compared to healthy

controls (Gomez & White, 2006; Mueller et al., 2015; Murphy, Rich, & Troyer, 2006; Raoux et al., 2008). Neuro-imaging studies have also reported fronto-parietal vs temporal neural correlates for these indices. Switching was associated with increased activation in the left inferior frontal gyrus and bilateral parietal cortex whereas clustering was associated with greater activation in the bilateral temporal cortex (Hirshorn & Thompson-Schill, 2006).

However, this model has been criticised because switching, in particular, may not denote executive processes apart from semantic processes (Mayr, 2002; Mayr & Kliegl, 2000). Additionally, studies relying on such indices of cognitive processes typically rely on subjective assessment of whether words conform to rules (Troyer et al., 1997). This has led to the development of computerised methods to categorise words and extract indices of stored representations from recorded fluency data using electronic lexical databases to quantify the degree of semantic similarity and relatedness between words (Pakhomov, Eberly, & Knopman, 2016; Pakhomov & Hemmy, 2014; Pakhomov, Hemmy, & Lim, 2012; Pakhomov et al., 2015). Such indices have successfully differentiated between clinical groups (Pakhomov et al., 2016; Pakhomov & Hemmy, 2014; Pakhomov et al., 2012). In a cohort ageing study of 239 participants, a higher mean cluster size as assessed by these methods has been associated with a reduced risk of dementia by 38% over six years and 26% over 17 years (Pakhomov & Hemmy, 2014). Another longitudinal study by Pakhomov et al. (2016) found that steeper decline in computer extracted indices of density of repeated words and semantic and lexical diversity (but not mean cluster size) were associated with future development of MCI and dementia. Verbal fluency scores extracted using machine learning and natural language processing outperformed structural MRI measures for predicting MCI conversion to AD (Clark et al., 2016). Such approaches have the potential to allow large scale analyses of fluency data from cohort studies and to provide objective clinical guidelines for diagnosing sub-optimal performance on fluency tasks.

Another technique to examine automated versus explicit cognitive processing in verbal fluency has been to compare the number of words generated across time on the task. The first part of such tasks is thought to be reflective of semi-automatic processes where word production is maximal, whereas the latter parts rely on effortful, time-consuming retrieval from the lexicon to produce words (Crowe, 1998; Fernaeus & Almkvist, 1998). Previous research has reported an interaction between severity of cognitive decline and number of words produced when performance was divided into time intervals (Ober et al., 1986). It has been reported that there was no differential impairment in either mode of retrieval on both types of fluency tasks in preclinical AD and VaD groups (Jones, Laukka, & Backman, 2006) or in AD (Weakley & Schmitter-Edgecombe, 2014). However, a study examining such discrepancy effects in MCI subgroups reported a significant difference compared to controls in the first part of phonological task for the non-amnestic MCI group but not the amnestic or multi-domain MCI subgroups (Weakley, Schmitter-Edgecombe, & Anderson, 2013). No discrepancies across time intervals on the category task were found for any MCI group.

However, another study by Demetriou and Holtzer (2017) reported a similar pattern for the phonological task but also impaired performance for all three MCI subgroups on the category fluency task. This may be due to differences in levels of impairments among samples or to differences in breakdown of time series. Demetriou and Holtzer (2017) examined fluency data in thirds (three sections of 20 seconds), whereas Weakley et al. (2013) examined their data in halves (two sections of thirty seconds).

The purpose of this chapter is to examine how ARHL may be associated with differences in stored semantic and phonological representations and in retrieval of these representations. The implications for fluency performance was explored by administering a semantic and phonological fluency task to a sample of older adults with or without hearing loss as defined by pure-tone audiometry. The data collected were analysed using both manual and computerised methods to extract indices of stored representations in long-term memory. There has been little previous research into how ARHL may contribute to altered performance in fluency tasks and on these markers. Such research is of interest as ARHL disrupts implicit processing of speech stimuli and ARHL patients resort to effortful, explicit processes to perceive and comprehend speech (Campbell & Sharma, 2013; Ronnberg et al., 2013; Tun et al., 2009). Additionally, acquired hearing loss has been associated with deterioration in both phonological (Classon, Rudner, Johansson, et al., 2013; Classon, Rudner, & Ronnberg, 2013; Lazard et al., 2010; Lazard et al., 2013) and semantic stores (Ronnberg et al., 2011; Ronnberg et al., 2013). This would predict that hearing loss participants would demonstrate poorer performance on indices of stored representations which may be compensated for by an increased number of switches. As acquired hearing loss may preferentially disrupt phonological stores (Classon, Rudner, Johansson, et al., 2013; Classon, Rudner, & Ronnberg, 2013; Lazard et al., 2010; Lazard et al., 2013), any discrepancy was predicted to be due to poorer phonological fluency. Additionally, changes in word production and indices across time (three sections of 20 seconds) within both fluency tasks were examined. Consistent with the proposed NIEAD hypothesis, it was predicted that ARHL participants would have poorer performance on the first time section (but not the middle or last sections) of the fluency tasks indicating poorer semi-automatic retrieval.

6.2 Methods

A summary of the methods is outlined below. See Chapter 4 for full details.

6.2.1 Participants

There were 32 hearing loss participants and 33 controls after matching participants for age (± 5 years), gender and pre-morbid IQ (+ 0.5 SDs/7.5 points) and excluding two participants as their phonological fluency scores were not recorded.

6.2.2 Background assessment

Background information was collected from all participants using questionnaires and assessed demographic, audiological, health and clinical factors. All measures were completed by included participants.

6.2.3 Audiological assessment

Objective and self-report measures of hearing loss were completed by all included participants.

6.2.4 Neuropsychological assessment

All neuropsychological measures were completed by included participants.

6.2.5 Fluency tasks

See Chapter 4 for full details on the fluency tasks used. Further analysis was conducted on the fluency tasks by examining discrepancy between semantic and phonological fluency scores, calculated by subtracting the individual phonological scores from individual semantic scores (Discrep). Additionally, the two groups were compared on manually calculated scores of mean cluster size (MCS), mean cluster size excluding single word clusters (MCS>1) and the number of switches between clusters (Swt). Clusters were defined as consecutive groups of semantically or phonologically related words and were grouped following the guidelines of Troyer et al. (1997). Where there was overlap (one or more words belonging to two overlapping clusters) the word was included in the score for both clusters. MCS was calculated by dividing the sum of all clusters by the number of clusters. MCS>1 was calculated by dividing the sum of cluster that contained more than one word by the number of those clusters (Troyer et al., 1997). Errors and repetitions were included when calculating cluster size. Switches were defined as the number of switches between all clusters (including those with only single words) (Troyer et al., 1997).

Further analysis was conducted on the fluency tasks using a computational approach for estimating indices of performance. An overview of the indices and the method used to calculate them is below (See Pakhomov et al. (2016) for a full explanation of this method). These indices were mean cluster size (MCS), mean cluster size excluding one word clusters (MCS>1), number of switches (Swt), cumulative relatedness/semantic diversity (CuRel), and repetition density (RepD) (Pakhomov et al., 2016). Briefly, the vocabulary of words generated in the fluency tasks was extracted and matched to an online dictionary. Words present in the dataset that were not in the dictionary were substituted with an exemplar of the category (e.g. "bird" for "bluetit"). The log likelihood ratio (G^2), a measure of the co-occurrence frequency count, was calculated to quantify the strength of semantic relatedness between each consecutive word (a higher G^2 value indicates that two words are more closely related). The threshold for semantic relatedness at which two words were deemed to be in the same cluster was empirically calibrated based on manual clustering assessments. MCS, MCS>1 and Swt were calculated in the same way as the manual indices. CuRel was calculated as the mean of all pairwise G^2 values. This measure represents the degree of how semantically diverse the

words are in the fluency tasks with greater semantic diversity (or less homogenous responses) indexed by lower CuRel scores. RepD was calculated as the ratio of the count of repeated words to the total number of words uttered in the fluency tasks (lower scores indicate better performance).

In addition to the total number of words for the 60 seconds of the task, the number of words for each third of the task (20 second sections) was calculated separately. The same was done for the discrepancy score and the manually calculated indices. The difference in scores between groups across each third of the tests was also examined.

6.2.6 Procedure

After recruitment, participants underwent neuropsychological and audiometric assessment independently and completed the background questionnaire at home. Participants were contacted if any items were not completed.

6.2.7 Statistical analysis

The statistical methods particular to this study are reported here. Please see Section 4.4.3 in Chapter 4 for a description of how the background and main neuropsychological data were treated, and how normality and group differences in effect sizes were assessed.

Differences between groups on manual and computerised indices of implicit (MCS and MCS>1) and explicit (Swt) function were assessed using either analysis of covariance (ANCOVA) or the non-parametric alternative test, rank analysis of covariance (Quade, 1967), as appropriate. Age, gender and years of education were included as covariates. Although the higher number of outcomes for this main analysis may have increased the risk of type 1 error, all indices were included in the analysis to explore possible differences in outcomes between fluency test (semantic and phonological), indices (MCS and MCS>1) and method of data extraction (manual and computerised).

The second main analysis of implicit and explicit function was conducted on task performance across time. Two-way mixed analysis of variance (ANOVA) was used to examine the differences between groups on mean scores per each third of the semantic and phonological fluency tests. The first third of the test was regarded as an index for implicit function with the following two thirds as an index for explicit function. Linear mixed models (LMM) were also performed to assess this relationship. Age, gender and years of education were included as covariates for both ANOVAs and LMMs.

6.3 Results

6.3.1 Participant characteristics

Based on results from Student's t-tests (two-tailed), Mann-Whitney U and Chi-square, there were no significant differences between groups in age, gender, pre-morbid IQ or education (years and level) (Table 6.1). There were no significant differences on any other background or demographic,

health, clinical and psychosocial factors. There was a significant difference between groups on all audiological measures ($p < 0.001$). This included the WHO pure-tone average in better and worse ear, averages for low and high frequencies and the HHIE-S score. Twenty-three (71.88%) of the participants in the hearing loss group wore hearing aids. None of the participants in the control group wore hearing aids. Fifteen (46.88%) participants in the hearing loss and six (15.15%) in the control group reported having previously experienced tinnitus. One participant in the control group reported difficulty with vision. No participant was excluded based on global cognitive domain score.

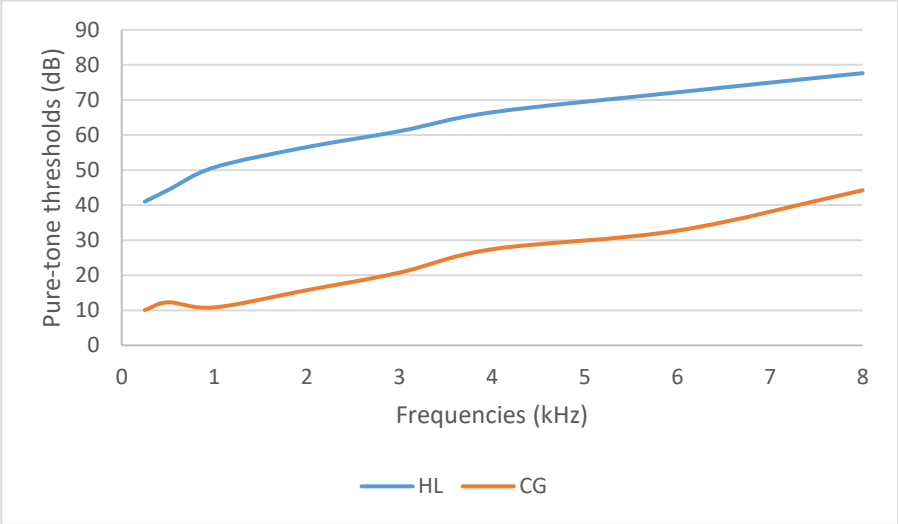

Figure 6.1: Difference in pure-tone threshold between the two groups at each frequency.

Table 6.1: Background data for the hearing loss and control groups					
	Hearing loss group *M (SD)*	**Control group** *M (SD)*	**Significance test**		
			Est.	*p*	*Cohen's d*
Demographic					
N	32	33	-	-	-
Age	71.44 (6.95)	68.48 (6.13)	*t*; -1.82	0.07	0.45
Gender (*female/male*)	19/13	25/8	χ^2; 1.99	0.16	0.36
Education *(years)*	13.98 (3.4)	13.61 (3.28)	*t*; -0.46	0.65	0.11
Education *(level)*	2.66 (0.83)	2.76 (0.83)	*U*; 480.5	0.5	0.17
Marital status *(partner/none)*	21/11	21/12	χ^2; 0.03	0.87	0.04
Audiological					
WHO better ear PTA	48.79 (17.02)	13.6 (6.72)	*U*; 0	**<0.001**	3.37
WHO worse ear PTA	60.27 (25.26)	19.55 (9.03)	*U*; 22	**<0.001**	2.91
Low freq. better ear PTA	39.74 (19.13)	8.18 (5.42)	*U*; 69	**<0.001**	2.25
Low freq. worse ear PTA	50.99 (25.21)	13.94 (7.98)	*U*; 62.5	**<0.001**	2.33
High freq. better ear PTA	61.25 (20.75)	22.47 (10.9)	*U*; 47	**<0.001**	2.52
High freq. worse ear PTA	71.93 (26.61)	31.46 (13.29)	*U*; 83.5	**<0.001**	2.1
Self-rated hearing *(HHIE-S)*	18.81 (9.78)	4.36 (6.35)	*U*; 123	**<0.001**	1.78
Health					
Self-rated physical health	3.72 (0.85)	3.7 (0.92)	*U*; 515	0.86	0.04
Self-rated mental health	4.06 (0.8)	3.91 (1.04)	*U*; 499	0.69	0.1
Alcohol consumption *(yes/no)*	25/7	26/7	χ^2; 0.004	0.95	0.02
Alcohol units *(per wk)*	8.53 (7.46)	9.54 (9.77)	*U*; 319.5	0.92	0.03
Smoker current *(yes/no)*	0/32	1/32	-	>0.99*	0
Smoker former *(yes/no)*	15/17	11/22	χ^2; 1.24	0.27	0.28
Sleep quality *(PSQI)*	5.34 (2.98)	4.76 (2.65)	*U*; 459.5	0.37	0.23
Clinical					
Pre-morbid IQ *(NART)*	112.08 (6.88)	111.23 (8.09)	*U*; 510.5	0.82	0.06
Self-rated memory	3.53 (0.88)	3.24 (0.66)	*U*; 427.5	0.16	0.36
Frailty *(SHARE score)*	0.28 (0.81)	0.22 (0.91)	*U*; 494	0.66	0.11
Depression *(CESD-10)*	5 (3.38)	5.42 (4.99)	*U*; 507.5	0.79	0.07
Anxiety *(HADS-A)*	3.69 (2.81)	4.36 (3.54)	*U*; 486.5	0.58	0.14
Apathy *(AES-S)*	27.22 (5.78)	27.91 (6.95)	*U*; 522	0.94	0.02
Psychosocial					
Social network *(LSNS)*	20.81 (5.13)	19.3 (6.21)	*U*; 455.5	0.34	0.24
Loneliness *(De Jong Gierveld)*	0.44 (0.72)	0.79 (1.29)	*U*; 466	0.35	0.23
Boredom proneness *(Conroy)*	1.44 (0.56)	1.52 (0.67)	*U*; 506	0.74	0.08
Perceived stress *(PSS-4)*	3.28 (2.45)	3.12 (3.23)	*U*; 469	0.44	0.19

AES-S; Apathy Evaluation Scale – Self-rated (Marin et al., 1991); CESD-10; Center for Epidemiologic Studies Depression Scale – 10 item (Radloff, 1977); Conroy; Conroy Boredom proneness (Conroy et al., 2010); De Jong Gierveld; 6-item De Jong Gierveld Loneliness Scale (De Jong Gierveld & Van Tilburg, 2006); HADS-A; Hospital Anxiety and Depression Scale-Anxiety subscale (Zigmond & Snaith, 1983); HHIE-S; Hearing Handicap Inventory for the Elderly Screening Version (Ventry & Weinstein, 1983); LSNS; Lubben Social Network Scale (Lubben et al., 2006); NART; National Adult Reading Test (Nelson, 1982); PSQI; Pittsburgh Sleep Quality Index (Buysse et al., 1989); PSS-4; Perceived Stress Scale-4 item (Cohen et al., 1983); PTA; Pure-tone average; SHARE; Survey of Health, Ageing and Retirement in Europe Frailty Instrument (Romero-Ortuno et al., 2010); WHO; World Health Organisation;

*Fisher's exact test (Cohen's d converted from odds ratio)

Table 6.2: Neuropsychological data for the hearing loss and control groups							
	HLG	**CG**	**HLG**	**CG**	**Significance test**		
	M (SD)	*M (SD)*	*Z (SD)*	*Z (SD)*	*Est.*	*p*	*Cohen's d*
Current sleepiness							
Stanford Sleepiness Scale	1.78 (1.16)	1.76 (0.9)	-0.01 (1.13)	0.01 (0.88)	*U*; 504.5	0.74	0.08
Episodic memory							
FCSRT immediate free recall	33.69 (6.77)	33.45 (5.72)	0.02 (1.09)	-0.02 (0.92)	*t*; -0.15	0.88	0.04
FCSRT immediate total recall	47.81 (1.38)	47.88 (0.55)	-0.03 (1.33)	0.03 (0.53)	*U*; 526	0.96	0.01
FCSRT delayed free recall	12.5 (2.71)	12.48 (2.4)	0 (1.07)	0 (0.95)	*t*; -0.02	0.98	0.01
FCSRT delayed total recall	15.91 (0.39)	15.94 (0.24)	-0.05 (1.21)	0.05 (0.75)	*U*; 526	0.95	0.02
WMS-III spatial span forward	7.09 (1.87)	6.73 (2.11)	0.09 (0.94)	-0.09 (1.06)	*t*; -0.74	0.46	0.18
Composite z-score			0.04 (0.8)	-0.04 (0.65)	*t*; -0.42	0.68	0.1
Executive function							
CAMDEX visual reasoning	3.5 (1.5)	3.85 (1.23)	-0.13 (1.1)	0.13 (0.9)	*U*; 465	0.4	0.21
SART commission errors	3.41 (2.54)	3.76 (2.87)	0.07 (0.94)	-0.06 (1.06)	*t*; 0.36	0.72	0.09
SART omission errors	6.66 (4.92)	7 (7.21)	0.03 (0.8)	-0.03 (1.17)	*t*; -0.16	0.87	0.04
SART total errors	10.06 (6.7)	10.76 (8.79)	0.05 (0.86)	-0.04 (1.13)	*t*; 0.36	0.72	0.09
Phon. fluency *(MoCA)*	14.13 (5.12)	15 (4.09)	-0.1 (1.11)	0.09 (0.89)	*t*; 0.76	0.45	0.19
Sematic fluency *(animals)*	21.66 (5.77)	22.33 (5.4)	-0.06 (1.04)	0.06 (0.97)	*t*; 0.49	0.63	0.12
WMS-III SS backward	6.28 (1.71)	6 (2.12)	0.07 (0.89)	-0.07 (1.11)	*t*; -0.59	0.56	0.15
WMS-III SS total	13.38 (3.09)	12.73 (3.69)	0.1 (0.91)	-0.09 (1.09)	*t*; -0.77	0.45	0.19
Composite z-score			-0.02 (0.61)	0.02 (0.62)	*t*; 0.25	0.8	0.06
Processing speed							
CRT motor mean RT (*ms*)	354.19 (149.51)	305.75 (81.01)	-0.2 (1.23)	0.2 (0.67)	*t*; 1.55	0.13	0.38
CRT cognitive mean RT (*ms*)	525.6 (198.14)	497.05 (76.89)	-0.1 (1.33)	0.09 (0.52)	*t*; 0.36	0.72	0.09
CRT total mean RT (*ms*)	875.8 (313.66)	800.33 (116.23)	-0.16 (1.33)	0.16 (0.49)	*t*; 1.28	0.21	0.32
SART mean RT (*ms*)	348.81 (78.13)	307.72 (44.49)	-0.32 (1.18)	0.31 (0.67)	*t*; 2.26	**0.03**	0.56
Semantic memory							
BNT	55.06 (4.02)	55.36 (3.28)	-0.04 (1.11)	0.04 (0.9)	*U*; 527	0.99	0
Visuospatial ability							
MCG complex figure	24.3 (4.19)	27.36 (4.73)	-0.33 (0.89)	0.32 (1.01)	*t*; 2.76	**0.01**	0.68
Global cognition							
MoCA	25.63 (2.848)	25.82 (3.29)	-0.03 (0.93)	0.03 (1.08)	*U*; 480.5	0.53	0.16
MoCA adj.*	17.47 (1.72)	17.42 (2.25)	0.01 (0.86)	-0.01 (1.13)	*U*; 491.5	0.63	0.12
Composite global z-score [+]			-0.04 (0.6)	0.04 (0.4)	*t*; 0.61	0.55	0.15

[*] Equal variances not assumed

+ Composite z-score calculated from the mean of the composite scores for episodic memory (except FCSRT and Spatial Span total scores), executive functions and from the scores for processing speed (CRT total mean RT), semantic memory and visuospatial ability.

All CRT reaction times and SART mean RT transformed to inverse scores to account for non-normality. SART commission and total errors were transformed to square root and omission errors to $\log_{10}(+1)$. Arithmetic signs on z-scores set so that higher scores indicated better performance.

6.3.2 **Neuropsychological performance**

There was no significant difference between groups on the Stanford Sleepiness Scale (Table 6.2). There was no differences in episodic memory and executive function measures or composite scores. This included the semantic and phonological fluency tasks. There were no significant differences in semantic memory or global cognition. There was a significant difference in the MCG Complex Figure Copy Test ($t(63) = 2.76$, $p = 0.01$, $d = 0.68$). This will be explored and discussed further in Chapter 7. As regards processing speed, there was no significant difference between groups on any of the CRT scores. However there was a significant difference between groups on SART RT ($t(63) = 2.26$ $p = 0.03$, Cohen's $d = 0.56$). This was explored and discussed further in Chapter 5.

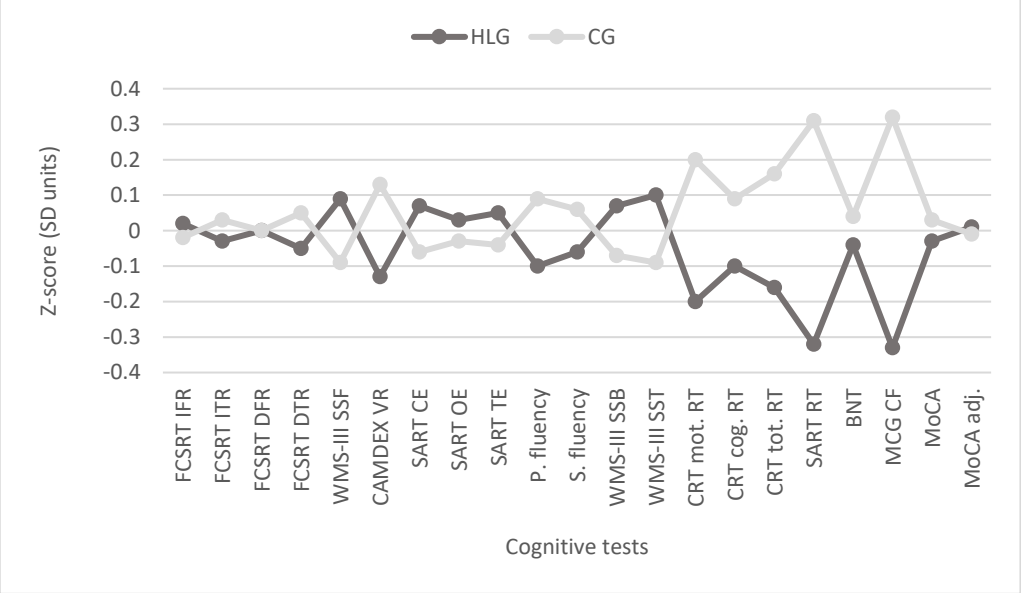

Figure 6.2: Difference in mean performance between the two groups on each cognitive test (based on z-scores).

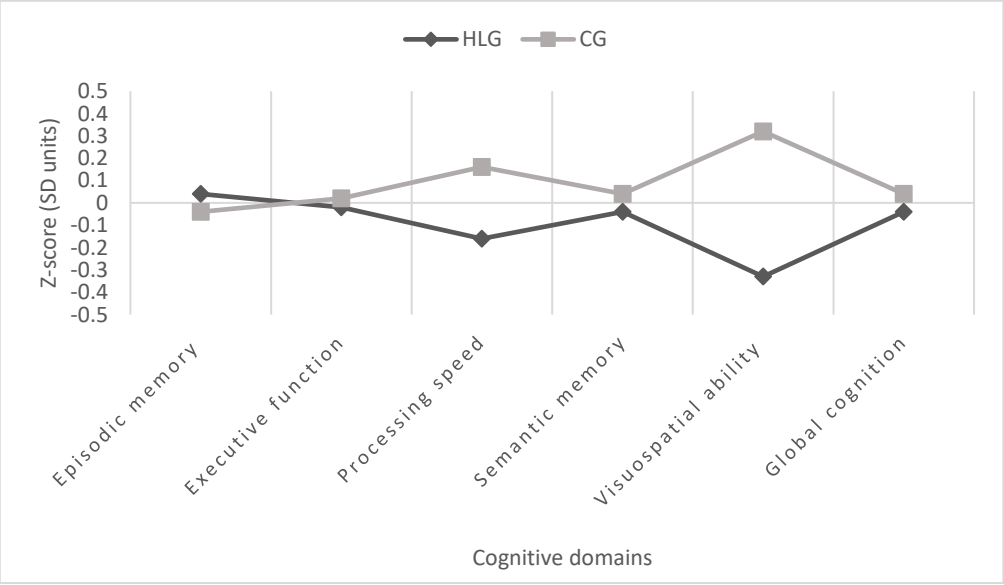

Figure 5.3: Difference in mean performance between the two groups on each cognitive domain (based on z-scores).

6.3.3 Fluency indices

All indices for both groups were compared using ANCOVA or the non-parametric alternative test, rank ANCOVA (Quade, 1967) with age, gender and years of education included as covariates (Table 6.3). There was no significant difference between groups on any of the fluency indices with the exception of the manual phonological MCS>1. The computerised phonological MCS>1 approached significance as did manual phonological MCS. The remaining indices were also explored using the same statistical analysis (Table 6.4). There was no difference between groups on the semantic/phonological discrepancy score. There was also no significant difference between groups on the CuRel and RepD.

Table 6.3: Fluency indices for the two groups of participants

	HLG *M (SD)*	CG *M (SD)*	HLG *Z (SD)*	CG *Z (SD)*	Significance test *Est.*	*p*	*Cohen's d*
Manual fluency indices of implicit/explicit function							
Semantic MCS	3.56 (1.15)	3.54 (1.09)	0.01 (1.04)	-0.01 (0.98)	*F*: 0.02	0.90	0.04
Phonological MCS	1.44 (0.28)	1.56 (0.37)	-0.19 (0.83)	0.19 (1.12)	*F*: 3.48	0.07	0.46
Semantic MCS>1	4.16 (1.34)	4.16 (1.2)	-0.002 (1.06)	0.002 (0.96)	*F*: 0.03	0.87	0.04
Phonological MCS>1	2.38 (0.92)	2.65 (0.67)	-0.17 (1.14)	0.17 (0.83)	*F*: 5.22*	0.03	0.57
Semantic Swt	6.03 (2.16)	6.3 (2.42)	-0.06 (0.95)	0.06 (1.06)	*F*: 0.004	0.95	0.02
Phonological Swt	9.81 (3.95)	9.91 (3.49)	-0.01 (1.07)	0.01 (0.94)	*F*: 0.13	0.72	0.09
Computerised fluency indices of implicit/explicit function							
Semantic MCS	1.45 (0.16)	1.51 (0.19)	-0.18 (0.9)	0.18 (1.07)	*F*: 1.01	0.32	0.25
Phonological MCS	1.57 (0.52)	1.65 (0.4)	-0.08 (1.14)	0.08 (0.86)	*F*: 2.56*	0.11	0.40
Semantic MCS>1	2.16 (0.14)	2.22 (0.19)	-0.17 (0.82)	0.16 (1.14)	*F*: 0.60*	0.44	0.19
Phonological MCS>1	2.22 (0.62)	2.29 (0.54)	-0.07 (1.07)	0.06 (0.94)	*F*: 3.62*	0.06	0.47
Semantic Swt	14.66 (4.65)	14.55 (4.61)	0.01 (1.01)	-0.01 (1.00)	*F*: 0.00	0.98	0
Phonological Swt	8.34 (3.41)	8.79 (3.07)	-0.07 (1.06)	0.07 (0.95)	*F*: 0.31	0.58	0.14

* Assessed using rank analysis of covariance (Quade, 1967).

Age, gender and years of education included in analyses as covariates.

Table 6.4: Additional fluency data for the two groups of participants

	HLG *M (SD)*	CG *M (SD)*	HLG *Z (SD)*	CG *Z (SD)*	Significance test *Est.*	*p*	*Cohen's d*
Sem/Phon discrepancy							
Discrep	7.53 (5.36)	7.33 (4.89)	0.02 (1.05)	-0.02 (0.96)	*F*; 0.07	0.80	0.07
Additional Computerised indices							
Semantic CuRel	0.43 (0.04)	0.42 (0.05)	0.11 (0.87)	-0.1(1.12)	*F*; 1.04	0.31	0.25
Phonological CuRel	0.28 (0.05)	0.28 (0.04)	-0.07 (1.15)	0.07 (0.84)	*F*; 0.52	0.47	0.18
Semantic RepD	0.02 (0.06)	0.01 (0.02)	0.11 (1.36)	-0.11 (0.42)	*F*; 0.17*	0.68	0.1
Phonological RepD	0 (0.01)	0 (0.01)	0.09 (1.21)	-0.09 (0.76)	*F*; 0.42*	0.52	0.16

* Assessed using rank analysis of covariance (Quade, 1967).

Age, gender and years of education included in analyses as covariates.

6.3.4 Mixed ANOVA on time series analysis for word generation

For the semantic task, two-way mixed ANOVAs were conducted to examine the differences between groups on mean scores per each third time section with age, gender and education (years) entered as covariates. There were no outliers, as assessed by examination of studentised residuals for values greater than ±3. There was homogeneity of variances ($p > .05$) and covariances ($p > .05$), as assessed by Levene's test of homogeneity of variances and Box's M test, respectively. Mauchly's test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $\chi^2(2) = 0.327$, $p = 0.849$. There was no statistically significant interaction between groups and fluency score across time $F(2, 120) = 0.830$, $p = 0.439$, $d = 0.23$. There was no significant effect for any of the covariates. However, the main effect of years of education with time approached significance $F(2, 120) = 2.839$, $p = 0.062$, $d = 0.42$. The main effect of time showed a statistically significant difference in semantic fluency score at the different time points, $F(2, 120) = 5.863$, $p = 0.004$, $d = 0.6$. Post hoc analysis with a Bonferroni adjustment revealed that fluency scores decreased significantly from the first section to the second (-6.11 95% CI: -7.1 to -5.13, $p < 0.001$) and from the second to the last (-1.38, 95% CI: -2.31 to -0.46, $p = 0.001$). The main effect of group was that there was no statistically significant difference in semantic fluency scores between groups $F(2, 120) = 0.209$, $p = 0.65$, $d = 0.11$.

For the phonological task, the same two-way mixed ANOVA analysis was conducted with age, gender and education (years) entered as covariates. There were no outliers, as assessed by examination of studentised residuals for values greater than ±3. There was homogeneity of variances ($p > .05$) and covariances ($p > .05$), as assessed by Levene's test of homogeneity of variances and Box's M test, respectively. Mauchly's test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $\chi^2(2) = 0.21$, $p = 0.9$. There was a statistically significant interaction between groups and fluency score across time $F(2, 120) = 3.948$, $p = 0.022$, $d = 0.49$. There was no significant effect for any of the covariates. There was a statistically significant difference in phonological fluency score between groups in the first section of the test (0-20 seconds), $F(1, 60) = 4.269$, $p = 0.043$, $d = 0.51$. There was no statistically significant difference between groups for the middle ($F(1, 60) = 0.999$, $p = 0.322$, $d = 0.25$) or last section of the test ($F(1, 60) = 1.308$, $p = 0.257$, $d = 0.28$). There was no significant effect for any of the covariates with the exception of gender in the 21-40 seconds section with a higher score for males ($F(1, 60) = 4.055$, $p = 0.049$, $d = 0.5$). There was no statistically significant effect for time, $F(2, 120) = 0.972$, $p = 0.381$, $d = 0.24$.

6.3.5 Linear mixed models on time series analysis

6.3.5.1 Linear mixed model construction

Linear mixed models were used to conduct further analysis of the relationship between hearing group and fluency scores and indices by time. As fixed effects, time section and group with a time by group interaction term were entered. Age, gender and education years were entered as

covariates. Subject was entered as a random effect. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality. Models were fitted and compared based on the -2 Restricted Log Likelihood and Akaike's Information Criterion. Another model was conducted with the slope added as a random factor. The first model was deemed the better fit. The covariance structure selected for the error terms was based on the above criteria (Heck, Thomas, & Tabata, 2011). The results for the final models are shown in Tables 6.5, 6.6, 6.7 and 6.8.

6.3.5.2 Word generation

With respect to category fluency, there was no significant main effect for any variable prior to adding the interaction term except for time (beta = -3.75, $p < 0.001$, d = 2.29). When the interaction term was added to the model, there was a significant main effect for time only (beta = -3.51, $p < 0.001$, d = 1.52). The main effect of group was not significant (beta = 0.1, p = 0.92, d = 0.02) nor was the interaction between group and time (beta = -0.16, p = 0.72, d = 0.09). There was no significant effect for any of the included covariates.

With respect to phonological fluency, there was no significant main effect for any variable prior to adding the interaction term except for time (beta = -1.65, $p < 0.001$, d = 3.09). When the interaction term was added to the model, there was a significant main effect of time (beta = -2.86, $p < 0.001$, d = 2.21). The main effect of group was significant (beta = -2, p = 0.006, d = 0.73). Additionally, the interaction between group and time was also significant (beta = 0.81, p = 0.008, d = 0.7). There was no significant effect for any of the included covariates. Between T1 and T2 there was a significant main effect for group (beta = -2.13, p = 0.03, d = 0.55) and for time (beta = -3.58, $p < 0.001$, d = 1.1), but no significant effect for the interaction term (beta = 0.85, p = 0.15, d = 0.37). Between T1 and T3 there was a significant main effect for group (beta = -1.92, p = 0.009, d = 0.7), for time (beta = -2.86, $p < 0.001$, d = 2.47) and for the interaction between group and time (beta = 0.81, p = 0.006, d = 0.74). There was no significant effect for group or the interaction between group and time between T2 and T3.

Table 6.5: Linear mixed effects model of word generation across time

	Estimate	Std. Error	*t*	Sig.
Semantic word generation				
Time	-3.51	0.71	-4.95	**<0.001**
Hearing group	0.1	1.02	0.1	0.92
Hearing group*Time	-0.16	0.45	-0.36	0.72
Age	-0.01	0.04	-0.35	0.73
Gender	-0.45	0.49	-0.92	0.36
Education (*years*)	0	0.07	0.04	0.97
Phonological word generation				
Time	-2.86	0.47	-6.07	**<0.001**
Hearing group	-2	0.71	-2.82	**0.01**
Hearing group*Time	0.81	0.3	2.71	**0.01**
Age	-0.01	0.03	-0.49	0.63
Gender	-0.74	0.4	-1.84	0.07
Education (*years*)	0.03	0.06	0.58	0.57

6.3.5.3 Semantic/phonological discrepancy

Linear mixed models were also conducted to examine the discrepancy between semantic and phonological fluency scores over time. A quadratic time term was added to improve model fit. There was no significant main effect for any variable prior to adding the interaction term except for time (beta = -8.9, $p < 0.001$, d = 1.72). When the interaction term was added to the model, there was a significant main effect for time (beta = -7.45, $p < 0.001$, d = 1.18). The main effect of group was significant (beta = 2.1, p = 0.047, d = 0.51). Additionally, the interaction between group and time was also significant (beta = -0.97, p = 0.042, d = 0.52). There was no significant effect for any of the included covariates. Between T1 and T2 there was a significant main effect for group (beta = 3.12, p = 0.04, d = 0.53) but not for time (beta = -1.38, p = 0.34, d = 0.24), or the interaction term (beta = -1.63, p = 0.08, d = 0.45). Between T1 and T3 there was a significant main effect for group (beta = 2.28, p = 0.042, d = 0.52) but not for time (beta = -0.65, p = 0.4, d = 0.21). There was a significant effect for the interaction between group and time (beta = -0.97, p = 0.047, d = 0.51). There was no significant effect for group or the interaction between group and time between T2 and T3.

Table 6.6: Linear mixed effects model of Phonological /Semantic Discrepancy across time

	Estimate	Std. Error	*t*	Sig.
Phonological/Semantic Discrepancy				
Time	-7.45	1.80	-4.13	**<0.001**
Hearing group	2.10	1.05	2.00	**0.047**
Hearing group*Time	-0.97	0.47	-2.05	**0.04**
Age	0.00	0.03	0.05	0.96
Gender	0.28	0.47	0.60	0.55
Education (*years*)	-0.03	0.07	-0.45	0.65
Quadratic time	1.70	0.41	4.14	**<0.001**

6.3.5.4 Manual fluency indices

The same linear mixed model procedure and analysis was repeated for MCS, MCS>1 and Swt. For semantic fluency, there was no significant effect for group or for the interaction term in any of these variables. With respect to phonological fluency, there was no significant effect for group or the interaction term on the MCS. For the MCS>1, there was a significant effect for group (beta = -1.59, p = 0.001, d = 0.91) and for time (beta = -1.49, $p < 0.001$, d = 1.27). There was a significant effect for the interaction between group and time (beta = 0.63, p = 0.004, d = 0.76). There was also a significant effect for gender with females generating smaller clusters (beta = -0.51, p = 0.01, d = 0.68). This was further explored across time sections. From T1 to T2, the group (beta = -2.57, $p < 0.001$, d = 1.03), time (beta = -2.38, $p < 0.001$, d = 0.95), and interaction terms (beta = 1.36, p = 0.002, d = 0.83) were significant. From T1 to T3, the group (beta = -1.81, $p < 0.001$, d = 1.09), time (beta = -0.76, $p < 0.001$, d = 1.37) and interaction terms (beta = 0.63, p = 0.003, d = 0.82) were also

significant. For T2 to T3, there were no significant results. For number of switches, there was no significant effect for group or the interaction term.

Table 6.7: Linear mixed effects model of manual indices

	Estimate	Std. Error	*t*	Sig.
Semantic MCS				
Time	-1.07	0.56	-1.9	0.06
Hearing group	-0.2	0.79	-0.25	0.8
Hearing group*Time	-0.02	0.36	-0.06	0.95
Age	0.01	0.02	0.25	0.81
Gender	0.06	0.34	0.18	0.86
Education (*years*)	-0.01	0.05	-0.29	0.77
Phonological MCS				
Time	-0.44	0.2	-2.21	**0.03**
Hearing group	-0.4	0.28	-1.43	0.16
Hearing group*Time	0.2	0.13	1.56	0.12
Age	0.004	0.01	0.53	0.6
Gender	-0.19	0.1	-1.94	0.06
Education (*years*)	0.02	0.01	1.77	0.08
Semantic MCS>1				
Time	-0.97	0.44	-2.18	**0.03**
Hearing group	0.10	0.62	0.17	0.87
Hearing group*Time	-0.19	0.28	-0.67	0.5
Age	0.02	0.03	0.64	0.53
Gender	0.03	0.37	0.08	0.94
Education (*years*)	-0.01	0.05	-0.10	0.92
Phonological MCS >1				
Time	-1.49	0.34	-4.35	**<0.001**
Hearing group	-1.59	0.47	-3.36	**0.001**
Hearing group*Time	0.63	0.22	2.9	**0.004**
Age	0.01	0.01	1.07	0.29
Gender	-0.51	0.19	-2.61	**0.01**
Education (*years*)	0.05	0.03	1.81	0.07
Semantic Swt				
Time	-1.09	0.33	-3.34	0.001
Hearing group	0.09	0.45	0.2	0.84
Hearing group*Time	-0.05	0.21	-0.25	0.81
Age	-0.02	0.01	-1.59	0.12
Gender	-0.09	0.18	-0.51	0.61
Education (*years*)	0.0004	0.03	0.02	0.99
Phonological Swt				
Time	-1.11	0.4	-2.76	0.01
Hearing group	0.22	0.6	0.37	0.72
Hearing group*Time	-0.13	0.26	-0.52	0.61
Age	-0.02	0.02	-0.75	0.46
Gender	-0.23	0.33	-0.69	0.5
Education (*years*)	-0.001	0.05	-0.03	0.98

Negative result for group indicates poorer performance with hearing loss. Negative results for gender indicates poorer performance for females.

6.3.5.5 Computerised fluency indices

The same linear mixed model procedure and analysis was repeated for the computerised fluency indices. Due to the low scores for RepD, no further analysis was conducted on this marker. There was no significant effect for group or the interaction term in any of these variables for semantic fluency with the exception of MCS for which group was significant (beta = -0.3, p = 0.02, d = 0.59). However, the interactions terms for MCS (beta = -0.12, p = 0.07, d = 0.46) and Swt (beta = -0.55, p = 0.08, d = 0.45) approached significance. With respect to phonological fluency, for the

MCS, there was a significant effect for group (beta = -0.51, p = 0.01, d = 0.71) and for time (beta = -0.4, p = 0.01, d = 0.69). There was a significant effect for the interaction between group and time (beta = 0.26, p = 0.01, d = 0.7). This was further explored across time sections. From T1 to T2, the group (beta = -0.75, p = 0.003, d = 0.83), time (beta = -0.76, p = 0.004, d = 0.8), and interaction terms (beta = 0.46, p = 0.01, d = 0.76) were significant. From T1 to T3, the group term was significant (beta = -0.47, p = 0.02, d = 0.64), and the interaction term approached significance (beta = 0.2, p = 0.06, d = 0.48). From T2 to T3 there were no significant results. For MCS>1 and Swt, there was no significant effect for group or the interaction term. For the phonological CuRel, there was a significant effect for group (beta = -0.08, p = 0.01, d = 0.66) and the effect for time approached significance (beta = -0.05, p = 0.07, d = 0.47). The interaction between group and time approached significance (beta = 0.03, p = 0.07, d = 0.46). There was also a significant effect for age (beta = 0.002, p = 0.04, d = 0.52).

Table 6.8: Linear mixed effects model of computerised indices

	Estimate	Std. Error	*t*	Sig.
Semantic MCS				
Time	-0.36	0.11	-3.34	**0.001**
Hearing group	-0.3	0.13	-2.3	**0.02**
Hearing group*Time	0.12	0.07	1.81	0.07
Age	0.0003	0.004	0.09	0.93
Gender	-0.03	0.05	-0.59	0.55
Education (*years*)	-0.001	0.01	-0.08	0.93
Phonological MCS				
Time	-0.4	0.15	-2.63	**0.01**
Hearing group	-0.51	0.19	-2.72	**0.01**
Hearing group*Time	0.26	0.1	2.68	**0.01**
Age	0.01	0.01	0.95	0.35
Gender	-0.14	0.11	-1.25	0.22
Education (*years*)	0.01	0.02	0.89	0.38
Semantic MCS>1				
Time	-0.38	0.21	-1.78	0.08
Hearing group	-0.11	0.23	-0.5	0.62
Hearing group*Time	-0.03	0.14	-0.24	0.81
Age	0.01	0.01	1.45	0.15
Gender	-0.03	0.1	-0.34	0.74
Education (*years*)	-0.01	0.01	-0.42	0.68
Phonological MCS >1				
Time	-0.38	0.21	-1.78	0.08
Hearing group	-0.11	0.23	-0.5	0.62
Hearing group*Time	-0.03	0.14	-0.24	0.81
Age	0.01	0.01	1.45	0.15
Gender	-0.03	0.1	-0.34	0.74
Education (*years*)	-0.01	0.01	-0.42	0.68
Semantic Swt				
Time	-1.34	0.48	-2.76	**0.01**
Hearing group	1.11	0.72	1.54	0.13
Hearing group*Time	-0.55	0.31	-1.78	0.08
Age	-0.01	0.03	-0.3	0.77
Gender	-0.2	0.42	-0.49	0.63
Education (*years*)	0.01	0.06	0.14	0.89
Phonological Swt				
Time	-1.55	0.37	-4.24	**<0.001**
Hearing group	-0.98	0.59	-1.68	0.1
Hearing group*Time	0.39	0.23	1.67	0.1
Age	-0.02	0.02	-1.2	0.24

Gender	-0.25	0.29	-0.85	0.4
Education (*years*)	0.03	0.04	0.62	0.54
Semantic CuRel				
Time	-0.03	0.03	-1.04	0.3
Hearing group	-0.01	0.03	-0.32	0.75
Hearing group*Time	-0.01	0.02	-0.27	0.79
Age	0.00001	0.001	0.01	1
Gender	-0.003	0.01	-0.19	0.85
Education (*years*)	-0.001	0.002	-0.33	0.75
Phonological CuRel				
Time	-0.05	0.03	-1.87	0.07
Hearing group	-0.08	0.03	-2.56	**0.01**
Hearing group*Time	0.03	0.02	1.83	0.07
Age	0.002	0.001	2.06	**0.04**
Gender	-0.01	0.02	-0.87	0.39
Education (*years*)	0.002	0.002	0.71	0.48

Negative result for group indicates poorer performance with hearing loss. Negative results for gender indicates poorer performance for females.

6.4 Discussion

This chapter examined the relationship between ARHL and indices of semantic and phonological memory and automated versus explicit access and retrieval from memory based on fluency performance. The purpose was to examine how ARHL may affect stored representations in memory and access to these representations. There was no significant difference between groups in background data apart from audiological measures. There was also no difference between groups in neuropsychological tests apart from SART mean reaction time and MCG Complex Figure Copy Test (examined in Chapters 5 and 7, respectively). There was no significant difference between groups in total number of words generated on semantic or phonological fluency tasks or in discrepancy between numbers of words generated on these two tasks. There was no difference between groups in total scores for either manual or computerised indices of mean cluster size, number of switches between clusters, or in semantic diversity (CuRel) and repetition density (RepD). The only exception was the manually calculated phonological MCS>1 which was significant ($p = 0.03$). This data was analysed further by examining differences in these scores across time with age, gender and years of education as covariates. Contrary to initial predictions, no statistically significant difference was found between groups across time for semantic fluency scores or indices, although, results for the computerised semantic MCS suggested that hearing loss was associated with smaller clusters and with an increased number of switches between clusters at the start of the task. This may indicate a compensatory strategy in the hearing loss group whereby there is increased reliance on explicit processes (switching) to compensate for decline in implicit processes (MCS) on the semantic task. Consistent with *a priori* predictions, there was a statistically significant interaction between groups and number of words generated on the phonological task across time. Further analysis found that this was due to poorer performance by the ARHL group in the first 20 seconds of the task and that hearing loss was associated with an attenuated rate of decline in word production across task. A similar pattern was observed for phonological manual MCS>1 and computerised MCS. Hearing loss was associated with poorer MCS in the first 20

seconds and with attenuated decline in MCS over time on task. Contrary to predictions, no significant effect was observed for the number of switches. However, for the phonological CuRel, a measure of diversity, results suggested that those with hearing loss were producing more diverse words and then gave more homogenous responses over time on the task. When the discrepancies in word production on semantic and phonological tasks were examined, hearing loss was associated with significantly higher discrepancy scores and with more attenuated decline in discrepancy across time.

The lack of significant difference between groups on total scores may have been due to more significant degradation being required before presenting a noticeable deteriorative effect on these outcomes (Raoux et al., 2008; Troyer, 2000). Total scores from fluency measures may not therefore be sensitive to the effects of hearing loss on phonological and semantic representations as observed using other methods (Andersson, 2002; Andersson & Lyxell, 1998; Lyxell et al., 2003). This may be due to compensatory efforts in working memory to support access to representations in memory or to support clustering. Phonological processing skills in working memory in those with acquired hearing loss have been reported to be maintained when representations of phonological sounds in memory have degraded (Andersson, 2002; Andersson & Lyxell, 1998; Lyxell et al., 2003). Additionally, if there are sufficient resources to access and organise lexical-semantic information on the fluency task there would be less need for hearing loss participants to rely on increased switching to compensate. Another possibility, discussed further below, is a switch to a semantic strategy to compensate for deterioration in phonological representations stored in memory and to complete the fluency task successfully.

The results from the time series analysis suggested that semi-automatic processes in phonological processing are impaired in the hearing loss group. Once explicit retrieval was initiated, both groups produced a similar number of words in the middle and last parts of the phonological fluency task (21-60 seconds) and produced a similar total score for the entire task. Interestingly, in the study by Demetriou and Holtzer (2017), using linear mixed models, the authors observed that MCI subgroups had an attenuated rate of decline in their performance over the one minute of administration in both semantic and phonological fluency tasks compared to controls (except for the amnestic MCI subgroup who demonstrated no difference in rate on the phonological fluency task). In this study, the same pattern was observed on the phonological task. The ARHL group had a poorer word count in the first 20 seconds but an attenuated rate of decline in word production compared to controls. Demetriou and Holtzer (2017) attributed this discrepancy between effect of group and group-by-time interaction as being due to impaired automatic retrieval in the MCI groups. The control group relied on faster, semi-automatic retrieval processes before switching to slower, more effortful retrieval leading to a greater discrepancy between the first time section and the subsequent two sections. It is worth noting that, in this study, despite this difference in the first third of the test, there was no significant difference between groups in total word output as

observed in MCI groups (Demetriou & Holtzer, 2017). This suggests that the hearing loss group relied increasingly on executive processes from an early stage in the phonological fluency task to maintain performance. Results from the phonological CuRel in conjunction with smaller MCS suggest that they relied more on switching to new clusters early in the task to produce words and less on connectivity within clusters, as controls did.

It is interesting to note that among MCI subgroups, both the amnestic and non-amnestic MCI subgroups demonstrated impaired automatic retrieval on the category fluency task, but only the non-amnestic group demonstrated this pattern on the phonological task (Demetriou & Holtzer, 2017). Therefore, those with ARHL may demonstrate a pattern of decline in fluency similar to that observed both in accelerated normal ageing (Baciu et al., 2016; Hoyau et al., 2017) and in non-amnestic cognitive impairment (Demetriou & Holtzer, 2017) whereby a slowing of implicit access to lexico-semantic storage and retrieval from it precedes loss of semantic representations (i.e. poorer total word count). This loss may become apparent with further decline (Ronnberg et al., 2011), possibly due to disrupted automatic mapping of acoustic signals to semantic representations (Li, Booth, et al., 2013). The poorer performance and faster, but non-significant, decline on computer calculated semantic MCS for the hearing loss group indicates milder decline in semantic compared to phonological retrieval. This perhaps also accounts for the significant difference in semantic-phonological discrepancy scores across time and for the smaller phonological clusters observed in the first 20 seconds of the task.

The finding that there was no significant impairment in semi-automatic retrieval on the semantic fluency test may be because phonological rules are harder to initiate compared to retrieval based on semantic rules (Demetriou & Holtzer, 2017; Stolwyk, Bannirchelvam, Kraan, & Simpson, 2015; Vaughan et al., 2016; Weakley & Schmitter-Edgecombe, 2014; Weakley et al., 2013) making the phonological task more sensitive to decline in these processes as a result of hearing loss. Additionally, there is some indication that semantic approaches may be the dominant or default mode of searching above phonological search strategies (Vonberg, Ehlen, Fromm, & Klostermann, 2014). Alternatively, phonological representations in those with acquired hearing loss may be more degraded or harder to access with greater explicit effort or compensatory strategies required to retrieve exemplars from working memory (Andersson, 2002; Andersson & Lyxell, 1998; Lyxell et al., 2003). A complementary possibility is that the semantic advantage may be preserved on par with controls due to increased reliance on lexico-semantic knowledge to support comprehension of degraded speech stimuli with hearing loss (Benichov, Cox, Tun, & Wingfield, 2012; DeCaro, Peelle, Grossman, & Wingfield, 2016; Friederici & Gierhan, 2013; Peelle & Wingfield, 2016; Zekveld, Rudner, Johnsrude, Heslenfeld, & Ronnberg, 2012). There is some indication that with onset of hearing loss, patients may switch from the normal dorsal, phonological route to a ventral temporo-frontal, semantic route to process visual phonological stimuli (Classon, Rudner, Johansson, et al., 2013; Classon, Rudner, & Ronnberg, 2013; Lazard et al., 2010; Lazard et al.,

2013). It was suggested that this reflects a substitution of phonological processing by lexico-semantic processing to access lexical information following decay of phonological representations (Lazard et al., 2010).

Research examining neurobiological correlates of semantic processing and fluency performance suggests that a possible mechanism for an association between ARHL and poorer fluency performance is decline in dopamine levels following acquired hearing loss. Sensory decline could hypothetically lead to decline in dopamine levels through less activation of the locus coeruleus (see Daulatzai, 2016 for a review). Optimal cognitive function relies on a balance between striatal and prefrontal dopamine transmission (Cools et al., 2010; Hills & Dukas, 2012). In the lexico-semantic network, dopamine plays a neuromodulatory role (Kim, Goel, Tivarus, Hillier, & Beversdorf, 2010; Pederzolli et al., 2008) particularly in activation of posterior regions which are mediated by the thalamus and associated with language (Kim et al., 2010). Neurobiological research suggests that dopamine facilitates focused semantic processing by increasing the signal-to-noise ratio and reducing spread through the semantic network (Kischka et al., 1996). Decline in dopamine levels may thus lead to more random searches in the semantic network (Hills & Dukas, 2012; Hills, Todd, Lazer, Redish, & Couzin, 2015) independent of concentration (Kischka et al., 1996). The phonological CuRel along with smaller clusters suggested that those with hearing loss had weaker connectivity within semantic networks compared to controls (Pakhomov et al., 2016) and relied on a more global rather than local search strategy to generate words (Hills & Dukas, 2012). Additionally, decline in dopamine can disrupt both automatic and controlled semantic processing (Arnott et al., 2011) and lead to slower semantic activation (Grossman et al., 2002) as was observed on the phonological fluency task. Such a pathway is speculative at this point but may be of interest in future research.

Decline in implicit phonological processes due to ARHL may have broader implications for cognitive ageing. In normal cognitive ageing and cognitive impairment, there are neurocognitive changes to support performance on fluency tasks. Neuroimaging studies report that compensatory processes support performance on phonological and fluency tasks in older adults (Ansado et al., 2013; Baciu et al., 2016; Heinzel et al., 2013; Heinzel et al., 2015), in MCI (Yeung et al., 2016) and AD patients (Fallgatter et al., 1997) and in asymptomatic carriers of ApoE e4 (*apolipoprotein E-epsilon4*) (Katzorke et al., 2017). If ARHL mechanistically contributes to decline through deterioration of implicit processes which are normally recruited in fluency tasks, it may further tax limited cognitive resources used to compensate for cognitive deficits due to normal ageing or dementia neuropathology. Intervention studies provide support for such a mechanistic association between ARHL and fluency performance and suggest that it may also have important clinical implications. A cochlear implantation (CI) study reported an improvement in semantic fluency and maintained phonological fluency at follow-up (mean 3.7 years) (Cosetti et al., 2016). Another CI study in elderly patients, Mosnier et al. (2015), reported a significant decrease in number of

abnormal scores on phonological and semantic fluency tasks one year after implantation. In a battery assessing a range of cognitive domains, phonological fluency was the only predictor of improvements in speech perception in noise after implantation (Mosnier et al., 2015). It is interesting to note in light of this finding that Lazard et al. (2010) reported that those that relied on the semantic ventral route adapted more poorly to cochlear implants than those who relied on the normal phonological dorsal route. The latter cohort adapted well. Markers of implicit phonological processing on fluency tasks may provide a marker for functional outcomes in future clinical trials.

Cognitive studies of ageing typically report an increased rate of decline in semantic fluency above phonological fluency (Brickman et al., 2005; Crossley et al., 1997; Herrmann et al., 2006; Kozora & Cullum, 1995; Mathuranath et al., 2003; Ravdin et al., 2003; Tomer & Levin, 1993; Vaughan et al., 2016). As there was a preferential effect of ARHL on phonological fluency, this provides some further support to previous hypotheses that posit that ARHL contributes to cognitive ageing apart from general age-related processes (Lin, Ferrucci, et al., 2011).

As in the previous chapter, this study has provided further support for the hypothesis that ARHL contributes to cognitive ageing through decline in semi-automatic, implicit cognitive processes. However, this should be explored further in cohort studies which use cognitive tests amenable to examining such markers. Future research projects could also examine how ARHL might alter neurocognitive activity to compensate for this decline in these processes on fluency tasks. Additionally, as tests of episodic memory and executive function showed no evidence of impairment in these functions, this finding suggests that decline in implicit processing in phonological fluency is a potential marker of early cognitive decline that precedes decline observed in those domains. This study also supports further research examining ARHL as a modifiable risk factor for cognitive decline and dementia.

Chapter 7 Age-related hearing loss, working memory and episodic memory: Temporary memory binding

7.1 Introduction

The purpose of this thesis is to explore how age-related hearing loss (ARHL) may contribute to outcomes in cognitive ageing and the possible causal or mechanistic basis for this association. The overall approach was to examine differences in previously established markers of advanced or pathological cognitive decline in an ARHL sample with a view to explicating pathways through which peripheral hearing loss may affect cognitive function. A hypothetical model, termed NIEAD, was constructed (reported in Chapter 4) which predicted that hearing loss may contribute to cognitive ageing through decline in implicit, semi-automatic processes. The previous two chapters explored how decline in implicit processes may contribute to differences in performance on tests of processing speed, executive function and lexico-semantic processes. The episodic memory domain is of great interest in cognitive ageing and clinical research due to its importance in indicating decline with dementia, particularly AD (Buckner, 2004; Toepper, 2017). Previous research has suggested that ARHL may contribute to decline in this domain (Lin, Ferrucci, et al., 2011; McCoy et al., 2005; Ronnberg et al., 2011; Ronnberg et al., 2013; Tun et al., 2009). This has been hypothesised to occur through the reallocation of limited attentional resources in working memory to improve speech perception leading to less resources to facilitate encoding in episodic memory and consequently to their decline through the effects of disuse (McCoy et al., 2005; Ronnberg et al., 2013; Tun et al., 2009). This was supported by a meta-analysis of observational studies (reported in Chapter 2). However, the pathway through which altered function of working memory leads to decline in long-term episodic memory systems has not been fully explicated. Decline in implicit encoding processes may provide such a pathway. This chapter examines a specific semi-automatic component of short-term episodic memory called temporary memory binding.

Working memory describes a limited capacity cognitive system in which information is actively maintained in short-term memory in support of an executive control system which simultaneously processes and manipulates this information (Eriksson, Vogel, Lansner, Bergstrom, & Nyberg, 2015; Logie, 2011). Baddeley and Hitch (1974) proposed a multicomponent model of working memory consisting of a 'central executive' or attentional control system, which can manipulate information in two subsidiary slave systems, the 'phonological loop' and the 'visuospatial sketchpad.' In an update, Baddeley added a fourth component, the episodic buffer, to address limitations of the prior model in accounting for how individuals can bind information from different systems in working memory (i.e. a representation with both visual and verbal components) (Baddeley, 2000). The episodic memory buffer is an interface with a multi-feature binding mechanism that allows interaction between a range of the subsystems of working memory,

long-term memory and the central executive (Baddeley, Allen, & Hitch, 2011). The central executive can access and influence representations held in these storage buffers by attending to perceptual stimuli, or representations held in the subsidiary systems and in long-term memory.

While numerous alternative models have been posited, typically all are variations of this essential structure which describe a distinction between storage buffers and executive functions (Baddeley et al., 2011; Wingfield, 2016). This division is supported by neuroimaging and EEG studies which describe working memory as emerging from interactions between neural regions such as pre-frontal cortex areas which mediate executive processes and cortical and subcortical regions specialised for mediating the current content held as a representation (Christophel, Klink, Spitzer, Roelfsema, & Haynes, 2017; Constantinidis & Klingberg, 2016; Eriksson et al., 2015; Kumar et al., 2016). Individual working memory capacity as assessed by tasks such as the backward digit span could be described as reflecting the interaction of both domain-specific ability (e.g. phonological loop capacity) and overall executive processing capacity (Logie, 2011). This has support from neuro-imaging research. In one study, visual working memory capacity was found to be predicted by the efficiency of a cognitive control neural network rather than specific neural sub-networks and circuits (Stevens, Tappon, Garg, & Fair, 2012) and in another study, by increased synchrony in the alpha-, beta-, and gamma-frequency bands between frontoparietal and visual neural areas (Palva, Monto, Kulashekhar, & Palva, 2010). One implication of this is a trade-off in distribution of neural resources between top-down executive control functions and bottom-up storage or information processing. For example, speech perception involves a nuanced trade-off between higher order attentional control processes and stimulus driven automatic processes with the ratio altering between contexts (Heald & Nusbaum, 2014; Peelle & Wingfield, 2016). Maintaining more information in the phonological loop leaves less resources for the executive manipulation of this information and, vice versa, increased use of the executive reduces the maintenance capacity of the phonological loop.

In normal cognitive ageing, there is typically a loss of efficiency in neural networks which are used to complete working memory tasks, particularly non-verbal tasks (see Dennis & Cabeza, 2011 for a review). Older adults who successfully complete such tasks show a pattern of decreased activation in task-relevant neural areas but show increased activation in other neural areas. Grady et al. (1994) noted that, on a visual perception task, older adults showed less activation in the occipital lobe but recruited additional areas in the pre-frontal and parietal cortex to maintain accuracy at the expense of slower reaction times. Such studies suggest an increased reliance on executive resources or cognitive reserve to compensate for inefficiencies in neural sub-systems (Cabeza, 2002; Stern, 2009, 2012). Interestingly, this pattern has also been found in studies examining neural activity in ARHL samples on speech perception tasks which report decreased activity in the primary auditory cortex and increased activation of other neural areas associated with executive control networks (Campbell & Sharma, 2013; Erb & Obleser, 2013; Peelle et al., 2011; Wong et al., 2009).

Wingfield (2016) defines successful speech perception not just as the accurate perception of words but the achievement of this with little or no mental effort. Under optimal conditions, incoming auditory signals are matched with stored phonological representations in long-term semantic memory through the episodic buffer and perceptual processing is smooth, implicit and effortless (Ronnberg et al., 2013). As auditory input becomes less clear, due to either noisy conditions or hearing loss, increased explicit processing of the auditory signal by executive resources in working memory is required to perceive speech (Heald & Nusbaum, 2014; Pichora-Fuller et al., 2016; Ronnberg et al., 2013; Schneider, 2011). Verbal working memory is a more accurate predictor of recall accuracy of acoustically degraded stimuli than levels of pure-tone thresholds (Ward, Rogers, Van Engen, & Peelle, 2016). Working memory may help speech perception, which is generally quite good among older adults, despite physiological decline in the auditory system (Peelle & Wingfield, 2016). However, as working memory is a limited capacity system, this recruitment of executive resources to promote perceptual acuity can have downstream consequences for higher order comprehension of speech (Wingfield, McCoy, Peelle, Tun, & Cox, 2006).

Recruitment of executive resources can also have implications for encoding and retrieval processes in episodic memory (McCoy et al., 2005; Peelle & Wingfield, 2016; Piquado, Benichov, Brownell, & Wingfield, 2012; Piquado, Cousins, Wingfield, & Miller, 2010). Rabbitt (1968) reported that acoustically masking a list of digits led to poorer recall even when the digits were accurately perceived at encoding. Executive resources recruited in working memory appear to disrupt encoding and storage of auditory stimuli (Cousins et al., 2014) and lead to more cognitive effort being required to retrieve these memories, even when perceived under optimal listening conditions and with near complete accuracy in the encoding phase (Tun et al., 2009). This compensatory effort may occur through alternate strategies such as increased reliance on semantic processing of verbal stimuli (Classon, Rudner, Johansson, et al., 2013; Classon, Rudner, & Ronnberg, 2013; Lazard et al., 2010; Lazard et al., 2013) which may interfere with the formation of new episodic memory associations (Long & Kahana, 2017). The Ease of Language Understanding (ELU) model predicted that reduced recruitment of episodic memory in conversation over time would lead to a more pronounced decline in its efficiency, whereas in contrast, it was hypothesised that working and short-term memory are less vulnerable to decline because they are recruited to aid speech perception (Ronnberg et al., 2011; Ronnberg et al., 2014; Ronnberg et al., 2013). Observational research has supported this hypothesis (see the meta-analysis reported in Chapter 2). It has been observed that representations of phonemic sounds in phonological memory have degraded subsequent to hearing loss whereas phonological processing in working memory is maintained (Andersson, 2002; Andersson & Lyxell, 1998; Lyxell et al., 2003). However, apart from a ‘disuse’ effect, it has not been explicated how disruption in episodic processes in speech may lead to decline in this domain.

One possible pathway, as predicted by the proposed NIEAD model, is through decline in implicit, automatic encoding processes as a result of ARHL which would have implications for cognitive ageing and dementia research. Research on the episodic buffer in working memory suggests that different neural regions are activated depending upon the qualitative type of information to be bound (Piekema, Rijpkema, Fernandez, & Kessels, 2010). An assessment of episodic memory deficits associated with cognitive ageing and AD consists of binding two objects or an object and location in memory (Logie et al., 2015). This relies on the integrity of the medial temporal lobe (Piekema et al., 2010). Older adults typically demonstrate a deficit compared to younger counterparts on these tasks (Old & Naveh-Benjamin, 2008) possibly due to altered frontal-related executive functioning (Buckner, 2004) or loss of hippocampal integrity (Logie et al., 2015). Another line of research has focused on older adults' ability to maintain associations between features within objects (e.g. shapes-colours). In contrast to the associative memory deficit, this function appears to be preserved in older adults with no evidence for a differential effect of age (Logie et al., 2015) and does not rely on the hippocampus (Parra, Della Sala, Logie, & Morcom, 2014; Rentz et al., 2013; Song & Jiang, 2006; Xu, 2007). Binding of visual features is automatic and is proposed as a way of reducing demand on working memory capacity (Baddeley, 2000; Kochan et al., 2011). However, maintenance of bound features in working memory is sensitive to task load (Baddeley et al., 2011; Kochan et al., 2011; Parra et al., 2014). Therefore, switching to higher executive processing to perceive auditory sound may disrupt capacity to maintain bound features in short-term memory (Morey & Cowan, 2005)

A growing body of research suggests that visual feature binding may be a promising pre-clinical marker for AD as it is insensitive to the effects of ageing (see Logie et al., 2015 for a review). Neuropsychological tests such as the FCSRT assess associative memory which relies on hippocampal function and are predictive of incident AD (Dubois et al., 2007). However, there is also decline in these functions with normal ageing (Yang, Goh, Chen, & Qiu, 2013) and therefore such tests lack specificity in AD diagnosis (Logie et al., 2015). However, temporary feature binding is independent of the hippocampus (Parra et al., 2014) and may be modulated by extra-hippocampal regions which are affected by AD pathology prior to the hippocampus (Logie et al., 2015). Subtle cognitive changes, including visual memory deficits (Kawas et al., 2003), can precede the onset of AD by as many as seven to ten years (Elias et al., 2000; Linn et al., 1995). Changes in visual-spatial processing may precede changes in declarative episodic memory in preclinical AD (Arnaiz et al., 2001; Balota et al., 2010) making this domain an area of great interest for clinical researchers. Furthermore, it has been reported that visual feature binding is not impaired in other age-related clinical conditions including depression, vascular dementia, dementia associated with Parkinson's disease and dementia with Lewy bodies and frontal lobe dementia (Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012).

The aim of this chapter is to extend the literature on how ARHL may contribute to decline in temporary memory binding using a visual short-term memory test. The *a priori* hypothesis was that ARHL is associated with a weaker capacity to form temporary feature bindings in working memory. To the best of the author's knowledge, this has not been examined previously. Previous research on cognitive decline due to ARHL has suggested that decline occurs in long-term episodic memory systems while short-term memory systems are relatively maintained (Ronnberg et al., 2013). However, the temporary binding test involves explicitly attempting to maintain information in working memory. If this function is impaired on a visual test, it lends support to the *a priori* hypothesis that ARHL mechanistically causes decline through suppressing and impairing implicit semi-automatic cognitive processes rather than through a disuse effect. This sub-study examined the difference in temporary memory binding function in a sample of older adults with hearing loss compared to a control group matched for age, gender and pre-morbid IQ. As this test of binding uses purely visual stimuli, it was controlled for any complications in testing due to hearing loss.

7.2 Methods

A summary of the methods is outlined below. See Chapter 4 for full details.

7.2.1 Participants

Participants who had taken part in the main study, 'Hearing ability, Cognitive Function and Lifestyle in Older Adults', were invited to take part in this sub-study. There were 101 participants in the main study who had completed all of the assessments. Hearing loss participants who had a potential control within five years of age, of the same gender and within 0.5 SDs (7.5 IQ points) of pre-morbid IQ were invited to take part. When a participant from the hearing loss group indicated that they would take part, the participants from the control group that matched that hearing loss participant according to the above criteria were also invited. Forty-one participants from the hearing loss group were invited; 32 expressed an interest and were tested. Among the control group, 42 participants were invited, 19 expressed an interest and 18 were tested. One control withdrew as they had gone abroad during the testing phase. In the sample for analysis, after matching groups for age, gender and pre-morbid IQ, there were 25 hearing loss participants and 18 controls. The matching procedure was the same as reported in Chapter 4. Ethical approval was given by the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin for both the main study and the sub-study. All participants gave written informed consent (Appendix D and G) before participating in the main study and again in the sub-study.

7.2.1.1 Background assessment

Background information was collected from all participants using questionnaires and assessed demographic, audiological, health and clinical factors. All measures were completed by included participants.

7.2.1.2 Audiological assessment

Objective and self-report measures of hearing loss were completed by all included participants.

7.2.1.3 Neuropsychological assessment

All neuropsychological measures were completed by included participants.

7.2.2 Temporary memory binding test

Participants were administered both a pre-assessment perceptual screening test and the temporary memory binding test using a computer. Responses were given verbally and the test administrator entered all participants' responses using the keyboard. Participants were given the perceptual screening test prior to administering the temporary memory binding test. This was to ensure that participants could accurately form bindings in perception. This pre-assessment required the participant to view two sets of three coloured shapes, one set on the top half of the screen and the other on the bottom half. In trials where the sets were the same, the coloured shapes were in the same colour-shapes combination. In the trials where sets were different, the same shapes and colours appeared in both sets but in different combinations. The participant was instructed to state verbally whether the two sets were the same or different. As there is no requirement to remember stimuli, this assessment measures the participant's capacity to form bindings in perception only. There are ten trials and it is recommended that only those with scores ≥8/10 are assessed using the temporary memory binding test. Prior to attempting the computerised trials, the participant was given practice trials using examples on a notepad.

Figure 7.1: The two conditions (shapes and shapes-colours) of the temporary memory binding test.

Following successful completion of the pre-assessment, participants were administered the temporary binding test which consisted of two conditions. The first condition assessed short-term memory for shapes only (all shapes were black) and the second assessed temporary memory binding (both colours and shapes) (see Figure 7.1). Both the shapes and binding conditions

consisted of 15 practice trials followed by 32 test trials. Of these 32, 16 were 'same trials' and 16 were 'different trials.' At the beginning of each trial, there was a fixation screen for 500 milliseconds (ms). A set of two shapes or coloured shapes (depending on condition) appeared for 2000 ms in the study phase. The screen was blank for an interval of 900 ms followed by the test phase or memory probe. The participant was instructed to state orally whether the stimulus in the test display was the 'same' or 'different' as the stimulus in the study display. The participants were instructed to ignore the location of the stimulus on the screen. For the shapes condition, the same or different set of shapes appeared randomly. For the shapes-colour condition, the same shapes and colours appeared but either in the same shape-colour combination ('same') or swapped around ('different'). The participant was allowed to respond in their own time. This test uses purely visual stimuli and so is appropriate for use with a hearing loss sample.

7.2.3 Procedure

Participants underwent the main neuropsychological and background battery and audiometric assessment as part of the main study 'Hearing ability, Cognitive Function and Lifestyle in Older Adults.' Testing for the sub-study took place between October 2016 and January 2017. Only participants who had completed the main study were recruited for this sub-study. Participants recruited for the main study after October 2016 were given the option to also take part in the sub-study. The test was administered as outlined above and took approximately 16 minutes to complete.

7.2.4 Statistical analysis

The statistical methods particular to this study are reported here. Please see Section 4.4.3 in Chapter 4 for a description of how the background and main neuropsychological data were treated, and how normality and group differences in effect sizes were assessed.

The difference between groups on response accuracy (i.e. number of correct responses for both change and no-change trials) for both the shapes and binding conditions were assessed using ANCOVA in which age, gender and years of education were included as covariates. Mean reaction times on shapes and binding conditions were also examined. An additional analysis assessing sensitivity for change detection was also conducted (Parra et al., 2010) implementing the calculation of the Signal Detection Theory (Stanislaw & Todorov, 1999). A' was selected as the sensitivity measure (Pollack & Norman, 1964) and was calculated according to the formulas provided by Xu (2002) which do not have indeterminacy when a participant does not make false alarms. If poor performance as assessed by response accuracy is accounted for by low sensitivity, it would suggest difficulties in keeping the signal separate from the noise in memory (Parra et al., 2010). The main analysis to assess difference between groups in across conditions (shapes-binding) was conducted using a linear mixed model with age, gender and years of education as covariates.

7.3 Results

7.3.1 Participant characteristics

Based on results from Student's t-tests (two-tailed), Mann-Whitney U and Chi-square, there were no significant differences between groups in age, gender, pre-morbid IQ or education (years and level) (Table 7.1). There were no significant differences on any other background or demographic, health, clinical or psychosocial factors. There was a significant difference between groups on all audiological measures ($p < 0.001$). This included the WHO pure-tone average in better and worse ear, averages for low and high frequencies and the HHIE-S score. Seventeen (68%) of the participants in the hearing loss group wore hearing aids. None of the participants in the control group wore hearing aids. Thirteen (52%) participants in the hearing loss and thirteen (72.22%) in the control group reported having previously experienced tinnitus. No participants reported difficulty with vision. No participant was excluded based on global cognitive domain score.

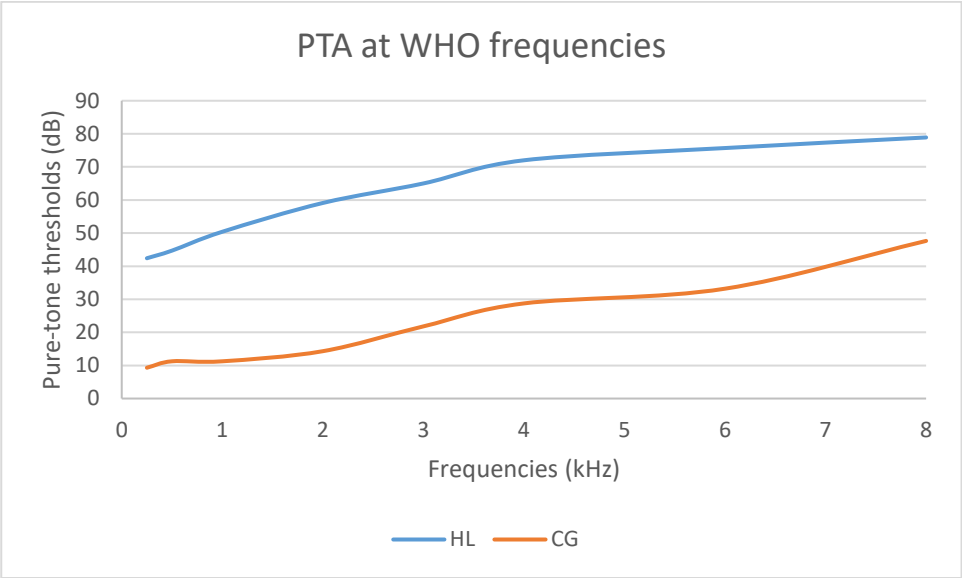

Figure 7.2: Difference in pure-tone threshold between the two groups at each frequency.

7.3.2 Neuropsychological performance

There was no significant difference between groups on the Stanford Sleepiness Scale (Table 7.2). There were no differences in episodic memory or executive function measures or composite scores. There were no significant differences in processing speed measures or in semantic memory or global cognition. There was a significant difference in the MCG Complex Figure Copy Test ($t(41) = 2.07$, $p = 0.045$, $d = 0.64$)

Table 7.1: Background data for the two groups of participants					
	Hearing loss group *M (SD)*	**Control group** *M (SD)*	**Significance test**		
			Est.	*p*	*Cohen's d*
Demographic					
N	25	18	-	-	-
Age	72.56 (5.79)	69.11 (6.63)	*t*; -1.81	0.08	0.56
Gender (*female/male)*	14/11	14/4	χ^2; 1.33	0.25	0.36
Education *(years)*	13.58 (3.62)	14.44 (3.09)	*t*; 0.82	0.42	0.25
Education *(level)*	2.8 (0.76)	2.94 (0.73)	*U*; 197.5	0.45	0.23
Marital status *(partner/none)*	17/8	11/7	χ^2; 0.02	0.89	0.04
Audiological					
WHO better ear PTA	49.9 (17.23)	13.61 (6.61)	*U*; 0	**<0.001**	3.16
WHO worse ear PTA	63.2 (25.76)	19.17 (8.73)	*U*; 5	**<0.001**	2.94
Low freq. better ear PTA	54.64 (13.29)	12.64 (9.38)	*U*; 33.5	**<0.001**	2.08
Low freq. worse ear PTA	68.93 (18.62)	19.89 (17.47)	*U*; 35.5	**<0.001**	2.03
High freq. better ear PTA	75.6 (14.8)	34.02 (16.56)	*U*; 3	**<0.001**	3.02
High freq. worse ear PTA	90.12 (21.41)	42.87 (19.36)	*U*; 11.5	**<0.001**	2.39
Self-rated hearing *(HHIE-S)*	20.0 (8.43)	4.44 (6.49)	*U*; 39	**<0.001**	2.69
Health					
Self-rated physical health	3.52 (1.01)	3.83 (1.04)	*U*; 188	0.34	0.29
Self-rated mental health	3.96 (0.84)	3.94 (1.11)	*U*; 219.5	0.89	0.04
Alcohol consumption *(yes/no)*	19/6	14/4	-	>0.99*	0.06
Alcohol units *(per wk)*	8.49 (7.11)	12.64 (11.74)	*U*; 102	0.26	0.35
Smoker current *(yes/no)*	1/24	0/18	-	>0.99*	0
Smoker former *(yes/no)*	10/15	7/11	χ^2; 0	>0.99	0
Sleep quality *(PSQI)*	5.24 (3.02)	4.78 (2.53)	*U*; 207	0.66	0.14
Clinical					
Pre-morbid IQ *(NART)*	112.87 (6.62)	115.17 (5.38)	*t*; 1.22	0.23	0.38
Self-rated memory	3.32 (0.85)	3.56 (0.86)	*U*; 189	0.35	0.29
Frailty *(SHARE score)*	0.26 (0.87)	0.21 (1.07)	*U*; 208.5	0.69	0.12
Depression *(CESD-10)*	4.24 (3.02)	4.83 (4.46)	*U;* 222.5	0.95	0.02
Anxiety *(HADS-A)*	3.48 (2.58)	3.83 (3.5)	*U;* 223	0.96	0.02
Apathy *(AES-S)*	26.92 (4.65)	27.83 (7.21)	*U;* 220	0.9	0.04
Psychosocial					
Social network *(LSNS)*	20.56 (5.55)	19.5 (6.17)	*U;* 220	0.9	0.04
Loneliness *(De Jong Gierveld)*	0.32 (0.69)	0.83 (1.62)	*U;* 197.5	0.39	0.26
Boredom proneness *(Conroy)*	1.36 (0.57)	1.61 (0.7)	*U;* 181	0.21	0.29
Perceived stress *(PSS-4)*	3.08 (2.18)	2.33 (2.72)	*U;* 166	0.14	0.46

AES-S; Apathy Evaluation Scale – Self-rated (Marin et al., 1991); CESD-10; Center for Epidemiologic Studies Depression Scale – 10 item (Radloff, 1977); Conroy; Conroy Boredom proneness (Conroy et al., 2010); De Jong Gierveld; 6-item De Jong Gierveld Loneliness Scale (De Jong Gierveld & Van Tilburg, 2006); HADS-A; Hospital Anxiety and Depression Scale-Anxiety subscale (Zigmond & Snaith, 1983); HHIE-S; Hearing Handicap Inventory for the Elderly Screening Version (Ventry & Weinstein, 1983); LSNS; Lubben Social Network Scale (Lubben et al., 2006); NART; National Adult Reading Test (Nelson, 1982); PSQI; Pittsburgh Sleep Quality Index (Buysse et al., 1989); PSS-4; Perceived Stress Scale-4 item (Cohen et al., 1983); PTA; Pure-tone average; SHARE; Survey of Health, Ageing and Retirement in Europe Frailty Instrument (Romero-Ortuno et al., 2010); WHO; World Health Organisation;

*Fisher's exact test (Cohen's d converted from odds ratio)

Table 7.2: Neuropsychological data for the two groups of participants							
	HLG	**CG**	**HLG**	**CG**	**Significance test**		
	M (SD)	*M (SD)*	*Z (SD)*	*Z (SD)*	*Est.*	*p*	*Cohen's d*
Current sleepiness							
Stanford Sleepiness Scale	1.72 (0.89)	1.89 (0.9)	0.08 (1.00)	-0.11 (1.01)	*U*; 198.5	0.48	0.22
Episodic memory							
FCSRT immediate free recall	33.28 (7.19)	34.39 (4.35)	-0.08 (1.17)	0.11 (0.71)	*t*; 0.63˜	0.53	0.19
FCSRT immediate total recall	47.64 (1.41)	48 (0)	-0.14 (1.3)	0.19 (0.0)	*U*; 198	0.13	0.47
FCSRT delayed free recall	12.52 (2.74)	12.11 (2.06)	0.07 (1.11)	-0.1 (0.84)	*t*; -0.53	0.6	0.16
FCSRT delayed total recall	15.92 (0.4)	16 (0)	-0.11 (1.31)	0.15 (0.0)	*U*; 216	0.4	0.26
WMS-III spatial span forward	7.08 (2.04)	7 (1.82)	0.02 (1.06)	-0.02 (0.94)	*t*; -0.13	0.9	0.04
Composite z-score			0.004 (0.85)	-0.01 (0.58)	*t*; -0.04	0.97	0.01
Executive function							
CAMDEX visual reasoning	3.68 (1.15)	3.83 (1.25)	-0.05 (0.97)	0.08 (1.06)	*t*; 0.42	0.68	0.13
SART commission errors	3.12 (2.37)	3.89 (2.97)	0.12 (0.9)	-0.17 (1.13)	*U*; 196	0.47	0.22
SART omission errors	6.24 (5.61)	10.33 (10.34)	0.21 (0.69)	-0.29 (1.28)	*U*; 178	0.25	0.36
SART total errors	9.36 (7.4)	14.22 (11.56)	0.21 (0.77)	-0.3 (1.21)	*U;* 170	0.18	0.42
Phon. fluency *(MoCA)*	15.04 (4.79)	14.22 (4.17)	0.08 (1.06)	-0.11 (0.92)	*t*; -0.58	0.56	0.18
Sematic fluency *(animals)*	22.84 (5.45)	22.83 (6.36)	0.001 (0.94)	0.001 (1.1)	*t*; -0.004	>0.99	0.001
WMS-III SS backward	6.44 (1.76)	6.67 (1.82)	-0.05 (1)	0.07 (1.03)	*t*; 0.41	0.68	0.13
WMS-III SS total	13.52 (3.33)	13.67 (3.2)	-0.02 (1.03)	0.03 (0.99)	*t;* 0.15	0.89	0.05
Composite z-score			0.05 (0.58)	-0.07 (0.66)	*t*; -0.63	0.53	0.19
Processing speed							
CRT motor mean RT (*ms*)	302.97 (76.65)	297.30 (56.19)	-0.03 (1.12)	0.05 (0.82)	*t;* -0.11	0.91	0.03
CRT cognitive mean RT (*ms*)	485.57 (66.29)	501.85 (66.15)	0.1 (1.01)	-0.14 (1)	*U*; 188	0.36	0.28
CRT total mean RT (*ms*)	788.46 (85.07)	797.43 (84.53)	0.04 (0.98)	-0.06 (1.05)	*t*; -0.34	0.74	0.11
SART mean RT (*ms*)	334.13 (82.29)	319.14 (62.53)	-0.07 (1.04)	0.1 (0.96)	*t*; 0.53	0.6	0.16
Semantic memory							
BNT	55.64 (3.6)	56.5 (2.33)	-0.11 (1.15)	0.16 (0.74)	*U*; 203.5	0.59	0.16
Visuospatial ability							
MCG complex figure	24.22 (4.38)	27.06 (4.5)	-0.26 (0.95)	0.36 (0.98)	*t*; 2.07	**0.045**	0.64
Global cognition							
MoCA	25.96 (2.85)	26 (2.74)	-0.01 (1.03)	0.01 (0.99)	*t*; 0.05	0.96	0.02
MoCA adj.*	17.72 (1.79)	17.72 (2.02)	0.001 (0.96)	-0.001 (1.08)	*t*; 0.004	>0.99	0.001
Composite global z-score +			-0.05 (0.57)	0.08 (0.4)	*t*; 0.83	0.41	0.26

* Equal variances not assumed

+ Composite z-score calculated from the mean of the composite scores for episodic memory (except FCSRT and Spatial Span total scores), executive functions and from the scores for processing speed (CRT total mean RT), semantic memory and visuospatial ability.

SART and CRT motor and total reaction times transformed to inverse scores to account for non-normality. For SART error scores, arithmetic signs on z-scores set so that higher scores indicated better performance.

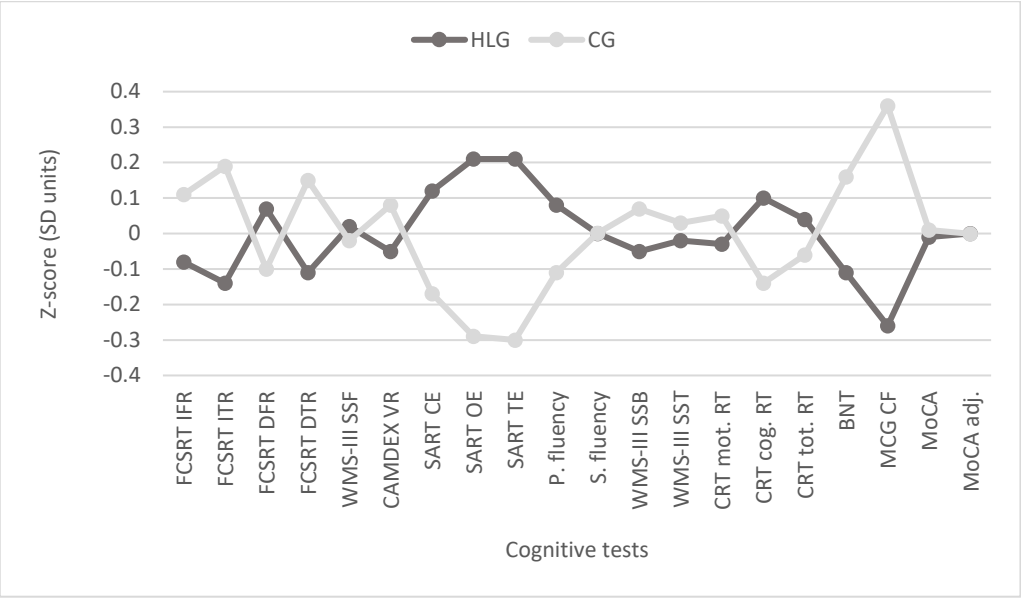

Figure 7.3: Difference in mean performance between the two groups on each cognitive test (based on z-scores).

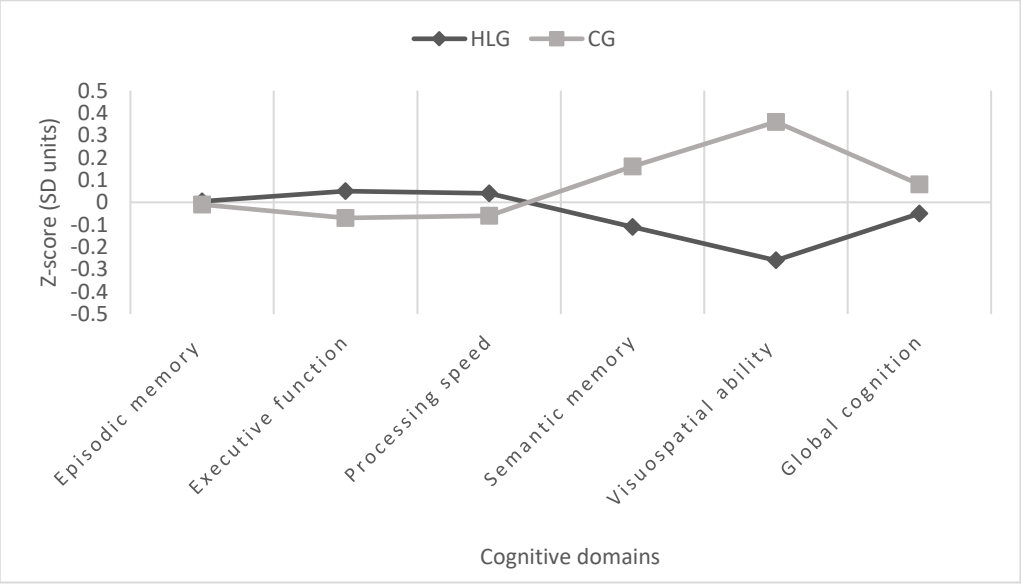

Figure 7.4: Difference in mean performance between the two groups on each cognitive domain (based on z-scores).

7.3.3 Temporary binding performance

All participants passed the perceptual binding screening assessment, with the lowest score for any participant being 9/10 (Table 7.3). For the shape only condition there was no significant difference between groups for either reaction time (t (41) = 0.69, p = 0.49, two-tailed, mean difference = 0.0004, 95% CI: -0.001 to 0.002) or accuracy (t (41) = 0.35, p = 0.73, two-tailed, mean difference = 0.005, 95% CI: -0.02 to 0.03). For the binding condition, there was no significant difference in reaction time (t (41) = 1.66, p = 0.1, two-tailed, mean difference = 0.001, 95% CI: -0.0002 to 0.002). However, there was a significant difference between the two groups in accuracy with the hearing loss group demonstrating poorer performance compared to the control group (t (41) = 2.66, p = 0.01, two-tailed, mean difference = 0.07, 95% CI: 0.02 to 0.12). There was no significant difference between groups in total time (t (41) = 1.52, p = 0.14, two-tailed, mean difference = 0.01, 95% CI: -0.004 to 0.03).

Table 7.3: Temporary binding data for the two groups of participants

	Hearing loss group		**Control group**	
	M (SD)	*Range*	*M (SD)*	*Range*
Shape mean RT (*ms*)	2153.96 (427.43)	1561-3514	2061.61 (319.21)	1507-2792
Shape Acc.	0.95 (0.05)	0.78-1	0.96 (0.04)	0.88-1
Shape *A'*	0.97 (0.05)	0.77-1	0.98 (0.03)	0.88-1
Bind mean RT (*ms*)	2562.36 (550.03)	1832-4455	2330.11 (559.68)	1435-3475
Bind Acc.	0.86 (0.11)	0.62-1	0.93 (0.06)	0.78-1
Bind *A'*	0.8 (0.23)	0.23-1	0.92 (0.08)	0.7-1

Mean reaction time for shapes transformed to inverse of square root to account for non-normality. Binding *A'* data transformed to a squared scale.
* Assessed using rank analysis of covariance (Quade, 1967).

Age, gender and years of education included in analyses as covariates.

Table 7.3 (Continued): Temporary binding data for the two groups of participants

	HLG	**CG**	**Significance test**		
	Z (SD)	*Z (SD)*	*Est.*	*p*	*Cohen's d*
Shape mean RT (*ms*)	-0.09 (1.05)	0.13 (0.94)	*F*; 0.26	0.61	0.13
Shape Acc.	-0.05 (1.12)	0.06 (0.84)	*F*; 0.24	0.63	0.12
Shape *A'*	-0.12 (1.17)	0.16 (0.7)	*F*; 0.74*	0.39	0.21
Bind mean RT (*ms*)	-0.21 (0.83)	0.29 (1.16)	*F*; 0.78	0.38	0.22
Bind Acc.	-0.3 (1.13)	0.41 (0.6)	*F*; 4.92	**0.03**	0.55
Bind *A'*	-0.26 (1.2)	0.36 (0.44)	*F*; 3.66	0.06	0.47

Mean reaction time for shapes transformed to inverse of square root to account for non-normality. Binding *A'* data transformed to a squared scale.
* Assessed using rank analysis of covariance (Quade, 1967).

Age, gender and years of education included in analyses as covariates.

7.3.4 Linear mixed models

Linear mixed models were used to conduct further analysis of the relationship between hearing group and accuracy scores across shape and binding conditions. As fixed effects, condition and group with a condition by group interaction term were entered. Age, gender and education years were entered as covariates. As a random effect, subject was entered. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality. Models were fitted and compared based on the -2 Restricted Log Likelihood and Akaike's Information Criterion. Another model was conducted with the slope added as a random factor. The first model was deemed the better fit. The covariance structure selected for the error terms based on the above criteria was a diagonal structure (which assumes a different variance at each time point and no correlation between time sections) (Heck et al., 2011).

There was no significant main effect for any variable prior to adding the interaction term except for condition (beta = -0.06, $p < 0.001$, d = 1.08). When the interaction term was added to the model there was no longer a significant main effect of condition (beta = 0.04, p = 0.42, d = 0.02) and there was no significant effect of group (beta = 0.06, p = 0.15, d = 0.37). However, the interaction between group and time was significant (beta = -0.06, p = 0.04, d = 0.54). There was no significant effect for any of the included covariates.

Table 7.4: Linear mixed effects model examining the effects of time, hearing status, and their interaction on binding performance

	Estimate	Std. Error	*t*	Sig.
Condition	0.04	0.05	0.82	0.42
Hearing group	0.06	0.04	1.48	0.15
Hearing group*Condition	-0.06	0.03	-2.11	**0.04**
Age	-0.0002	0.001	-0.19	0.85
Gender	-0.02	0.02	-1.11	0.28
Education (*years*)	0.001	0.002	0.55	0.59

7.4 Discussion

The main purpose of this chapter was to investigate if age-related hearing loss (ARHL) is associated with poorer short-term memory encoding and therefore, more broadly, with decline in semi-automatic cognitive processes. Two groups of older adults, one with at least a mild pure-tone audiometric hearing loss and the other with normal hearing, were assessed using a visual test of temporary memory binding and their performance was compared. The two groups were otherwise matched for background characteristics and neuropsychological performance (with the exception of visuospatial ability as assessed by the MCG Complex Figure Copy Test). The key finding is that those with hearing loss had a poorer ability to maintain feature bindings in visual short-term memory. This appeared to be due to an impaired ability to maintain a high signal-to-noise ratio in short-term memory (Parra et al., 2010). There was no difference in accuracy between groups on the shapes-only task suggesting maintained explicit visual short-term memory function. There was no difference in reaction times for either the shapes or the binding task. There was a significantly

smaller discrepancy in scores between shapes and binding conditions for controls compared to the hearing loss group. When further analyses were conducted using hierarchical multiple regression, the result on the binding task was found to be independent of demographic factors (age, gender and years of education) and MoCA performance. Furthermore, hearing loss was associated with a greater decline in accuracy score from the shapes to the binding condition. As instructions were administered with visual aids and practice trials were given before taking the test, the tests were controlled for any methodological implications of hearing loss for neuropsychological assessment. . Additionally, all participants had passed the perceptual binding pre-assessment. Therefore, the impairment identified from the test was in maintaining the signal of the bound features in short-term memory and not in perceptual difficulties.

Historically, research into hearing loss and short-term memory has focused on recall for verbal stimuli under challenging listening conditions due to either hearing loss or degraded auditory acuity of stimuli such as speech-in-noise tasks (Pichora-Fuller et al., 2016; Ronnberg et al., 2013; Schneider, Daneman, & Murphy, 2005; Wingfield et al., 2015). Based on this, it has been posited that, in ARHL samples, visual and auditory short-term memory is relatively preserved compared to long-term memory due to increased recruitment in processing speech (Ronnberg et al., 2011; Ronnberg et al., 2014; Ronnberg et al., 2013). This study suggests that ARHL is associated with decline in implicit processes in short-term memory prior to any observed decline in delayed episodic memory. This would suggest that weakened efficiency in episodic memory is not solely due to disuse but also due to deterioration of automatic encoding processes. The findings suggest that this may be a primary mechanistic pathway through which acquired hearing loss may affect cognition. As this study used a purely visual task, this effect seems to extend beyond the auditory modality affecting a general encoding process in short-term or working memory which may have implications for learning and long-term episodic memory (Logie, Brockmole, & Vandenbroucke, 2009; Yonelinas, 2013). This is similar to what has been noted in previous studies assessing samples at risk for AD that demonstrated a binding impairment on both verbal and visual tasks (Parra et al., 2009; Parra et al., 2010).

Analysis of background neuropsychological tests found a significant difference between groups only on the MCG Complex Figure Copy Test. There was no difference for MoCA performance or in the composite global score or in executive or episodic and semantic memory domains. Therefore, the two groups were well matched for cognitive function. There was no difference on the WMS-III Spatial Span (Forward and Backward) suggesting that both groups had equivalent visual working memory capacity in terms of storage and executive abilities. Additionally, performance on the FCSRT free recall and total score was the same, indicating there was no general impairment in encoding or retrieval mechanisms in immediate or delayed episodic memory. Interestingly, Parra et al. (2010), in their comparison of asymptomatic familial AD to a control group, reported a lower, but non-significant performance for the asymptomatic carriers on

the Rey–Osterrieth Complex Figure copy task which is identical to the MCG Complex Figure copy task. This particular task was a copy, not a recall, task and therefore did not have an explicit memory component. Performance on visuospatial construction tasks is modulated by frontal and posterior temporal-parietal cortex regions (Forstl et al., 1993; Melrose et al., 2013; Salmon et al., 2009; Teipel et al., 2006; Tippett & Black, 2008) possibly reflecting recruitment of both visual perceptual skills and top-down executive control (Melrose et al., 2013). As the hearing loss group did not demonstrate any impairment in executive functions, this would indicate that their poorer performance was due to difficulties forming accurate representations, such as item-location binding, in working memory and reconstructing them. Deficits in the ability to draw objects, defined as constructional apraxia, has been associated with decline in several neural regions including those classically associated with episodic memory such as the right middle temporal gyrus (Chechlacz et al., 2014) and the hippocampus and parahippocampal gyrus (Forstl et al., 1993). It is worth noting that Lin, Ferrucci, et al. (2014) observed accelerated decline in the right parahippocampal gyrus in a longitudinal, neuro-imaging study examining the association of ARHL with brain volumes in 126 participants over a mean period of 6.4 years. This region may underlie the encoding and maintenance of bound information in working memory (but not its retrieval) (Luck et al., 2010). Lin, Ferrucci, et al. (2014) observed that the extent of increased rates of brain atrophy associated with hearing loss was comparable to those previously observed in individuals developing incident MCI (Driscoll et al., 2009).

While the primary risk factor for both ARHL and cognitive decline is age (Panza, Solfrizzi, & Logroscino, 2015; Panza, Solfrizzi, Seripa, et al., 2015), feature binding has proved to be insensitive to the effects of ageing (Brockmole, Parra, Della Sala, & Logie, 2008). This suggests that the link of ARHL with cognitive decline is a specific one rather than part of a broader physiological decline. Feature binding appears to place a greater load on frontal regions (Smith et al., 2017) and requires communication between independent neural regions (O'Reilly, Busby, & Soto, 2003; Parra et al., 2015). While regions such as the hippocampus decline with age (Yang, Goh, et al., 2013), other regions such as the dorsolateral prefrontal cortices and the entorhinal cortex in the lower areas of the brain, known as the ventral stream, appear to undergo functional re-organisation (Grady & Craik, 2000) and maintain temporary memory binding (Logie et al., 2015; Parra et al., 2014). Compensatory changes in cortical resources due to ARHL (Campbell & Sharma, 2013) may disrupt maintenance of feature bindings encoded in short-term memory (Morey & Cowan, 2005) and alter these pathways (Husain, Medina, et al., 2011). In the early stages of ARHL, there is a shift toward ventral stream processing including activation of auditory temporal cortex in response to visual stimuli (Campbell & Sharma, 2014). Additionally, as attentional resources are limited (Tun et al., 2009), prolonged reliance on these resources to support perceptual function may have costs for implicit cognitive processes through their suppression (Stock et al., 2016). Higher auditory working memory load impairs visual ventral stream processing and causes a reduction in processing of task-irrelevant stimuli (Klemen et al., 2010). Working memory load can

lead to decreased pre-cortical processing of task-irrelevant stimuli, even in other modalities, and subsequently to increased cross-modal connectivity to support brain regions processing primary tasks when attentional resources are challenged (Regenbogen et al., 2012). Such cross-modal connectivity (increased activation in auditory cortex regions in response to visual stimuli) was noted by Campbell and Sharma (2014) as occurring even in the early, milder stages of ARHL.

Decline in automatic encoding processes in working memory may account for the decline observed in long-term episodic and semantic memory systems in ARHL samples (Lin, Ferrucci, et al., 2011; Ronnberg et al., 2011; Ronnberg et al., 2014; Ronnberg et al., 2013). Research suggests that episodic encoding of novel stimuli in long-term memory may rely on both explicit and implicit cognitive processes (Nelson, McKinney, Gee, & Janczura, 1998). Furthermore, integrated (multi-feature) representations in visual short-term memory are more likely to be transferred into long-term memory than individual features and can influence behavioural learning outcomes (Logie et al., 2009; Xu, 2002). This is consistent with the ELU model which posits that cognitive decline due to impaired speech perception in ARHL patients is characterised by impaired long-term memory prior to any decline in executive processes (Ronnberg et al., 2013). However, in contradiction to this model, this study suggests that decline in feature binding in short-term memory may precede any decline in long-term memory as hearing loss participants did not demonstrate any decline on the FCSRT, the BNT or semantic fluency compared to controls (consistent with the proposed NIEAD model). This decline in implicit resources may tax executive resources further, leading to further consequences for cognition in cascading fashion and may underlie the faster cognitive decline observed with ARHL which may culminate in deteriorative effects for cognitive function (Lin et al., 2013) and increase risk of incident dementia (Lin, Metter, et al., 2011).

Another possible basis for this association is due to a common pathological mechanism affecting both the cochlea and neural structures (Panza, Solfrizzi, & Logroscino, 2015). Impaired feature binding has been reported previously in asymptomatic carriers of a mutation for AD (Parra et al., 2010). It is not clear how a common pathology can affect both feature binding and peripheral auditory structures with no impairment observed in other episodic memory or executive functions. Neuropathologic studies report pathophysiologic features of AD (i.e., plaques and tangles) in central auditory neural regions but none has been reported to be observed in the peripheral auditory structures (Sinha et al., 1993). However, genetic risk factors may account for decline in the cochlea and the brain. ApoE e4 (*apolipoprotein E-epsilon4*) is a key genetic risk factor strongly linked in isoform-dependent manner with sporadic AD (Risacher et al., 2015; Ward et al., 2012) and with ARHL (Kurniawan et al., 2012; Mener et al., 2014) through hypercholesterolemia in the main vasculature and associated atherosclerosis (Guo et al., 2005; Lathe et al., 2014; McNeill et al., 2010).

This study contributes to the literature on ARHL and cognition, specifically working memory and encoding in episodic memory. Further research is required to examine the mechanism underpinning

the association of hearing loss with temporary memory binding. Genetic markers for both hearing loss and AD could also be assessed. Neuro-imaging studies assessing how speech may affect feature binding would be illuminating. Additionally, future studies might examine if difference in presentation times affects performance. Increased executive processing may compensate for any decline in binding function and improve performance (Rhodes, Parra, & Logie, 2016). This study also has clinical implications. Studies examining preclinical markers for AD should include assessments for hearing loss. Therapies aimed at maintaining or rehabilitating cognitive function in ARHL could include this function as a target. Hearing aids can reduce attentional costs, particularly with algorithms to improve speech-in-noise perception (Ronnberg et al., 2013) and benefits for visuospatial working memory have been noted (Ronnberg et al., 2014). Working memory training can develop capacity (Constantinidis & Klingberg, 2016; Ferguson & Henshaw, 2015). However, it is worth noting that the majority of hearing loss participants included in this study reported the wearing of hearing aids. Additionally, as preclinical periods may present a critical opportunity for intervention, temporary memory binding may offer a preclinical marker for assessing cognitive decline in ARHL patients.

Chapter 8 Discussion

8.1 Background

The approach of this thesis was to examine the possible mechanisms through which ARHL may be associated with cognitive ageing and possibly contribute to cognitive decline. The research reported in this thesis began with an exploratory approach to examine the association of ARHL with cognitive ageing. The reviews of the current literature reported in Chapters 1, 2, and 3 were used to inform the empirical research reported in Chapters 5, 6, and 7.

Based on a meta-analysis of observational studies and a review of potential causal mechanisms in the literature it was elected to examine a potential mechanistic pathway through which hearing loss causes altered cognitive functioning as support was found for such a pathway. The results of the meta-analysis indicated a significant association between hearing loss and cognitive decline, cognitive impairment and dementia. The results of the meta-analysis of specific cognitive functions indicated a possible mechanistic pathway in that the rate of decline in executive processes was smaller compared to decline in long-term memory. These results are consistent with findings in speech research. Research on speech perception in those with acquired hearing loss consistently reports increased recruitment of executive function to maintain perceptual function and concomitant neuroplastic changes in the frontal lobes and in regions classically associated with speech processing (Campbell & Sharma, 2013; Lin, Ferrucci, et al., 2014; Peelle et al., 2011; Peelle & Wingfield, 2016; Ronnberg et al., 2013; Wingfield et al., 2015). Frontal and parietal regions become more activated to support processing of auditory input (Campbell & Sharma, 2013; Peelle et al., 2011) and the primary auditory cortex demonstrates re-organisation to process visual signals (Campbell & Sharma, 2014). There is also a switch from dorsal to ventral pathways possibly indicating a switch from phonological processing of speech stimuli to lexico-sematic processing (Classon, Rudner, Johansson, et al., 2013; Classon, Rudner, & Ronnberg, 2013; Lazard et al., 2010; Lazard et al., 2013). This has led to suggestions that the increased cognitive load resulting from impaired speech perception may be a prime causal factor underpinning the association of ARHL with cognitive decline, cognitive impairment and dementia (Lin, Ferrucci, et al., 2011; Lin, Metter, et al., 2011; Ronnberg et al., 2013). While there was support for other pathways such as vascular risk factors or depression, it was decided to focus on the cognitive load pathway for this thesis. This possible mechanism has not been fully delineated and the pathway through which cognitive load may extend to a general decline in cognitive function has not been made clear.

This review of evidence also outlined how loss of stimulation leads to less activation of subcortical structures and altered neurotransmission, particularly in dopamine (Daulatzai, 2016). It was posited that this may lead to preferential decline in implicit cognitive processes which occur below the threshold of conscious, explicit processing and may be mediated by striatal structures (Cools & M., 2010; Cools et al., 2010; Milton & Pothos, 2011). Additionally, increased executive recruitment on challenging tasks may cause suppression of implicit neural processes or draw resources away from

them (Klemen et al., 2010; Regenbogen et al., 2012; Stock et al., 2016). Cognitive control is adaptive in that it inhibits automatic processes to optimise perception (Tun et al., 2009), but high levels of control may also suppress automatic cognitive processes even when they are beneficial (Stock et al., 2016). A hypothetical model was developed termed Neurocognitive Implicit-Explicit Asymmetric Decline (NIEAD), that posited that in the long-term this may lead to preferential decline in these implicit functions. Individuals with ARHL increasingly rely on explicit processing to perceive speech. As a result, these processes are maintained, leading to an asymmetric profile in implicit and explicit functions in the ARHL population. This may have a cascade effect whereby explicit processes must increasingly compensate for both hearing loss and for decline in bottom-up, implicit cognitive functions. As hearing aids do not fully compensate for hearing loss or ameliorate cognitive load (Humes, 2007; McCoy et al., 2005), it was hypothesised that this effect would be observed regardless of hearing aid use.

8.2 Methods and results

The approach used was to explore if there were differences in implicit cognitive function in adults with ARHL that were asymmetric relative to explicit cognitive functions. This was examined through assessing differences between a group of older adults with acquired hearing loss and a group of controls in neuropsychological markers of implicit and explicit function in three broad domains of cognitive function which are of primary interest in the literature on normal cognitive ageing and dementia. A group of older adults with hearing loss was matched to controls for age, gender and education. The NIEAD model was evaluated across a range of different tests purporting to assess different domains. These tests have been used extensively in other samples which provided a significant amount of background data for comparison of results. As all these tests did not use auditory stimuli, any differences cannot be attributed to hearing difficulties during test administration.

The first broad domain studied was executive function, sustained attention and processing speed. The markers of implicit and explicit function were extracted from differences in intra-individual variability on a speeded accuracy task. The second domain studied was executive function and the lexical-sematic domain. The markers were extracted from two fluency tasks using both manual and computerised methods. The third domain studied was episodic memory. The markers were extracted using a test of temporary memory binding. Across all three studies, the ARHL sample performed poorly compared to controls on markers of implicit functions but performed similarly on markers of explicit functions. This difference was observed to be asymmetric within the ARHL group i.e. their implicit processes were poorer relative to their explicit functions, whereas for controls individual differences in implicit functions were on par with differences in explicit functions.

The results of the three empirical chapters support the NIEAD hypothesis that ARHL is associated with decline in semi-automatic cognitive processes which is asymmetric to performance of explicit processes. This suggests a potentially new model or research paradigm for future research into the association of ARHL with cognitive ageing.

8.3 Limitations and future directions

The ARHL sample demonstrated a qualitatively different cognitive pattern compared to controls suggesting that there is a distinct neuropsychological profile associated with ARHL. Research on cognitive ageing has focused on executive function, processing speed and episodic memory which often show the earliest signs of decline due to either normal or pathological processes (Buckner, 2004; Dennis & Cabeza, 2011; Salthouse, 2010b). The findings of this thesis suggest that the ARHL population demonstrates a similar level of function in these domains as assessed by standard tests compared to controls but decline in automated processes as posited by the NIEAD model.

The hypothetical model and studies described in this thesis were exploratory and there were limitations to the methodological approach. As such, the conclusions of this thesis are speculative. Further research is required, replicating the tests conducted for this thesis with larger numbers of individuals and under experimental conditions, to assess the mechanisms that the NIEAD model describes and to explore its potential implications for cognitive ageing in the ARHL population. The limitations of this research and several possible directions for future research are outlined below.

Implicit processing could potentially be a marker of early cognitive decline that precedes decline observed in the main cognitive domains such as episodic memory. Furthermore, this dysfunction in implicit processes may mediate or cause the decline that has been observed in these domains (Lin, Ferrucci, et al., 2011). This bottom-up, deteriorative pathway would account for the small but consistent effect observed in epidemiological studies examining the association of ARHL with cognitive decline. It would also account for the linear and exponential relationship observed between severity of hearing loss and rate of cognitive decline, for the association of ARHL with cognitive decline and for this association being independent of ageing and vascular factors (Lin et al., 2013).

The results of this thesis provide a novel hypothetical construct and paradigm for research into ARHL and cognitive function. The research has inherent limitations. The principles underlying the NIEAD model and the assumptions derived therewith require further examination, particularly as testing all of the predictions of the model was beyond the scope of this thesis. Several approaches are required to test the validity of the model. A key priority is to replicate the approach used in this thesis in other studies, using different samples and larger numbers to assess the robustness of these findings. Further research is required to test the predictions of the model using different

methodological approaches to test and fully elicit the pathway described here. The SART and the fluency tasks were not designed for assessment of explicit versus implicit function and are imprecise measures of these processes. The temporary memory binding task allowed for a more accurate assessment of the hypothesis as it was developed to assess an automatic process. Similar instruments assessing other cognitive domains are required to elucidate the extent to which this hypothesis may explain cognitive changes with hearing loss.

It would be useful to examine data from epidemiological studies which have used tests of cognitive function that allow for differentiation between implicit and explicit processes. Such studies could provide more statistical power to test differences between participants with or without ARHL and to explore possible contributing factors. This study used a small sample size and thus the ability to test other factors that may mediate this relationship was limited. For example, a large portion of the hearing loss sample had tinnitus and also wore hearing aids. Such factors may account for some of the variance in asymmetry between implicit and explicit functions in the hearing loss sample. It was suggested that this implicit-explicit asymmetry occurs regardless of hearing aid use. However, a common causal factor such as a genetic or vascular factor which affects both hearing and cognitive function would also account for such an observation. Additionally, this model posited that the decline in implicit processes is driven mechanistically by the loss of stimulation and the increased effort to perceive auditory stimuli following hearing loss. Other factors such as loneliness or genetic factors may better account for this pattern if, in other studies, it is demonstrated to be observed with ARHL.

A methodological limitation is that beyond pure-tone audiometry and self-reported hearing loss there were no other measures of hearing loss. Other measures of alterations in peripheral hearing loss may have a closer relationship with the earliest stages of cognitive changes in ARHL samples (Wayne & Johnsrude, 2015). Additionally, if the relationship between hearing loss and cognitive decline is better accounted for by a mechanistic speech based pathway, then speech-in-noise tasks may provide more accurate assessment of functional hearing loss which predicts implicit-explicit asymmetry more closely than pure-tone audiometry. In the literature, ARHL is broadly defined in terms of its aetiological processes which are described as multi-factorial with factors such as vascular or genetic contributing. Further consideration of these factors in future studies would be of interest as there may be distinct neurocognitive profiles apart from that outlined by the NIEAD model depending on which pathways are dominant in contributing to cognitive decline with ARHL.

Research is required to identify the neural correlates of implicit and explicit processes in ARHL samples. Similar previous research has been conducted looking at implicit and explicit processes in other samples (Ramponi et al., 2011; Stock et al., 2016). The definition of implicit and explicit processes were derived from these prior studies. However, further research is required to define and determine what implicit and explicit processes are and how they may be assessed. The results of this thesis suggest a neurocognitive profile where there is intact frontal lobe and hippocampal

functioning but decline in implicit processes possibly mediated by altered subcortical processes (Daulatzai, 2016) and specific implicit processing neural regions (Ramponi et al., 2011). Neuro-imaging studies that assess the relationship between performance on implicit-explicit cognitive tasks and neural changes with ARHL would be informative. This requires mapping of implicit and explicit processes onto their neural structures in both ARHL samples and controls and would enable further testing of the NIEAD model. Examining whether there are differences in individuals with ARHL on implicit and explicit functions which may be correlated with altered neural processes compared to controls would provide further validity to this model.

Following mapping of implicit-explicit processes to their neural correlates, there are several possible avenues for neuro-imaging research to test the NIEAD model. One approach would be to assess if there are morphological changes with ARHL in neural regions that modulate these functions. Another would be to assess if there are functional differences in neural networks when performing tasks such as the temporary memory binding task (Parra et al., 2017). Of further interest would be to examine whether an asymmetric relationship between implicit and explicit function can account for the neural changes previously observed in the literature on ARHL such as the increased connectivity within nodes of the default mode network (DMN) and between nodes of the DMN with nodes of cognitive control networks (Husain et al., 2014; Wang, Fan, et al., 2014). Prior research has reported altered activation in the DMN on implicit processing tasks of memory (Yang, Weng, Zang, Xu, & Xu, 2010), emotional faces perception (Shi et al., 2015), as well as phonological (Wilson, Tregellas, Slason, Pasko, & Rojas, 2011) and language processing (Seghier & Price, 2012). Additionally, research is required to examine how ARHL samples may rely on increased executive recruitment to compensate for this decline in implicit processes on non-auditory cognitive tasks. Research could also explore altered neurotransmitter function such as in dopamine as done in previous studies assessing the association of dopamine production with cognitive ageing (Backman et al., 2000; Erixon-Lindroth et al., 2005; Mozley, Gur, Mozley, & Gur, 2001; Volkow et al., 1998). Based on these findings, it is posited that dopamine transmitter production would be altered in neural structures linked to implicit processes in ARHL samples.

This research has clinical implications for future hearing rehabilitative trials and for dementia prevention trials. Additionally, as preclinical periods may present a critical opportunity for intervention to delay cognitive decline, this research approach may lead to the development of a preclinical marker for assessing future cognitive decline in ARHL patients. If people with ARHL use increased executive processing to compensate for decline in bottom-up processes, cognitive tests which directly assess implicit processes rather than explicit processes may be required to detect these changes during earlier stages of decline. This would be particularly relevant to those with higher cognitive reserve (Stern, 2009, 2012). It may also give identifiable neuropsychological markers for younger adults in the primary stages of ARHL who may not demonstrate or notice any differences in cognitive function compared to their peers. Interestingly, as the NIEAD hypothesis

posits that hearing loss mechanistically causes an asymmetry between explicit and implicit processes, this asymmetry could make it a more useful clinical marker of cognitive decline at the individual level. As any decline in implicit processes is defined relative to level of explicit function, individual performance on these tasks can be used to determine cognitive decline rather than in comparison to norms which must be adjusted for age or education. Additionally, it may assist in identifying candidates for hearing intervention studies. Markers of implicit function may provide a more accurate assessment of the benefits of interventions for hearing loss than standard neuropsychological instruments. Such trials could use these markers as targets to improve hearing assistive devices. Standard neuropsychological instruments may not sufficiently assess any benefit due to hearing aids as explicit function may compensate for any underlying deficit in bottom-up cognitive processes.

The NIEAD hypothesis may also potentially explain other health related links between ARHL and cognitive decline as ARHL has been associated with a constellation of age-related health difficulties. The effects observed in implicit cognitive processes may extend into other areas such as motor function which older adults maintain by relying on executive control (Lindenberger, Marsiske, & Baltes, 2000). People with ARHL are more likely to report falls, a relationship which was linear with level of hearing loss (Kamil et al., 2015; Lin & Ferrucci, 2012). Further research is needed to assess the extent to which hearing loss may alter function and health through this hypothetical pathway. The NIEAD model also has broader applications beyond the relationship between ARHL and cognitive decline. Any disorder in which sustained executive processing is extensively recruited to maintain daily functioning would be predicted to elicit a similar asymmetric neurocognitive profile thus extending this model to the broader cognitive ageing literature. ARHL may be a more acute condition among several which could cause this distinctive neurocognitive profile.

8.4 Conclusions

The results of the empirical studies provided support for the hypothesis outlined in this thesis that ARHL is associated with decline in implicit cognitive processes but with maintained explicit processes. Further research is necessary to replicate and explore the potential implications of these findings for cognitive ageing in the ARHL population. Further research is also warranted to explore the implications for current methods of diagnosing cognitive impairment in ARHL and for treatment. This hypothesis was based on previous research examining neurocognitive change in speech perception with ARHL. This suggests that cognitive decline in the ARHL population may not be due purely to advanced physiological ageing or frailty (Lindenberger & Baltes, 1994; Panza, Solfrizzi, & Logroscino, 2015; Panza, Solfrizzi, Seripa, et al., 2015) but may also be due to a unique mechanistic contribution that alters the trajectory of cognitive ageing that cumulatively appears as accelerated age-related cognitive decline (Lin et al., 2013). Further research examining

the NIEAD hypothesis and its implications for the association of hearing loss with cognitive decline is warranted.

Supplementary Appendices

Appendix A: Supplementary meta-analysis data

Table 1: Search terms & results

PubMed		
Terms	**Returns – 26.08.2015**	**New returns – 15.04.2016**
("hearing") AND ("cognition") AND ("older adults" OR "elderly")	282	11
("hearing") AND ("dementia") AND ("older adults" OR "elderly")	156	11
("hearing") AND ("Alzheimer's disease") AND ("older adults" OR "elderly")	29	15
Total	467	37/504
Cochrane Library		
Terms	**Returns – 26.08.2015**	**New returns – 15.04.2016**
("hearing") AND ("cognition") AND ("older adults" OR "elderly")	12	6
("hearing") AND ("dementia") AND ("older adults" OR "elderly")	11	2
("hearing") AND ("Alzheimer's disease") AND ("older adults" OR "elderly")	1	0
Total	24	8/32
EMBASE – (mapping – limit to terms indexed in article as major focus)		
Terms	**Returns – 26.08.2015**	**New returns – 15.04.2016**
("hearing") AND ("cognition") AND ("older adults" OR "elderly")	13	1
("hearing") AND ("dementia") AND ("older adults" OR "elderly")	0	0
("hearing") AND ("Alzheimer's disease") AND ("older adults" OR "elderly")	1	0
Total	14	1/15
SCOPUS		
Terms	**Returns – 26.08.2015**	**New returns – 15.04.2016**
("hearing") AND ("cognition") AND ("older adults" OR "elderly")	714	42
("hearing") AND ("dementia") AND ("older adults" OR "elderly")	418	22
("hearing") AND ("Alzheimer's disease") AND ("older adults" OR "elderly")	72	5
Total	1204	69/1273
Results		
Total	1709	115/1824
After removing duplicates	1075	82
Other sources	57	-
After removing articles found in original search/additional records	-	53
Total	1132	1185

Table 2: Planned variables for sensitivity analyses

Moderator analysis (categorical variables)
1. Study characteristics
Country/region in which the study was conducted (*Australia, Europe, USA, other*)
2. Subject characteristics
Race *(single, mixed or not declared*)
Participants with any of the following risks factors were removed from the sample either at baseline or in analysis (*cognitive impairment, dementia, cardiovascular risk, cerebrovascular risk, & neurological risk*) (*yes or no*)
3. Audiometric factors
Ear used
Hearing loss decibel (dB) criteria (e.g. >25dB);
Frequency range (e.g. > 4kHz)
Sound-treated room or booth used (*yes or no*)
Audiometric criteria followed WHO criteria (*yes or no*)
Hearing aid users were removed (*yes or no*)
4. Cognitive measures
Cognitive test used
Test stimuli were accessible to a hearing loss sample e.g. visual (*yes or no*)
5. Statistical analysis
Type of statistical analysis
Authors reported results as significant (*yes or no*)
Analysis/design controlled or adjusted for covariates (*yes or no*) – age, sex, race, education, occupation, income, vascular factors (stroke, hypertension, diabetes, cardiovascular and cerebrovascular disease), body mass index (BMI), alcohol intake, smoking, depression, hearing aid users, pre-morbid intelligence, and processing speed.
Meta-regression (continuous variables)
1. Study characteristics
Year of publication
Attrition rate (*cohort studies only*)
Time to final follow-up (*cohort studies only*)
Journal impact factor
STROBE score (*0-22*)
2. Subject characteristics
Age (*mean, minimum and maximum age of sample*)
Gender *(% female*)
Race *(% white, black or other*)
Education *(% primary, secondary or tertiary*)
Occupation *(% manual or professional*)
Low income (*%*)
Alcohol intake (*mean unit*)
Smoking *(% current, previous or never*)
3. Audiometric factors
Pure-tone average (PTA) dB of sample
Hearing loss rate (*% of participants diagnosed as having a hearing loss by study authors*)
Hearing aid user (*%*)

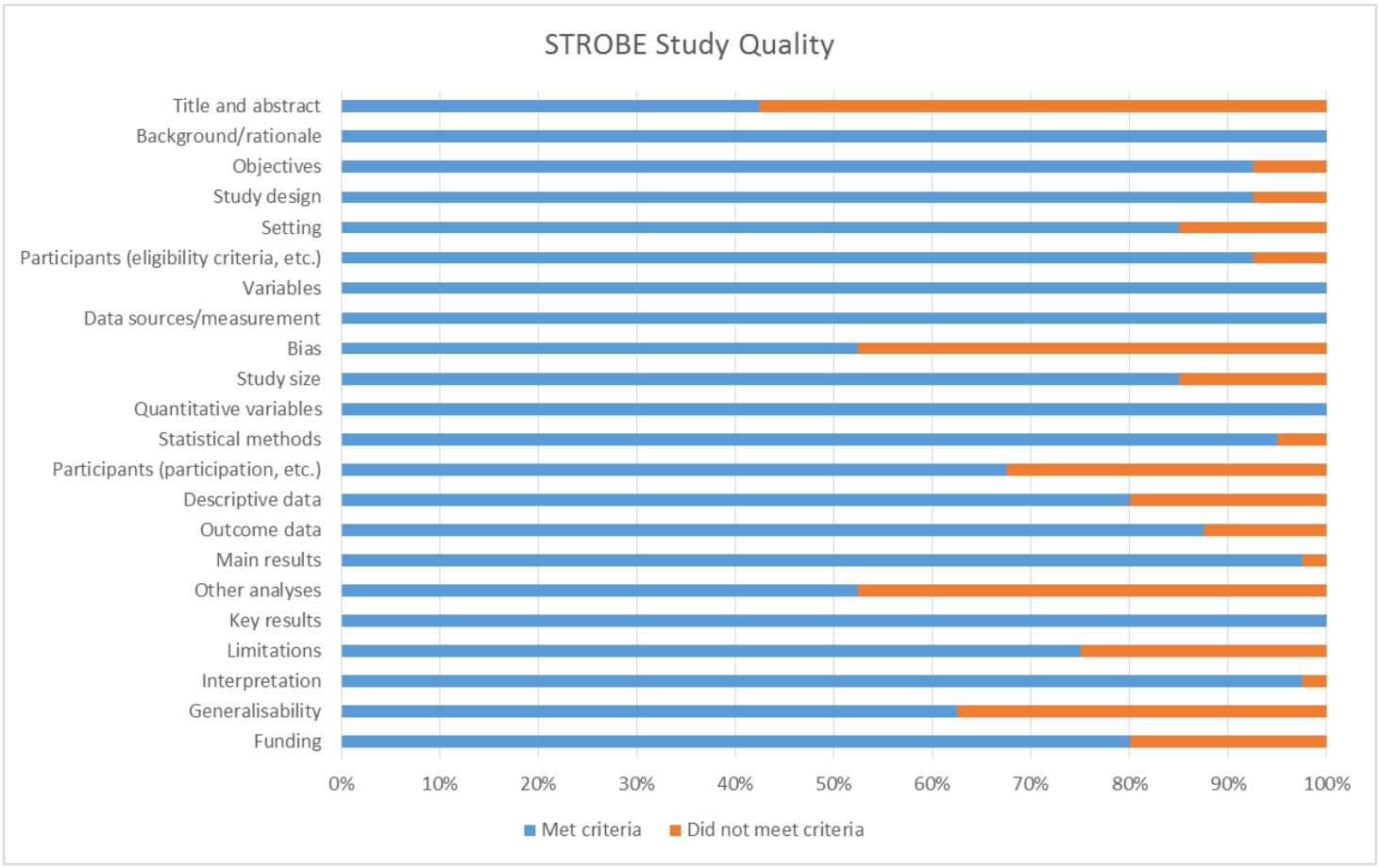

Figure 1: Study quality. Pooled results using the STROBE Instrument

Table 3: Hearing loss & cognitive function: main cross-sectional results

Variable	Studies (*n*)	Outcomes (*n*)*	ES (*n*)	Participants (*n*)	*r*	95% CI
Attention	9	16	11	5,159	-0.156	-0.237, -0.073
Delayed recall	6	7	7	3,808	-0.098	-0.157, -0.037
Fluency	7	15	9	4,629	-0.081	-0.121, -0.041
Global cognition	13	15	15	7,702	-0.146	-0.182, -0.109
Immediate recall	13	20	15	6,747	-0.143	-0.198, -0.088
Processing speed	18	45	20	10,660	-0.128	-0.176, -0.079
Reasoning	9	20	12	3,128	-0.178	-0.253, -0.101
Semantic memory	8	11	10	2,906	-0.141	-0.204, -0.076
Visuospatial ability	3	8	5	669	-0.107	-0.185, -0.027
Working memory	7	15	9	4,855	-0.098	-0.148, -0.047
Overall	26	172	113	15,620	-0.122	-0.139, -0.105

Notes: ES, effect size; CI, confidence interval; *, number of effect sizes prior to collapsing them for analysis; Std. Err., standard error;

Table 3 (Continued): Hearing loss & cognitive function: main cross-sectional results

Variable	Fisher's Z	Std. Err.	Z(*p*)	Q(*p*)	I^2 (%)
Attention	-0.157	0.043	**-3.64 (<0.001)**	79.9 (<0.001)	87.5
Delayed recall	-0.098	0.031	**-3.13 (0.002)**	17.1 (0.01)	64.8
Fluency	-0.081	0.02	**-3.97 (<0.001)**	11.6 (0.2)	30.8
Global cognition	-0.147	0.019	**-7.55 (<0.001)**	31.0 (0.01)	54.8
Immediate recall	-0.144	0.029	**-5.01 (<0.001)**	72.1 (<0.001)	80.6
Processing speed	-0.128	0.025	**-5.08 (<0.001)**	127.4 (<0.001)	85.1
Reasoning	-0.18	0.04	**-4.55 (<0.001)**	45.9 (<0.001)	76.0
Semantic memory	-0.142	0.033	**-4.23 (<0.001)**	26.3 (0.002)	65.8
Visuospatial ability	-0.107	0.041	**-2.63 (0.01)**	4.3 (0.4)	7.3
Working memory	-0.098	0.026	**-3.73 (<0.001)**	18.1 (0.02)	55.9
Overall	-0.123	0.009	**-13.97 (<0.001)**	482.0 (<0.001)	76.8

Notes: ES, effect size; CI, confidence interval; *, number of effect sizes prior to collapsing them for analysis; Std. Err., standard error;

Table 4: Hearing loss & cognitive function: results of further analysis for cross-sectional studies

Variable	Egger's test of the intercept				
	β_0	**95% CI**	**t**	**df**	***p* (1-tailed)**
Attention	-3.11	-7.26, 1.04	1.7	9	0.06
Delayed recall	*NA*	*NA*	*NA*	*NA*	*NA*
Fluency	*NA*	*NA*	*NA*	*NA*	*NA*
Global cognition	-0.71	-2.41, 0.999	0.89	13	0.19
Immediate recall	0.56	-3.7, 4.82	0.29	13	0.39
Processing speed	-2.09	-5.07, 0.88	1.48	18	0.08
Reasoning	-2.13	-5.65, 1.4	1.34	10	0.1
Semantic memory	3.87	0.66, 7.09	2.78	8	**0.01**
Visuospatial ability	*NA*	*NA*	*NA*	*NA*	*NA*
Working memory	*NA*	*NA*	*NA*	*NA*	*NA*

Notes: β_0, intercept; CI, confidence interval; df, degrees of freedom; ND (no difference), means results remained statistically significant when each study was deleted from the model once; NA, not applicable.

Table 4 (Continued): Hearing loss & cognitive function: results of further analysis for cross-sectional studies

Variable	One study removed		Cumulative analysis
	Study	**Point difference smallest/largest (%)**	**Significant since**
Attention	ND	0.046 (26.6)	1960
Delayed recall	ND	0.048 (41.4)	2005
Fluency	ND	0.036 (37.1)	1986
Global cognition	ND	0.026 (16.6)	1983
Immediate recall	ND	0.032 (20.8)	1960
Processing speed	ND	0.023 (16.8)	1960
Reasoning	ND	0.041 (21.1)	1960
Semantic memory	ND	0.035 (22.4)	1967
Visuospatial ability	Clark (1960)	0.064 (44.1)	1960
Working memory	ND	0.041 (36.0)	1983

Notes: β_0, intercept; CI, confidence interval; df, degrees of freedom; ND (no difference), means results remained statistically significant when each study was deleted from the model once; NA, not applicable.

Table 5: Hearing loss & cognitive function: main cohort results

Variable	Studies (*n*)	Outcomes (*n*)*	ES (*n*)	Participants (*n*)	*r*	95% CI
Attention	1	2	1	391	-0.1	-0.197, 0.0
Delayed recall	3	5	4	1,774	-0.101	-0.147, -0.054
Fluency	3	4	4	1,233	-0.067	-0.139, 0.006
Global cognition	4	7	6	4,227	-0.139	-0.189, -0.089
Immediate recall	5	7	6	4,225	-0.061	-0.102, -0.02
Processing speed	7	15	10	6,462	-0.084	-0.136, -0.031
Reasoning	1	1	1	1,057	-0.064	-0.124, -0.003
Semantic memory	1	3	1	707	-0.141	-0.23, -0.05
Overall	9	44	33	8,233	-0.09	-0.112, -0.068

Notes: ES, effect size; CI, confidence interval; *, number of effect sizes prior to collapsing them for analysis; Std. Err., standard error;

Table 5 (Continued): Hearing loss & cognitive function: main cohort results

Variable	Fisher's Z	Std. Err.	Z(*p*)	Q(*p*)	I^2 (%)
Attention	-0.1	0.051	**-1.98 (0.048)**	0.0 (>0.99)	0.0
Delayed recall	-0.101	0.024	**-4.14 (<0.001)**	2.1 (0.55)	0.0
Fluency	-0.067	0.037	-1.79 (0.07)	7.1 (0.07)	57.5
Global cognition	-0.14	0.026	**-5.36 (<0.001)**	18.9 (0.002)	73.5
Immediate recall	-0.061	0.021	**-2.91 (0.004)**	40.7 (<0.001)	87.7
Processing speed	-0.084	0.027	**-3.12 (0.002)**	285.9 (<0.001)	96.9
Reasoning	-0.064	0.031	**-2.08 (0.04)**	0.00 (>0.99)	0.00
Semantic memory	-0.142	0.047	**-3.01 (0.003)**	0.00 (>0.99)	0.00
Overall	-0.09	0.01	**-8.74 (<0.001)**	552.8 (<0.001)	94.2

Notes: ES, effect size; CI, confidence interval; *, number of effect sizes prior to collapsing them for analysis; Std. Err., standard error;

Table 6: Hearing loss & cognitive function: results of further analysis for cohort studies

Variable	Egger's test of the intercept				
	β_0	95% CI	t	df	*p* (1-tailed)
Attention	*NA*	*NA*	*NA*	*NA*	*NA*
Delayed recall	*NA*	*NA*	*NA*	*NA*	*NA*
Fluency	*NA*	*NA*	*NA*	*NA*	*NA*
Global cognition	*NA*	*NA*	*NA*	*NA*	*NA*
Immediate recall	*NA*	*NA*	*NA*	*NA*	*NA*
Processing speed	-4.03	-9.5, 1.41	1.71	8	0.06
Reasoning	*NA*	*NA*	*NA*	*NA*	*NA*
Semantic memory	*NA*	*NA*	*NA*	*NA*	*NA*

Notes: β_0, intercept; CI, confidence interval; df, degrees of freedom; ND (no difference), means results remained statistically significant when each study was deleted from the model; $^+$, results were non-significant and became significant with this study (mild hearing loss vs normal hearing subgroup) removed;

Table 6 (Continued): Hearing loss & cognitive function: results of further analysis for cohort studies

Variable	One study removed		Cumulative analysis
	Study	Point difference smallest/largest (%)	Significant since
Attention	*NA*	*NA*	*NA*
Delayed recall	ND	0.025 (21.6)	2005
Fluency	Deal et al. (2015)	0.061 (58.7)	Not sig.
Global cognition	ND	0.039 (24.5)	2012
Immediate recall	ND	0.05 (60.2)	2003
Processing speed	ND	0.029 (31.2)	2003
Reasoning	*NA*	*NA*	*NA*
Semantic memory	*NA*	*NA*	*NA*

Notes: β_0, intercept; CI, confidence interval; df, degrees of freedom; ND (no difference), means results remained statistically significant when each study was deleted from the model; $^+$, results were non-significant and became significant with this study (mild hearing loss vs normal hearing subgroup) removed;

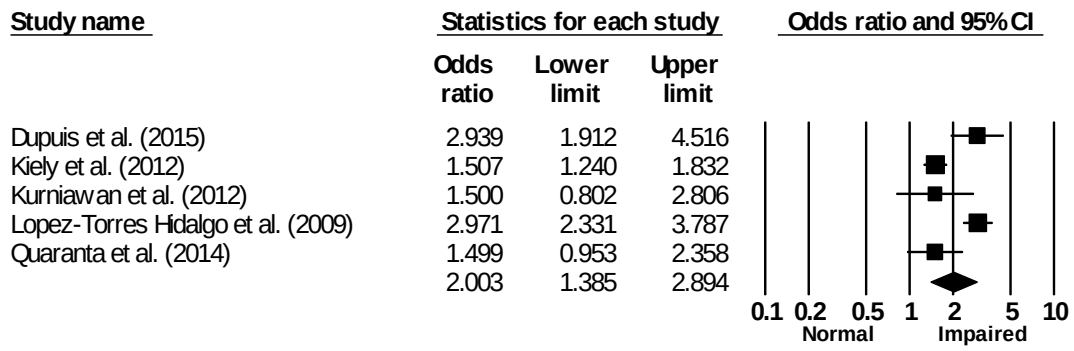

Figure 2: Forest plot of odds ratios for cognitive impairment/cross-sectional outcomes.

The black squares represent the OR while the lines represent the corresponding 95% confidence intervals. The middle of the black diamond represents the overall OR while the left and right extremes of the diamond represent the corresponding 95% confidence intervals.

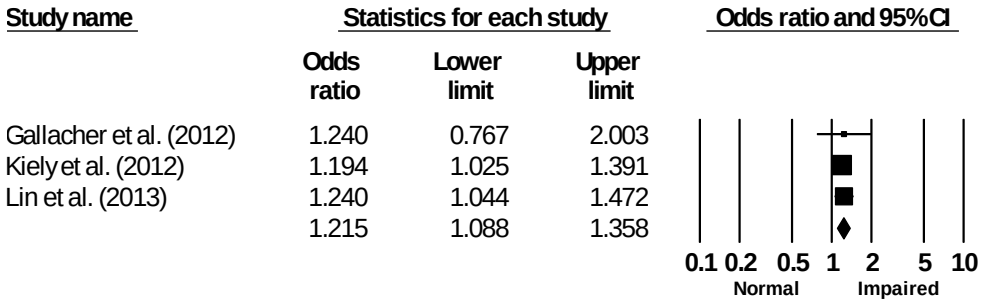

Figure 3: Forest plot of odds ratios for cognitive impairment/cohort outcomes.

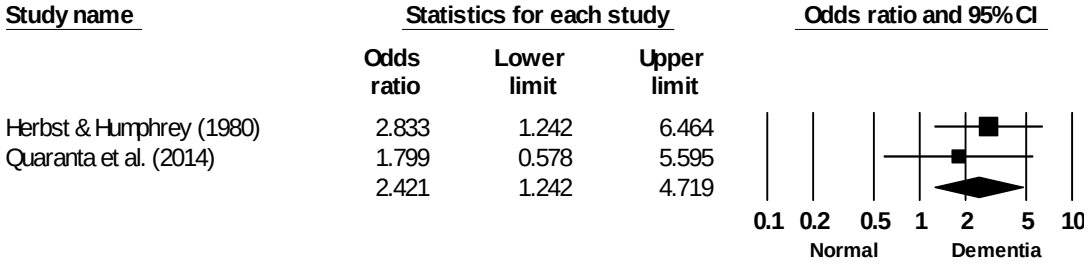

Figure 4: Forest plot of odds ratios for dementia+AD/cross-sectional outcomes.

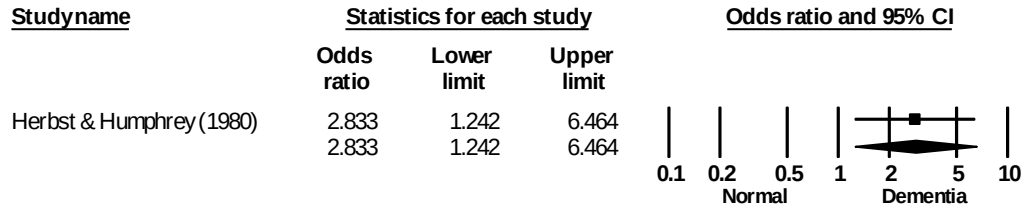

Figure 5: Dementia/cross-sectional (Forest plot of odds ratios)

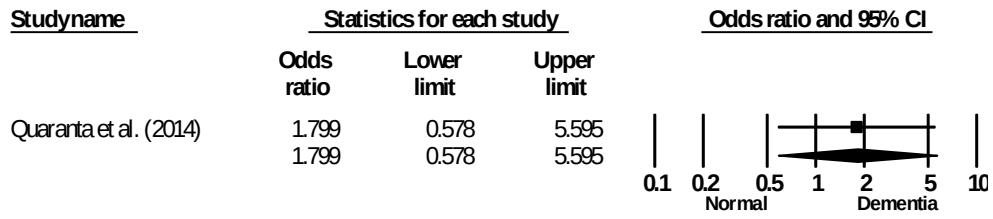

Figure 6: AD/cross-sectional (Forest plot of odds ratios)

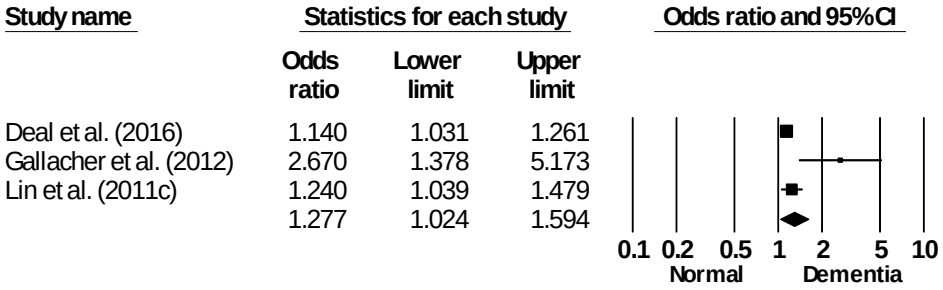

Figure 7: Forest plot of odds ratios for dementia/cohort outcomes.

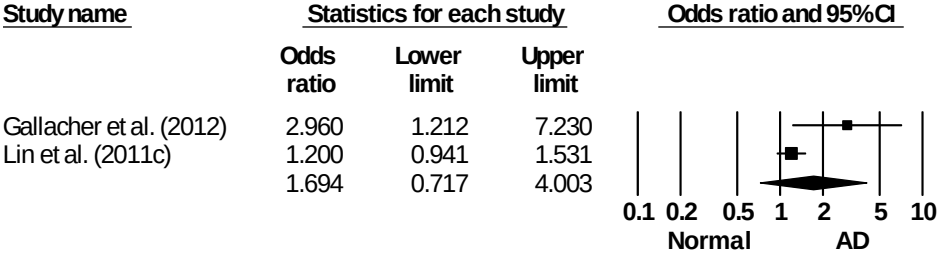

Figure 8: Forest plot of odds ratios for AD/cohort outcomes.

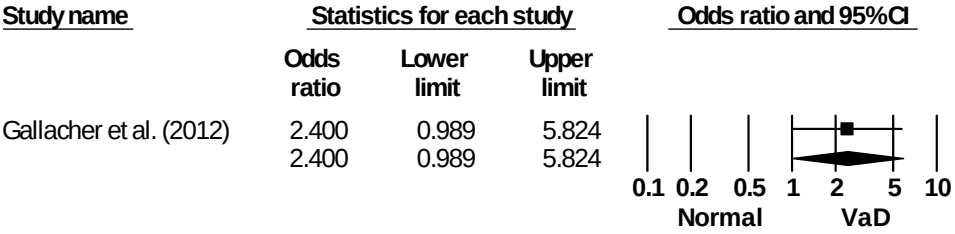

Figure 9: VaD/cohort (Forest plot of odds ratios)

Table 7: Hearing loss & clinical outcomes: main cross-sectional and cohort results

Variable	Studies (*n*)	ES (*n*)	Participants (*n*)	Cases (*n/%*)	Odds Ratio
CS/Cognitive impairment	5	5	6,553	797 (12.2)	2.003
Co/Cognitive impairment	3	3	6,825	1,395 (20.4)	1.215
CS/Dementia + AD	2	2	679	59 (8.7)	2.421
CS/Dementia	1	1	245	39 (15.9)	2.833
CS/AD	1	1	434	20 (4.6)	1.799
Co/Dementia	3	3	3,439	366 (10.6)	1.277
Co/AD	2	2	1,491	78 (5.2)	1.694
Co/VaD	1	1	870	38 (4.4)	2.4

Notes: Co, Cohort; CS, Cross-sectional; ES, effect size; CI, confidence interval;

Table 7 (Continued): Hearing loss & clinical outcomes: main cross-sectional and cohort results

Variable	95% CI	Z(*p*)	Q(*p*)	I^2 (%)
CS/Cognitive impairment	1.385 – 2.894	**3.70 (<0.001)**	23.7 (<0.001)	83.1
Co/Cognitive impairment	1.088 – 1.358	**3.45 (<0.001)**	0.11 (0.95)	0.00
CS/Dementia + AD	1.242 – 4.719	**2.60 (0.01)**	0.40 (0.53)	0.00
CS/Dementia	1.242 – 6.464	**2.47 (0.01)**	*NA*	*NA*
CS/AD	0.578 – 5.595	1.01 (0.31)	*NA*	*NA*
Co/Dementia	1.024 – 1.594	**2.17 (0.03)**	6.61 (0.04)	69.74
Co/AD	0.717 – 4.003	1.20 (0.23)	3.65 (0.06)	72.64
Co/VaD	0.989 – 5.824	1.94 (0.053)	*NA*	*NA*

Notes: Co, Cohort; CS, Cross-sectional; ES, effect size; CI, confidence interval;

Table 8: Hearing loss & cognitive function: moderator analysis (Qb scores & p-values) for cross-sectional and cohort studies

Moderator	Attention (CS)	Delayed recall (CS)	Fluency (CS)	Global cognition (CS)	Immediate recall (CS)	Processing speed (CS)
Country/Region	**4.02 (0.045)**	0.06 (0.8)	-	1.15 (0.28)	0.04 (0.85)	**7.88 (0.02)**
CI removed (BL)	-	-	-	3.64 (0.06)	-	**5.52 (0.02)**
Dementia removed (BL)	-	-	0.06 (0.8)	**5.02 (0.03)**	0.85 (0.36)	2.42 (0.12)
CVR removed (BL)	-	-	-	**5.28 (0.02)**	-	-
Race	-	-	-	**5.17 (0.02)**	-	**7.47 (0.01)**
Ear used	2.15 (0.14)	-	0.079 (0.78)	2.82 (0.09)	0.28 (0.59)	**4.32 (0.04)**
Frequencies >4kHz	-	-	0.001 (0.97)	0.05 (0.82)	**4.76 (0.03)**	**4.59 (0.03)**
Sound-treated booth/room	**7.47 (0.01)**	0.01 (0.94)	0.02 (0.89)	0.48 (0.49)	**4.04 (0.04)**	**8.04 (0.01)**
Used WHO criteria	**7.47 (0.01)**	0.01 (0.94)	-	**6.34 (0.01)**	2.15 (0.14)	**10.02 (0.002)**
Hearing loss criteria (>25dB)	-	-	-	0.26 (0.61)	-	-
Hearing aid user removed*	2.87 (0.09)	-	0.03 (0.87)	1.14 (0.29)	**3.99 (0.046)**	3.5 (0.06)
Cognitive test accessible	**6.59 (0.01)**	0.06 (0.81)	-	0.5 (0.48)	0.88 (0.35)	-
Analysis used	**32.26 (<0.0001)**	-	-	3.82 (0.15)	1.21 (0.27)	**10.67 (0.01)**
Reported significant	**8.75 (0.003)**	**10.75 (0.001)**	**11.84 (0.001)**	0.004 (0.95)	**13.67 (<0.0001)**	**10.12 (0.001)**
CI removed*	-	-	-	-	-	-
Dementia removed*	-	-	-	-	-	-
Age*	**37.96 (<0.0001)**	-	**4.01 (0.045)**	-	1.54 (0.22)	**4.57 (0.03)**
Sex*	**37.96 (<0.0001)**	-	-	**6.34 (0.01)**	2.11 (0.15)	**4.09 (0.04)**
Race*	2.94 (0.09)	-	-	**8.96 (0.003)**	-	**7.47 (0.01)**
Education (level/years)*	**4.58 (0.03)**	-	0.69 (0.41)	**7.03 (0.01)**	1.0 (0.32)	**4.06 (0.04)**
Education (level)*	-	-	-	1.21 (0.27)	1.85 (0.17)	3.38 (0.07)
Education (years)*	-	-	-	**6.25 (0.01)**	-	-
Vascular risk factors*	2.94 (0.09)	1.07 (0.3)	-	**8.96 (0.003)**	0.89 (0.35)	**7.45 (0.01)**
Stroke*	-	-	-	**8.08 (0.004)**	0.89 (0.35)	**7.45 (0.01)**
Hypertension*	2.94 (0.09)	-	-	**8.96 (0.003)**	0.94 (0.33)	**7.47 (0.01)**
Diabetes*	-	-	-	**8.08 (0.004)**	0.94 (0.33)	**7.47 (0.01)**
Current smokers*	3.27 (0.07)	-	-	**6.34 (0.01)**	2.15 (0.14)	**8.33 (0.004)**
Previous smokers*	3.27 (0.07)	-	-	**6.34 (0.01)**	2.15 (0.14)	**8.33 (0.004)**
Depression*	**7.42 (0.01)**	0.01 (0.94)	-	2.84 (0.09)	-	-
Pre-morbid IQ*	1.53 (0.22)	1.25 (0.26)	-	-	-	-
Study site*	-	-	-	-	**5.34 (0.02)**	**6.7 (0.01)**

Table 8 (Continued): Hearing loss & cognitive function: moderator analysis (Qb scores & p-values) for cross-sectional and cohort studies

Moderator	Reasoning (CS)	Semantic memory (CS)	Working memory (CS)	Global cognition (Co)	Immediate recall (Co)	Processing speed (Co)
Country/Region	-	3.23 (0.2)	**4.33 (0.04)**	-	-	0.44 (0.51)
CI removed (BL)	-	-	-	-	-	**12.6 (<0.001)**
Dementia removed (BL)	-	-	-	-	-	1.06 (0.3)
CVR removed (BL)	-	-	-	-	-	-
Race	-	-	-	-	-	-
Ear used	1.92 (0.17)	3.29 (0.07)	1.51 (0.22)	-	-	-
Frequencies >4kHz	1.87 (0.17)	0.002 (0.96)	-	-	-	-
Sound-treated booth/room	2.78 (0.1)	3.29 (0.07)	0.01 (0.93)	-	-	0.41 (0.52)
Used WHO criteria	-	3.29 (0.07)	-	-	-	0.41 (0.52)
Hearing loss criteria (>25dB)	-	-	-	-	-	0.44 (0.51)
Hearing aid user removed*	-	**3.88 (0.049)**	-	-	**27.12 (<0.001)**	0.65 (0.42)
Cognitive test accessible	0.24 (0.62)	-	-	-	-	-
Analysis used	-	-	**6.16 (0.01)**	-	-	-
Reported significant	**27.59 (<0.001)**	-	**8.13 (0.004)**	1.89 (0.17)	-	**28.32 (<0.001)**
CI removed*	-	-	-	-	-	**20.9 (<0.001)**
Dementia removed*	-	-	-	-	-	**23.63 (<0.001)**
Age*	1.92 (0.17)	1.86 (0.17)	0.4 (0.53)	-	-	-
Sex*	0.69 (0.41)	0.52 (0.47)	-	-	-	-
Race*	-	3.29 (0.07)	-	-	-	0.41 (0.52)
Education (level/years)*	-	3.29 (0.07)	-	-	-	-
Education (level)*	-	-	-	-	**27.12 (<0.001)**	0.65 (0.42)
Education (years)*	-	-	-	-	-	-
Vascular risk factors*	-	3.29 (0.07)	-	-	-	0.41 (0.52)
Stroke*	-	-	-	-	-	0.65 (0.42)
Hypertension*	-	3.29 (0.07)	-	-	-	0.41 (0.52)
Diabetes*	-	-	-	-	-	0.65 (0.42)
Current smokers*	-	3.29 (0.07)	-	-	-	0.41 (0.52)
Previous smokers*	-	3.29 (0.07)	-	-	-	0.41 (0.52)
Depression*	-	-	-	-	-	0.34 (0.56)
Pre-morbid IQ*	-	-	-	**7.53 (0.006)**	-	0.5 (0.48)
Study site*	-	-	-	-	-	0.65 (0.42)

Table 9: Hearing loss & cognitive function: meta-regression analysis (Z scores & p-values) for cross-sectional and cohort studies

Covariate	Attention (CS)	Delayed recall (CS)	Fluency (CS)	Global cognition (CS)	Immediate recall (CS)	Processing speed (CS)
Year of publication	**5.47 (<0.001)**	-0.52 (0.6)	1.2 (0.23)	0.34 (0.74)	1.57 (0.12)	**4.61 (<0.0001)**
Impact factor	-0.19 (0.85)	-1.04 (0.3)	-0.91 (0.36)	1.6 (0.11)	0.74 (0.46)	0.92 (0.36)
STROBE	-0.35 (0.73)	-1.08 (0.28)	0.43 (0.67)	0.54 (0.59)	0.39 (0.7)	0.07 (0.95)
Length to follow-up (yrs)	-	-	-	-	-	-
Age (mean BL)	0.42 (0.67)	0.09 (0.93)	-0.71 (0.48)	0.26 (0.8)	0.32 (0.75)	-0.19 (0.85)
Age (min BL)	**2.63 (0.01)**	0.49 (0.62)	-1.93 (0.054)	0.24 (0.81)	0.99 (0.32)	1.85 (0.06)
Age (max BL)	0.46 (0.65)	-0.36 (0.72)	0.02 (0.98)	-0.74 (0.46)	-0.46 (0.64)	-0.15 (0.88)
Sex (% female BL)	0.8 (0.43)	0.56 (0.58)	0.19 (0.85)	0.33 (0.74)	1.12 (0.26)	0.65 (0.52)
Sex (% female FU)	-	-	-	-	-	-
Race (% white)	0.93 (0.35)	-	-	-0.91 (0.37)	**-2.0 (0.046)**	-0.68 (0.5)
Race (% black)	-0.86 (0.39)	-	-	0.92 (0.36)	**1.99 (0.047)**	1.55 (0.12)
Race (% other)	-1.18 (0.24)	-	-	-0.86 (0.39)	-1.65 (0.1)	-0.98 (0.33)
Education (mean years)	-	-	-	-0.59 (0.56)	-	0.46 (0.65)
Education (% primary)	-	-	-	0.02 (0.98)	-0.79 (0.43)	**-3.23 (0.001)**
Education (% secondary)	-	-	-	-0.12 (0.91)	0.35 (0.73)	0.45 (0.65)
Education (% tertiary)	**5.74 (<0.0001)**	-	-	-0.05 (0.96)	**3.07 (0.002)**	**7.18 (<0.0001)**
Current smoker (%)	-	-	-	-	-	-
Previous smoker (%)	-	-	-	-	-	-
Never smoked (%)	-	-	-	-	-	-
Sample PTA	**2.93 (0.003)**	0.04 (0.97)	-0.53 (0.6)	-0.28 (0.78)	**2.05 (0.04)**	0.35 (0.72)
Hearing loss (%)	0.93 (0.35)	0.33 (0.74)	0.93 (0.35)	0.35 (0.73)	**2.74 (0.01)**	0.51 (0.61)
Hearing aid user (%)	0.41 (0.68)	-0.02 (0.99)	-0.47 (0.64)	-0.21 (0.83)	0.57 (0.57)	-0.92 (0.36)

Notes: Positive values indicate a weaker effect size (Fisher's Z). BL, baseline; Co, cohort study; CI, cognitive impairment; CS, cross-sectional study; FU, follow-up; IQ, intelligence quotient; PTA, pure-tone average

Table 9 (Continued): Hearing loss & cognitive function: meta-regression analysis (Z scores & p-values) for cross-sectional and cohort studies

Covariate	Reasoning (CS)	Semantic memory (CS)	Visuospatial ability (CS)	Working memory (CS)	Delayed recall (Co)
Year of publication	**3.97 (0.0001)**	1.26 (0.21)	1.93 (0.053)	**3.41 (0.001)**	-0.23 (0.82)
Impact factor	-0.02 (0.98)	0.57 (0.57)	-	-1.12 (0.26)	0.35 (0.73)
STROBE	-1.32 (0.19)	0.26 (0.8)	1.5 (0.13)	**2.88 (0.004)**	-0.39 (0.7)
Length to follow-up (yrs)	-	-	-	-	-0.22 (0.82)
Age (mean BL)	0.33 (0.74)	0.01 (0.996)	-	-0.87 (0.38)	-0.05 (0.96)
Age (min BL)	**2.52 (0.01)**	-0.13 (0.9)	0.85 (0.39)	-0.5 (0.62)	0.03 (0.97)
Age (max BL)	0.26 (0.79)	-0.35 (0.73)	0.39 (0.7)	0.13 (0.9)	-
Sex (% female BL)	-0.04 (0.97)	-0.29 (0.77)	1.02 (0.31)	1.9 (0.06)	-
Sex (% female FU)	-	-	-	-	-0.21 (0.83)
Race (% white)	-	-	-	-	-
Race (% black)	-	-	-	-	-
Race (% other)	-	-	-	-	-
Education (mean years)	-	-	-	-	-
Education (% primary)	-	-	-	-	-
Education (% secondary)	-	-	-	-	-
Education (% tertiary)	-	1.79 (0.07)	-	-	-
Current smoker (%)	-	-	-	-	-
Previous smoker (%)	-	-	-	-	-
Never smoked (%)	-	-	-	-	-
Sample PTA	1.79 (0.07)	-0.52 (0.6)	0.3 (0.77)	0.35 (0.73)	-0.66 (0.51)
Hearing loss (%)	-	-	-	-0.75 (0.45)	-
Hearing aid user (%)	-	-	-	-	-

Notes: Positive values indicate a weaker effect size (Fisher's Z). BL, baseline; Co, cohort study; CI, cognitive impairment; CS, cross-sectional study; FU, follow-up; IQ, intelligence quotient; PTA, pure-tone average

Table 9 (Continued): Hearing loss & cognitive function: meta-regression analysis (Z scores & p-values) for cross-sectional and cohort studies

Covariate	Fluency (Co)	Global cognition (Co)	Immediate recall (Co)	Processing speed (Co)
Year of publication	1.37 (0.17)	0.55 (0.58)	**6.12 (<0.001)**	0.45 (0.65)
	2.12 (0.03)			
Impact factor	1.94 (0.053)	**-2.35 (0.02)**	0.86 (0.39)	**-4.94 (<0.0001)**
STROBE	1.24 (0.21)	**2.41 (0.02)**	**4.65 (<0.0001)**	0.74 (0.46)
Length to follow-up (yrs)	-1.75 (0.08)	**2.61 (0.009)**	-1.14 (0.25)	0.74 (0.46)
Age (mean BL)	-1.78 (0.08)	**-2.69 (0.007)**	0.51 (0.61)	-0.62 (0.54)
Age (min BL)	-1.92 (0.054)	**-2.53 (0.01)**	1.37 (0.17)	-0.36 (0.72)
Age (max BL)	-	-1.87 (0.06)	-	0.09 (0.92)
Sex (% female BL)	-	-	-	-
Sex (% female FU)	-	-0.11 (0.91)	0.74 (0.46)	-0.15 (0.88)
Race (% white)	-	1.01 (0.31)	-	0.05 (0.96)
Race (% black)	-	-1.01 (0.31)	-	-0.05 (0.96)
Race (% other)	-	-	-	-
Education (mean years)	-	-	-	-
Education (% primary)	-	-	-	0.07 (0.94)
Education (% secondary)	-	-	-	-0.75 (0.45)
Education (% tertiary)	-	-1.18 (0.24)	-	-0.16 (0.87)
Current smoker (%)	-	-	-	0.6 (0.55)
Previous smoker (%)	-	-	-	**-3.56 (0.0004)**
Never smoked (%)	-	-	-	**2.32 (0.02)**
Sample PTA	-	0.3 (0.76)	-	0.56 (0.58)
Hearing loss (%)	-	-	-	-
Hearing aid user (%)	-	-	-	-0.54 (0.59)

Notes: Positive values indicate a weaker effect size (Fisher's Z). BL, baseline; Co, cohort study; CI, cognitive impairment; CS, cross-sectional study; FU, follow-up; IQ, intelligence quotient; PTA, pure-tone average

SUPPLEMENTARY FOREST PLOTS

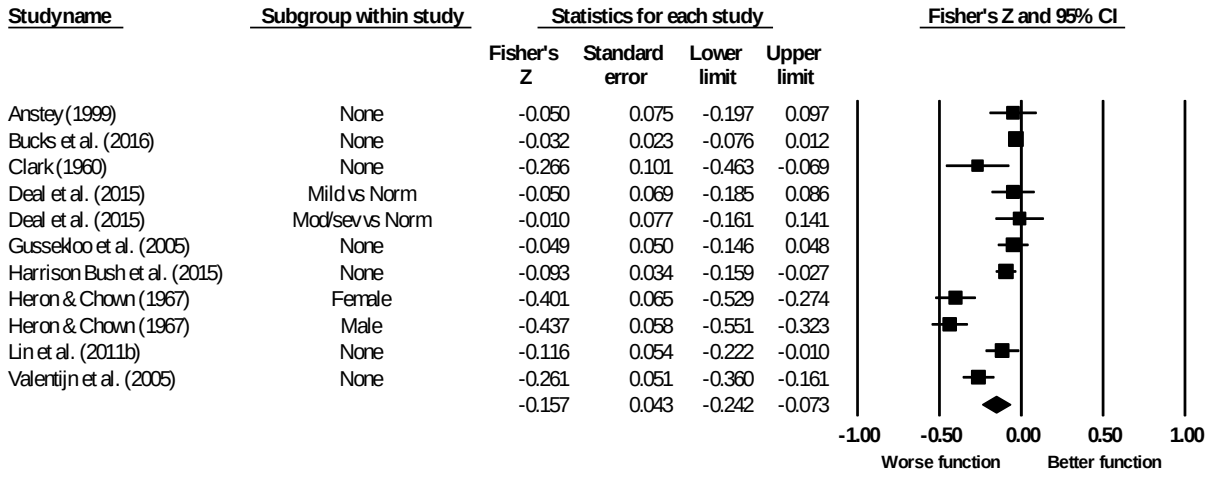

Figure 10: Attention – cross-sectional (Forest plot of Fisher's Z)

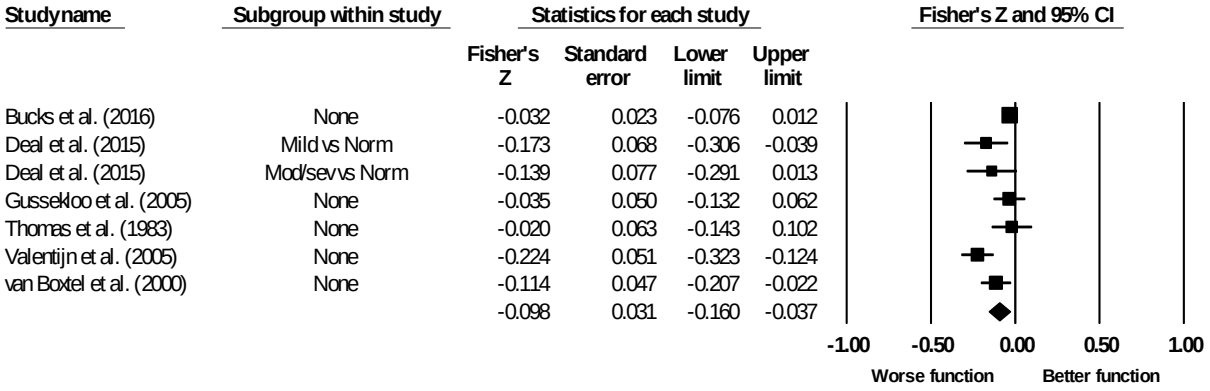

Figure 11: Delayed recall – cross-sectional (Forest plot of Fisher's Z)

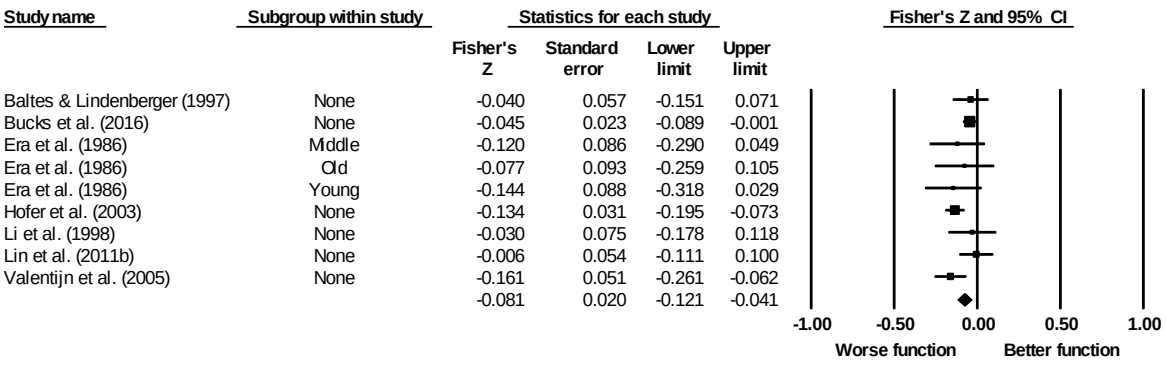

Figure 12: Fluency – cross-sectional (Forest plot of Fisher's Z)

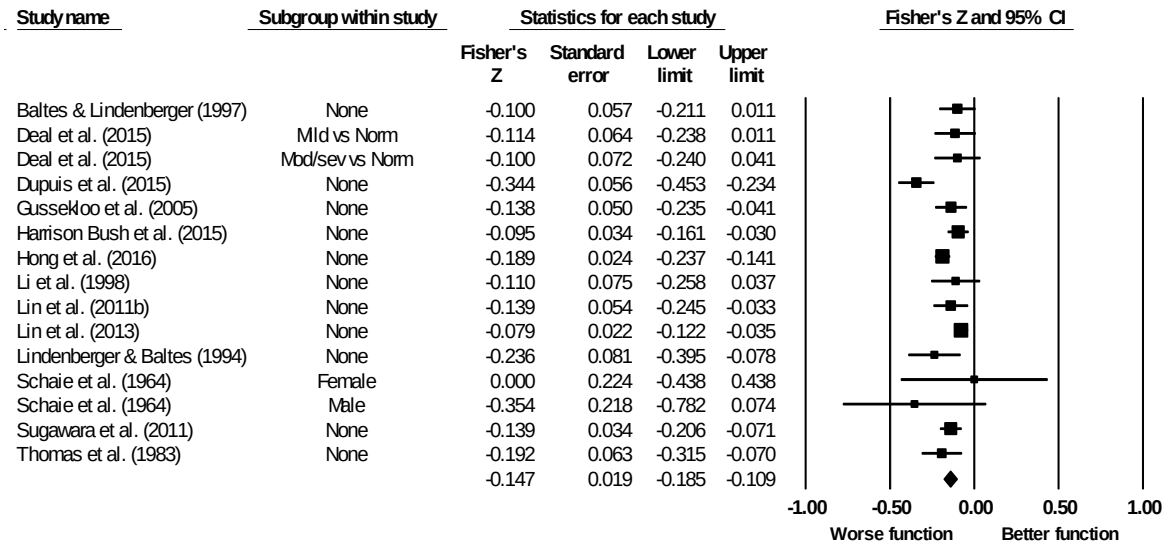

Figure 13: Global cognition – cross-sectional (Forest plot of Fisher's Z)

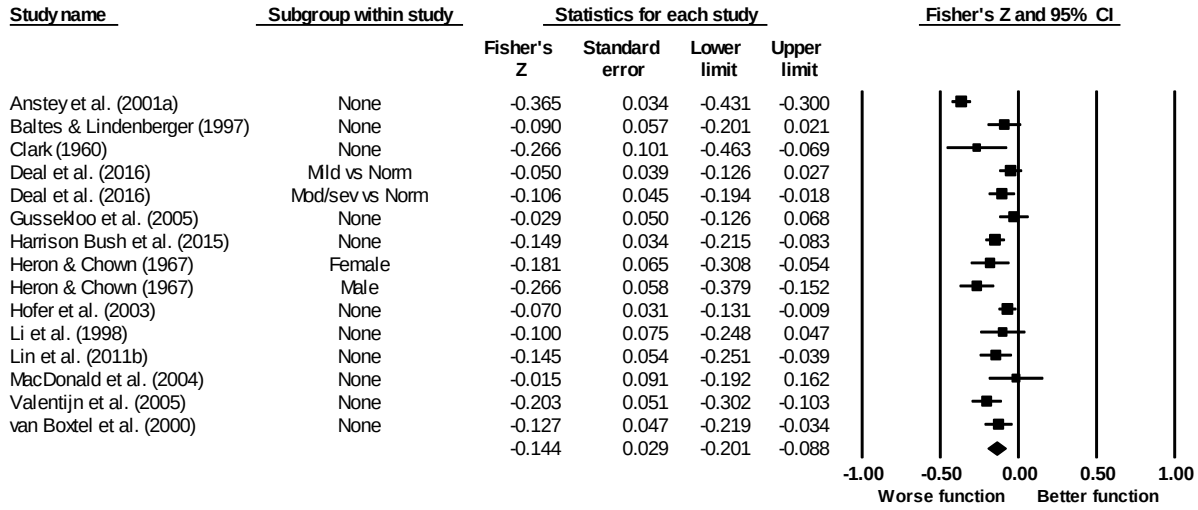

Figure 14: Immediate recall – cross-sectional (Forest plot of Fisher's Z)

Study name	Subgroup within study	Fisher's Z	Standard error	Lower limit	Upper limit
Anstey & Smith (1999)	None	-0.100	0.075	-0.248	0.047
Anstey (1999)	None	-0.121	0.075	-0.268	0.026
Anstey et al. (2001a)	None	-0.332	0.034	-0.397	-0.266
Baltes & Lindenberger (1997)	None	-0.080	0.057	-0.191	0.031
Bucks et al. (2016)	None	-0.044	0.023	-0.088	0.001
Clark (1960)	None	-0.239	0.101	-0.436	-0.042
Deal et al. (2016)	Mld vs Norm	-0.025	0.035	-0.093	0.043
Deal et al. (2016)	Mod/sev vs Norm	-0.053	0.041	-0.134	0.027
Gussekloo et al. (2005)	None	-0.110	0.050	-0.208	-0.013
Harrison Bush et al. (2015)	None	-0.080	0.034	-0.146	-0.014
Heron & Chown (1967)	Female	-0.376	0.065	-0.503	-0.248
Heron & Chown (1967)	Male	-0.380	0.058	-0.494	-0.267
Hofer et al. (2003)	None	-0.105	0.031	-0.166	-0.044
Li et al. (1998)	None	-0.110	0.075	-0.258	0.037
Lin (2011a)	None	-0.090	0.041	-0.170	-0.010
Lin et al. (2011b)	None	-0.085	0.054	-0.191	0.021
Lin et al. (2013)	None	-0.040	0.022	-0.084	0.004
MacDonald et al. (2004)	None	0.100	0.091	-0.077	0.278
Valentijn et al. (2005)	None	-0.269	0.051	-0.369	-0.170
van Boxtel et al. (2000)	None	-0.071	0.047	-0.164	0.021
		-0.128	0.025	-0.178	-0.079

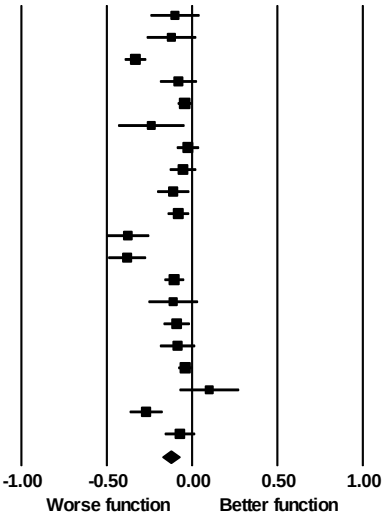

Figure 15: Processing speed – cross-sectional (Forest plot of Fisher's Z)

Studyname	Subgroup within study	Fisher's Z	Standard error	Lower limit	Upper limit
Anstey & Smith (1999)	None	-0.250	0.075	-0.397	-0.103
Baltes & Lindenberger (1997)	None	-0.090	0.057	-0.201	0.021
Clark (1960)	None	-0.347	0.101	-0.544	-0.150
Era et al. (1986)	Middle	-0.221	0.086	-0.390	-0.052
Era et al. (1986)	Old	-0.063	0.093	-0.245	0.119
Era et al. (1986)	Young	-0.167	0.088	-0.340	0.007
Heron & Chown (1967)	Female	-0.328	0.065	-0.456	-0.201
Heron & Chown (1967)	Male	-0.407	0.058	-0.521	-0.293
Hofer et al. (2003)	None	-0.067	0.031	-0.128	-0.006
Li et al. (1998)	None	-0.100	0.075	-0.248	0.047
MacDonald et al. (2004)	None	-0.100	0.091	-0.278	0.077
Thomas et al. (1983)	None	-0.050	0.063	-0.173	0.072
		-0.180	0.040	-0.258	-0.103

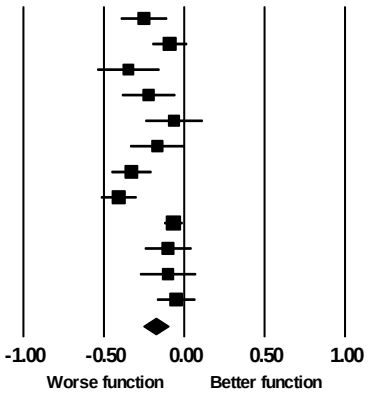

Figure 16: Reasoning – cross-sectional (Forest plot of Fisher's Z)

Study name	Subgroup within study	Fisher's Z	Standard error	Lower limit	Upper limit
Anstey & Smith (1999)	None	-0.250	0.075	-0.397	-0.103
Anstey et al. (2001a)	None	-0.277	0.034	-0.343	-0.211
Baltes & Lindenberger (1997)	None	-0.100	0.057	-0.211	0.011
Deal et al. (2015)	Mld vs Norm	-0.054	0.069	-0.190	0.081
Deal et al. (2015)	Mod/sev vs Norm	-0.109	0.078	-0.262	0.043
Heron & Chown (1967)	Female	-0.205	0.065	-0.332	-0.078
Heron & Chown (1967)	Male	-0.201	0.058	-0.314	-0.087
Li et al. (1998)	None	-0.090	0.075	-0.238	0.057
Lin et al. (2011b)	None	-0.065	0.054	-0.171	0.041
MacDonald et al. (2004)	None	0.025	0.091	-0.152	0.203
		-0.142	0.033	-0.207	-0.076

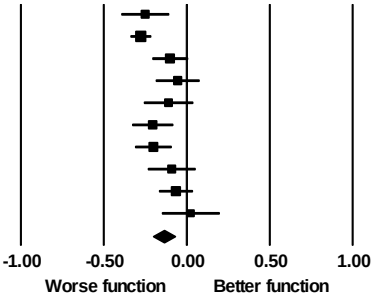

Figure 17: Semantic memory – cross-sectional (Forest plot of Fisher's Z)

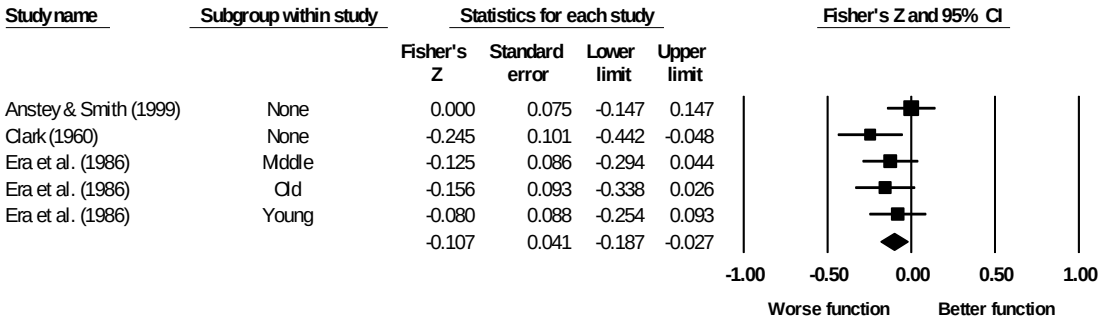

Figure 18: Visuospatial ability – cross-sectional (Forest plot of Fisher's Z)

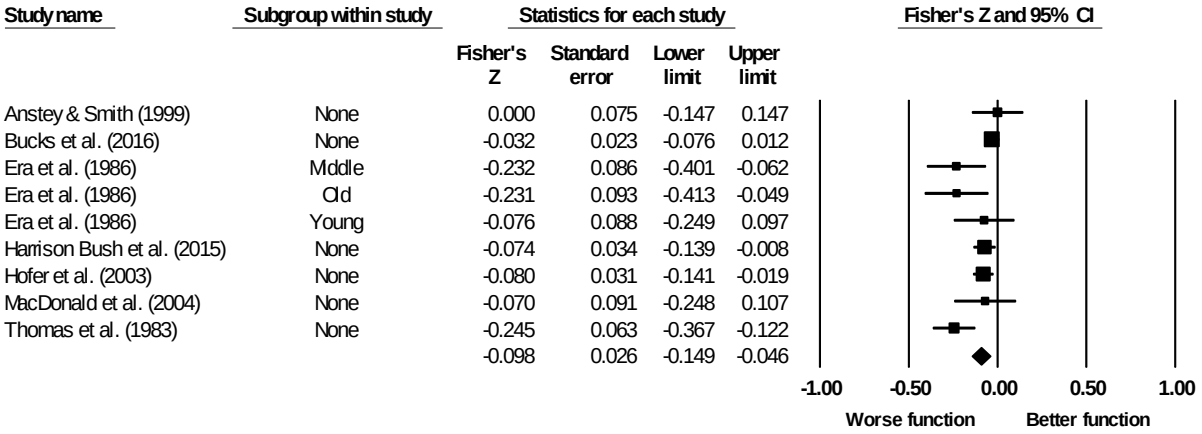

Figure 19: Working memory – cross-sectional (Forest plot of Fisher's Z)

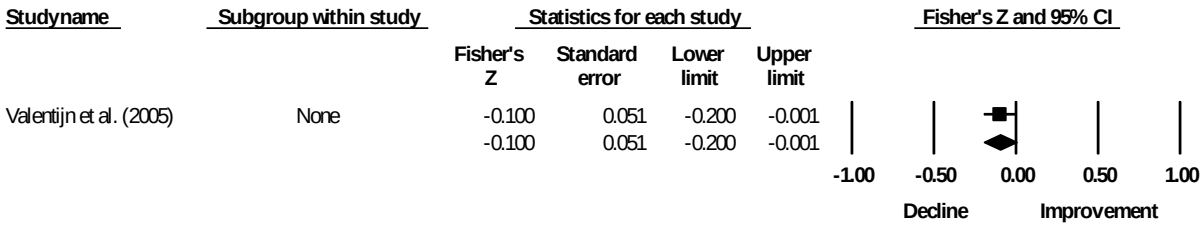

Figure 20: Attention – cohort (Forest plot of Fisher's Z)

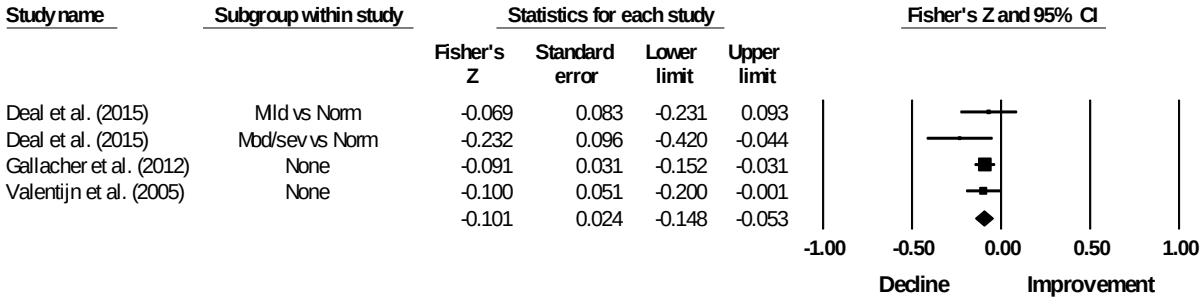

Figure 21: Delayed recall – cohort (Forest plot of Fisher's Z)

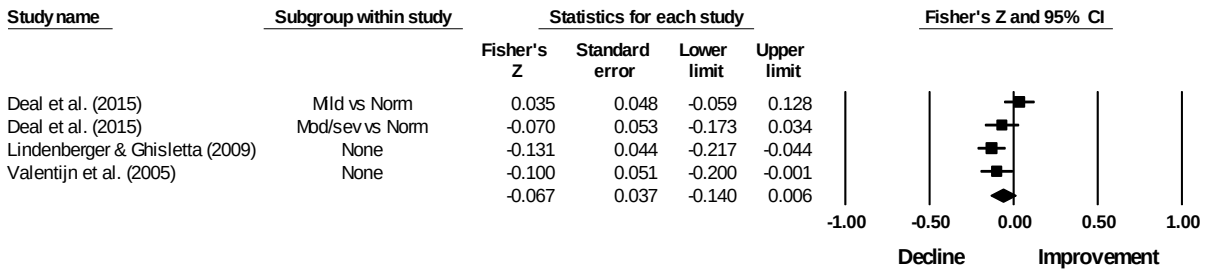

Figure 22: Fluency – cohort (Forest plot of Fisher's Z)

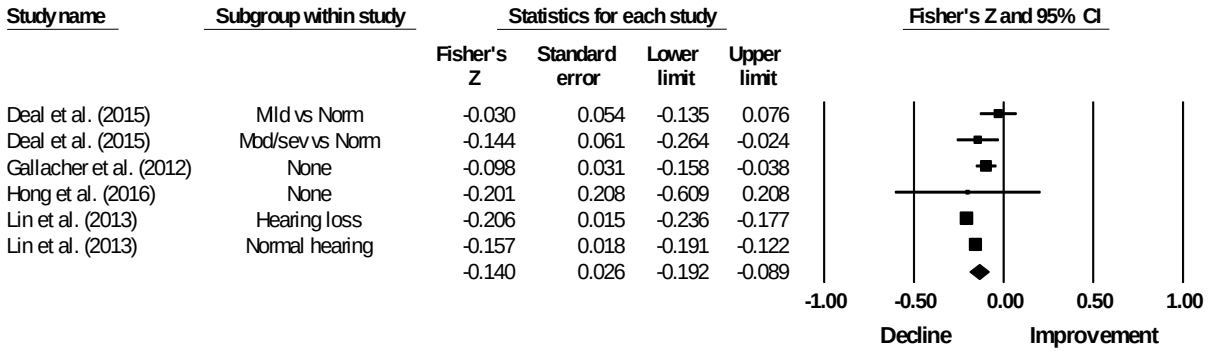

Figure 23: Global cognition – cohort (Forest plot of Fisher's Z)

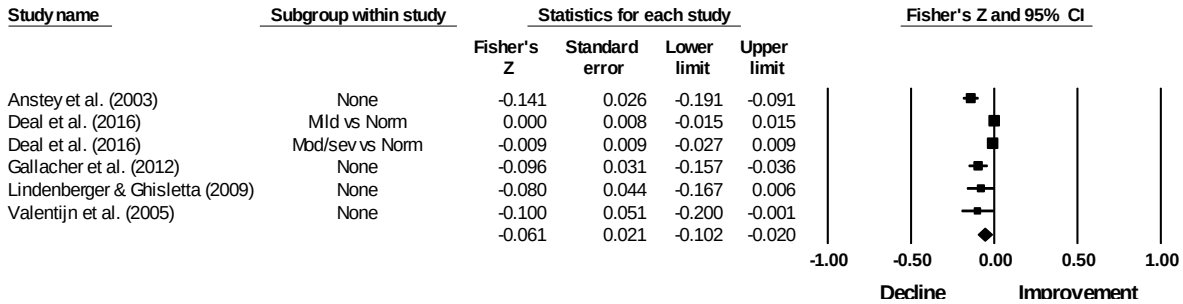

Figure 24: Immediate recall – cohort (Forest plot of Fisher's Z)

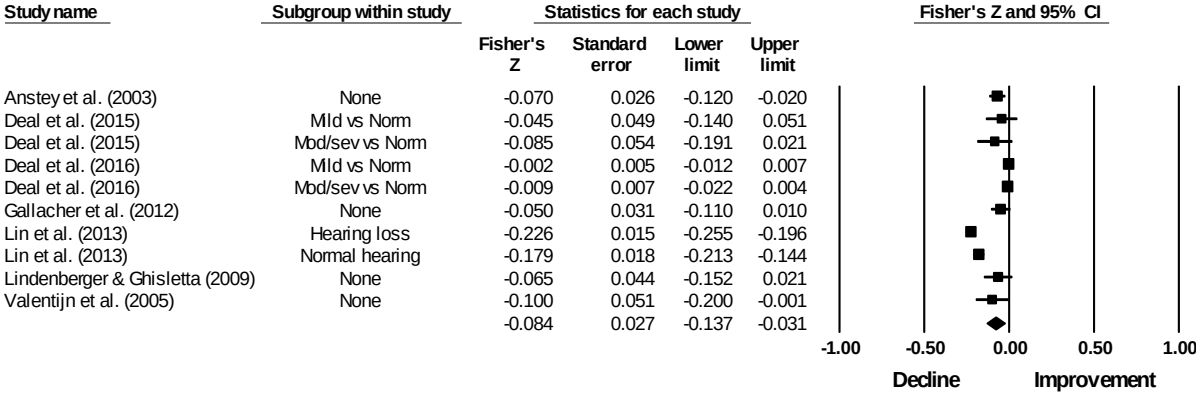

Figure 25: Processing speed – cohort (Forest plot of Fisher's Z)

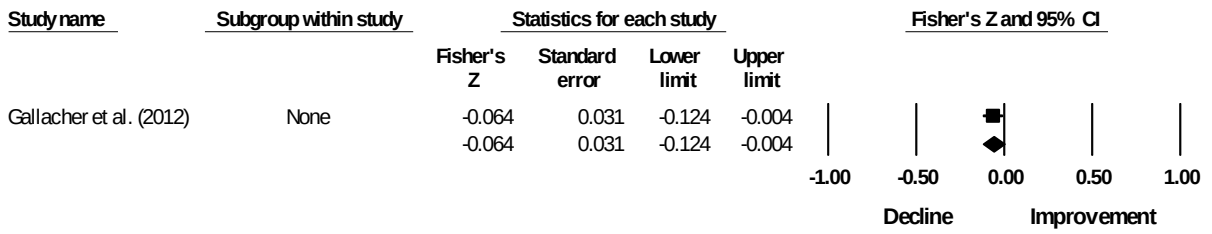

Figure 26: Reasoning – cohort (Forest plot of Fisher's Z)

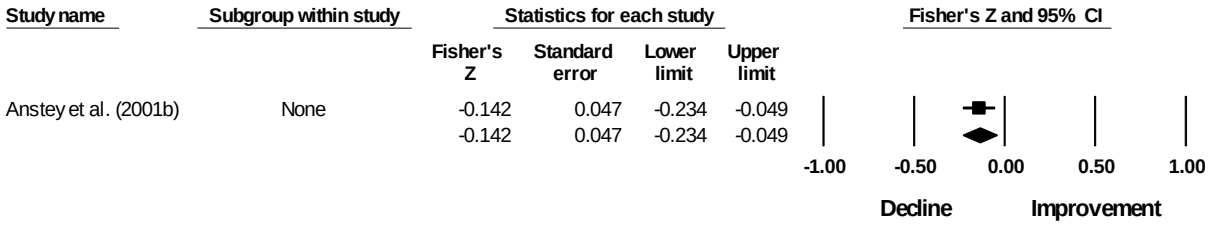

Figure 27: Semantic memory – cohort (Forest plot of Fisher's Z)

FUNNEL PLOTS

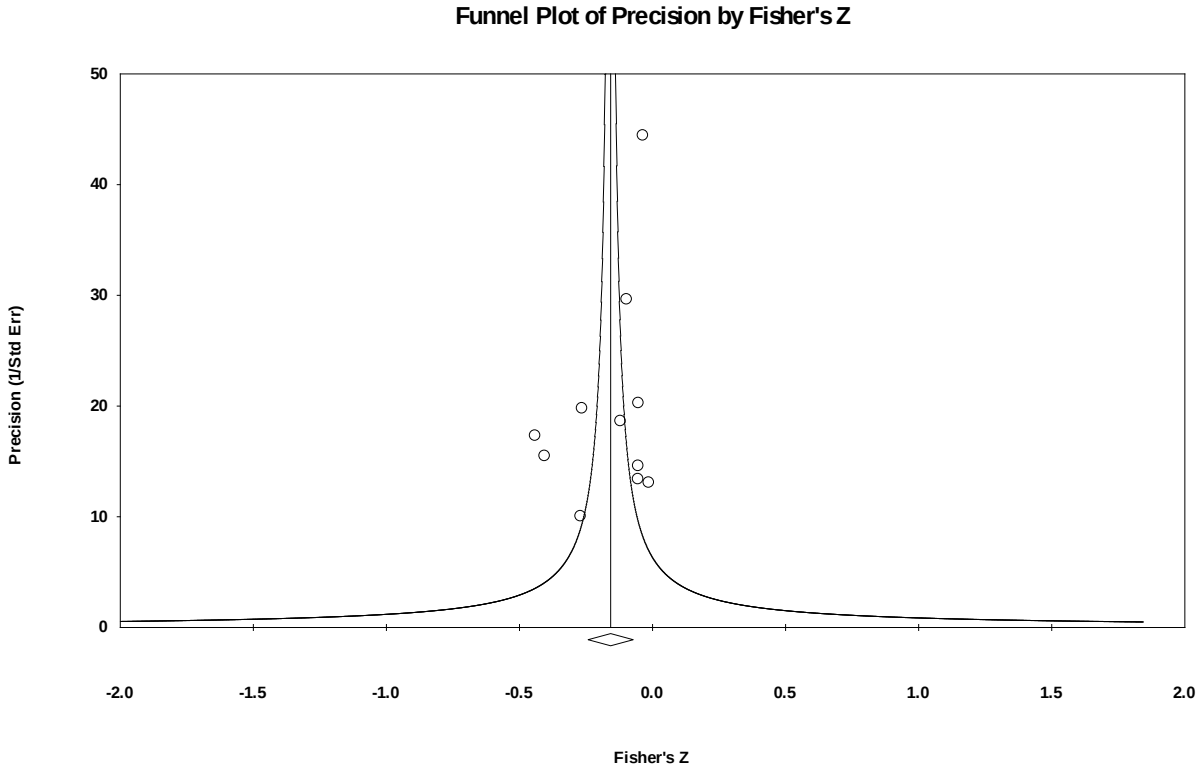

Figure 28: Attention – cross-sectional (Funnel plot)

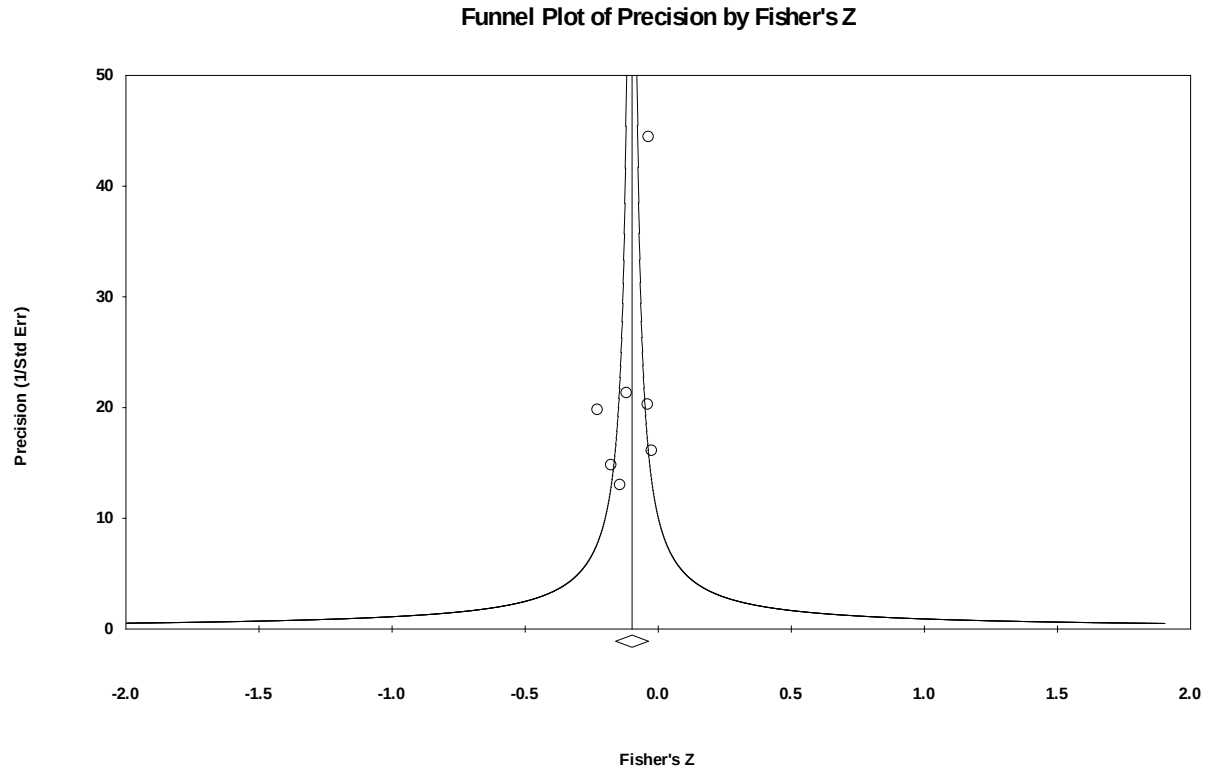

Figure 29: Delayed recall – cross-sectional (Funnel plot)

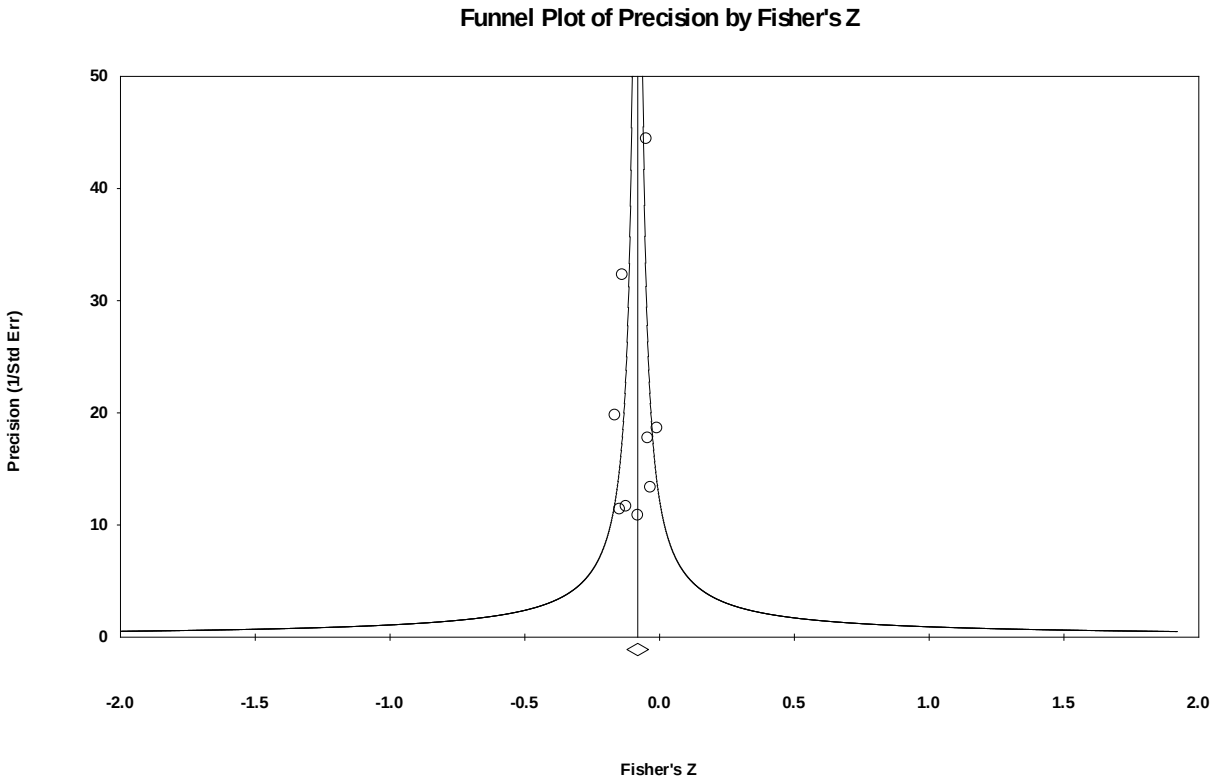

Figure 30: Fluency – cross-sectional (Funnel plot)

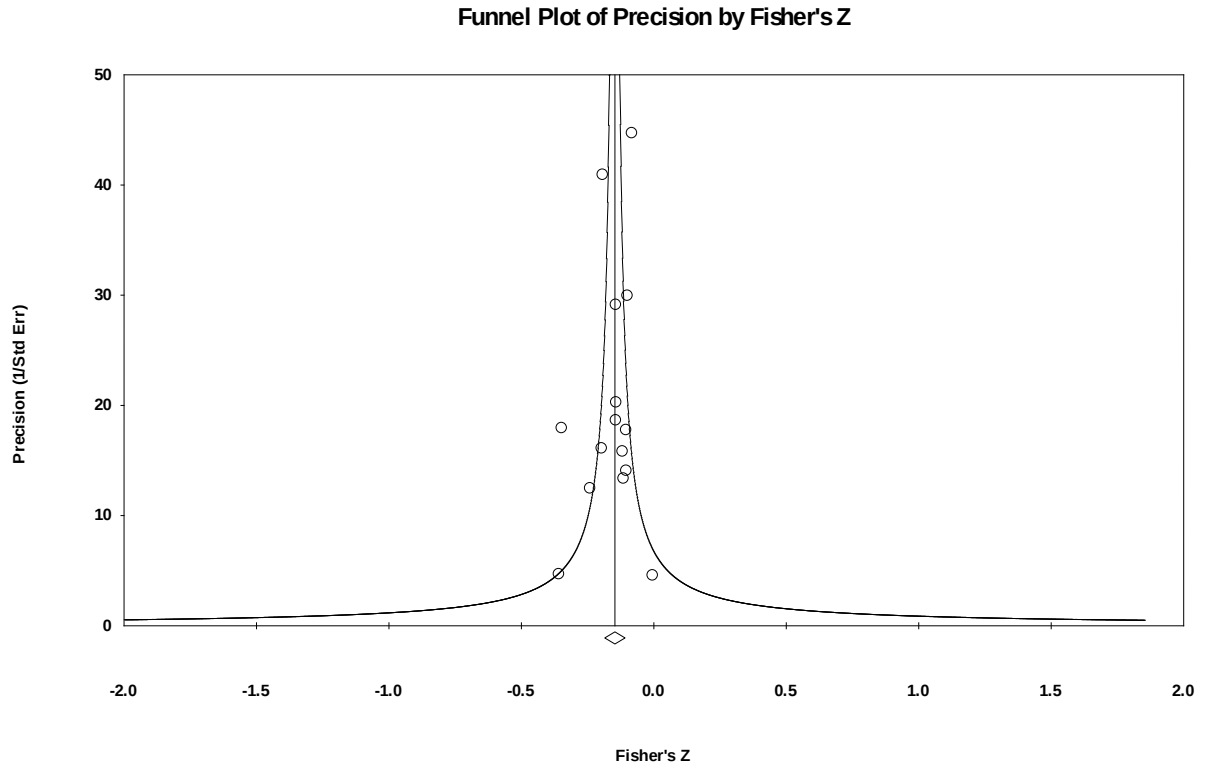

Figure 31: Global cognition – cross-sectional (Funnel plot)

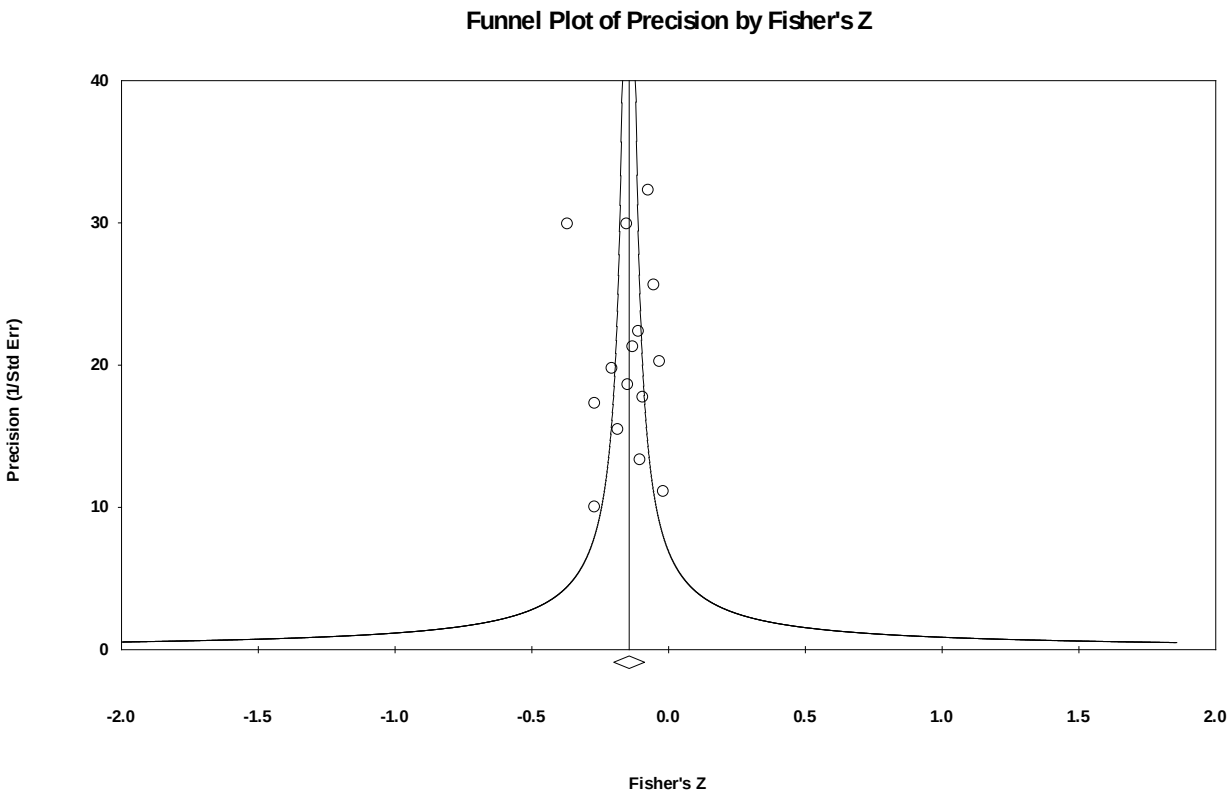

Figure 32: Immediate recall – cross-sectional (Funnel plot)

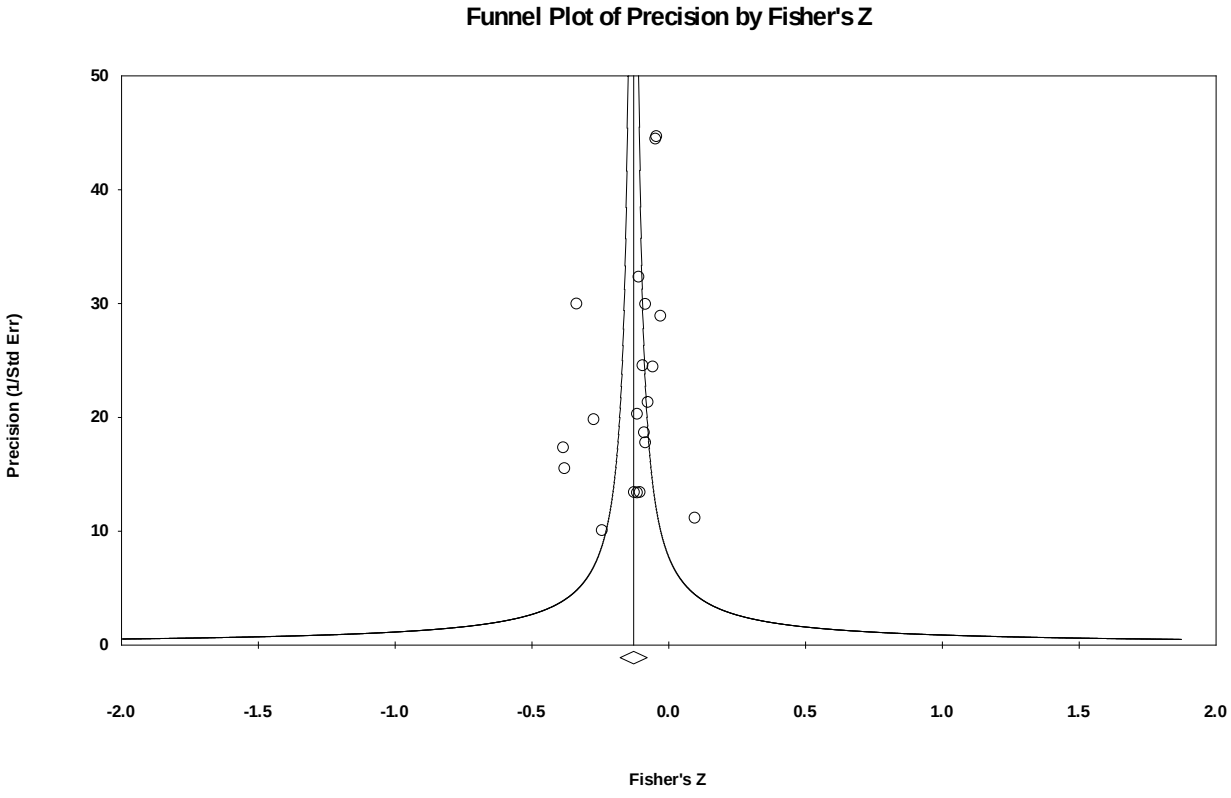

Figure 33: Processing speed – cross-sectional (Funnel plot)

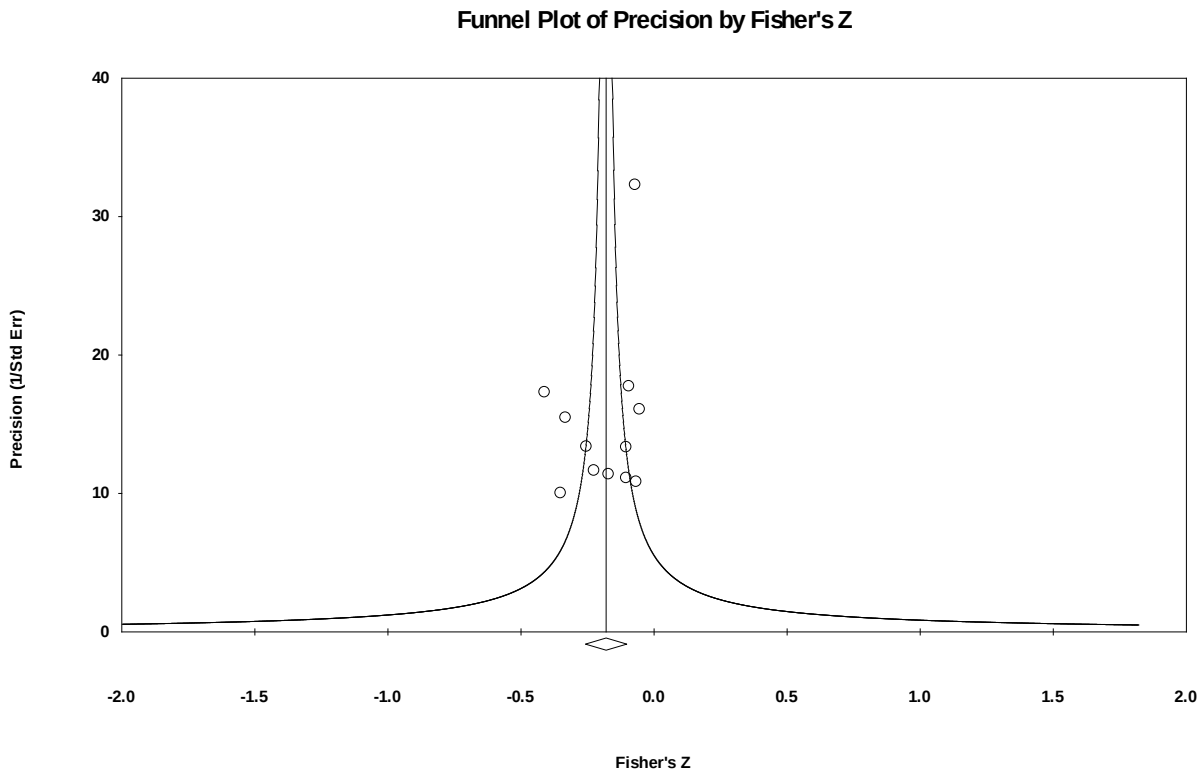

Figure 34: Reasoning – cross-sectional (Funnel plot)

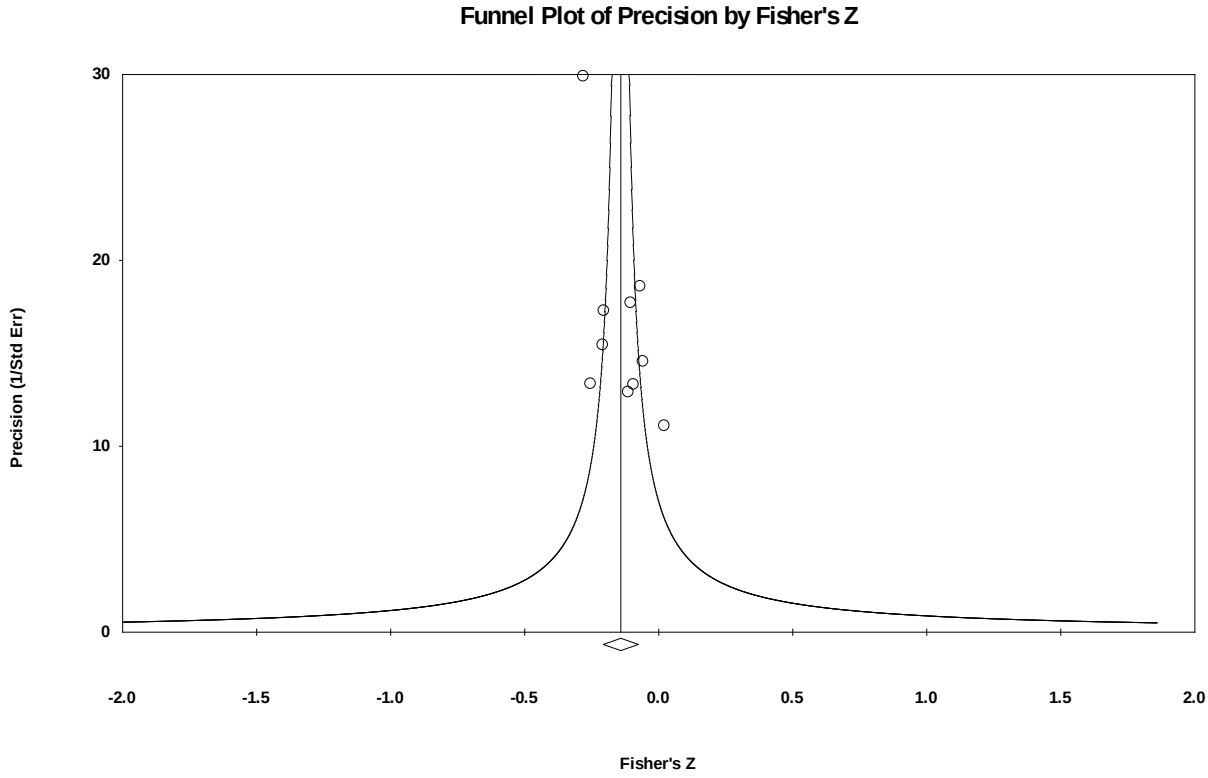

Figure 35: Semantic memory – cross-sectional (Funnel plot)

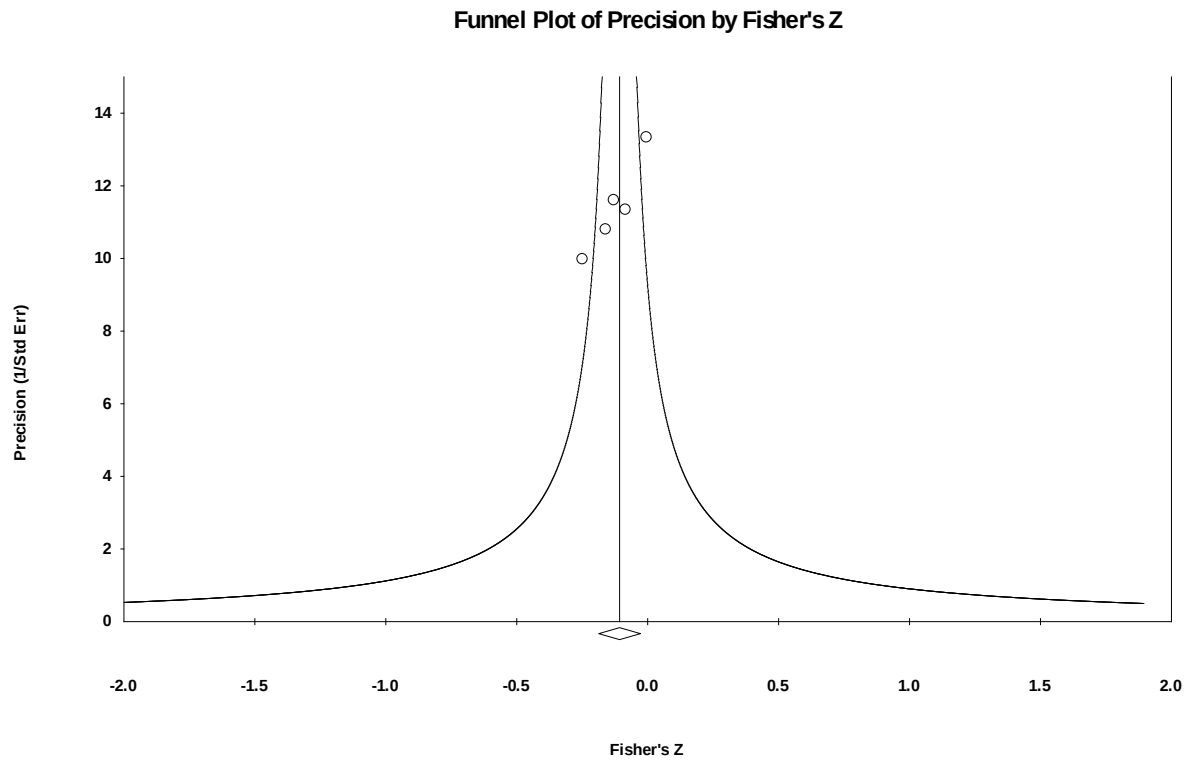

Figure 36: Visuospatial ability – cross-sectional (Funnel plot)

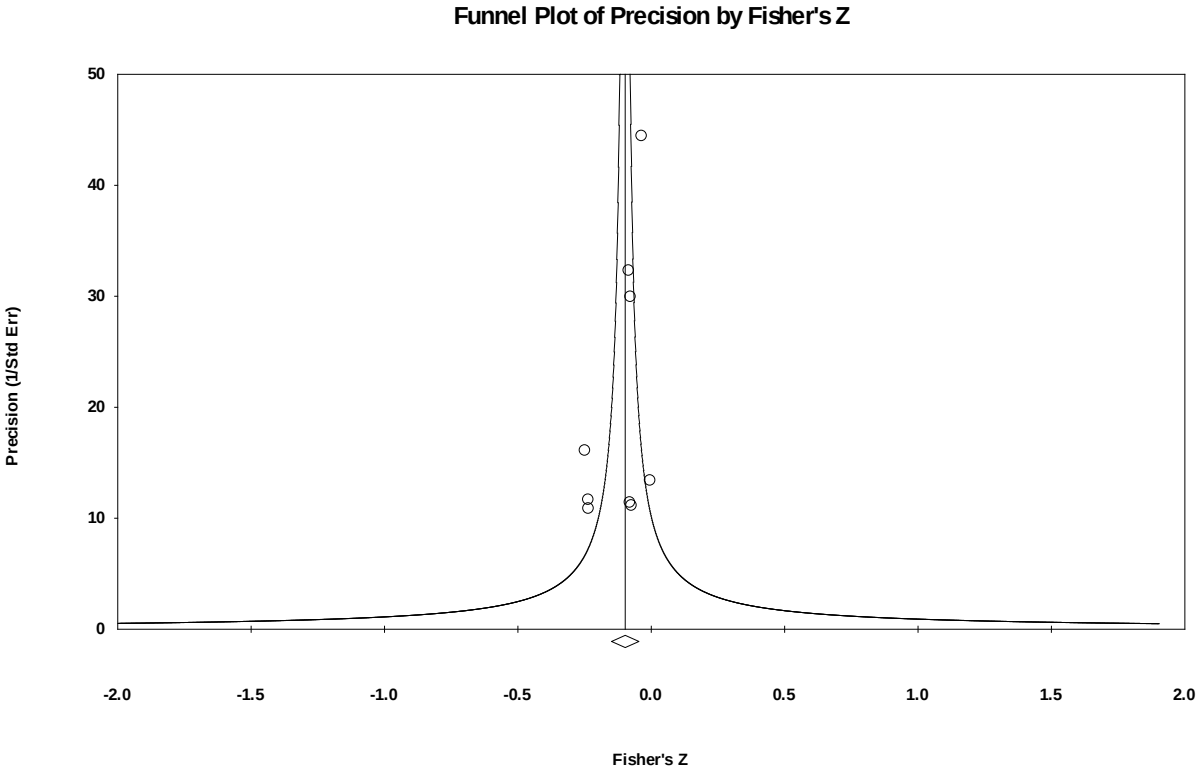

Figure 37: Working memory – cross-sectional (Funnel plot)

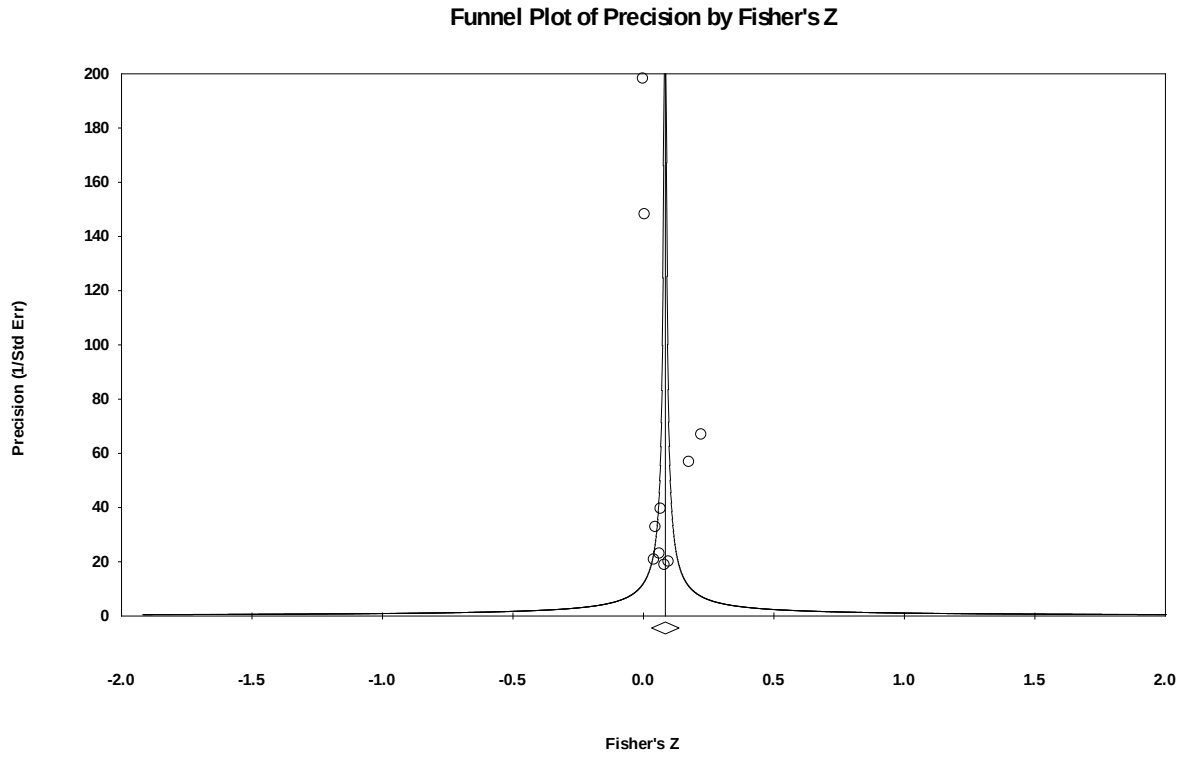

Figure 38: Processing speed – cohort (Funnel plot)

INFLUENCE ANALYSIS

Studyname	Subgroup within study	Statistics with studyremoved			
		Point	Standard error	Lower limit	Upper limit
Heron & Chown (1967)	Male	-0.127	0.037	-0.199	-0.055
Heron & Chown (1967)	Female	-0.133	0.041	-0.213	-0.053
Valentijn et al. (2005)	None	-0.146	0.045	-0.235	-0.058
Clark (1960)	None	-0.149	0.045	-0.238	-0.061
Lin et al. (2011b)	None	-0.162	0.048	-0.255	-0.069
Harrison Bush et al. (2015)	None	-0.165	0.051	-0.265	-0.066
Anstey (1999)	None	-0.167	0.046	-0.258	-0.077
Deal et al. (2015)	Mild vs Norm	-0.168	0.046	-0.259	-0.077
Gussekloo et al. (2005)	None	-0.169	0.048	-0.263	-0.076
Deal et al. (2015)	Mod/sev vs Norm	-0.171	0.046	-0.261	-0.081
Bucks et al. (2016)	None	-0.173	0.047	-0.266	-0.080
		-0.157	0.043	-0.242	-0.073

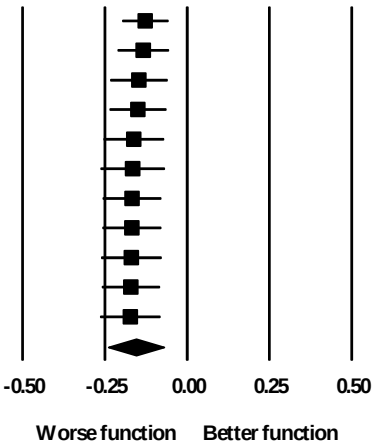

Figure 39: Attention – cross-sectional (Influence analysis for changes in Fisher's Z)

Studyname	Subgroup within study	Statistics with studyremoved			
		Point	Standard error	Lower limit	Upper limit
Valentijn et al. (2005)	None	-0.068	0.024	-0.115	-0.022
Deal et al. (2015)	Mild vs Norm	-0.089	0.033	-0.154	-0.024
Deal et al. (2015)	Mod/sev vs Norm	-0.094	0.034	-0.162	-0.027
van Boxtel et al. (2000)	None	-0.097	0.037	-0.169	-0.024
Thomas et al. (1983)	None	-0.110	0.035	-0.180	-0.041
Gussekloo et al. (2005)	None	-0.111	0.037	-0.183	-0.039
Bucks et al. (2016)	None	-0.116	0.034	-0.183	-0.050
		-0.098	0.031	-0.160	-0.037

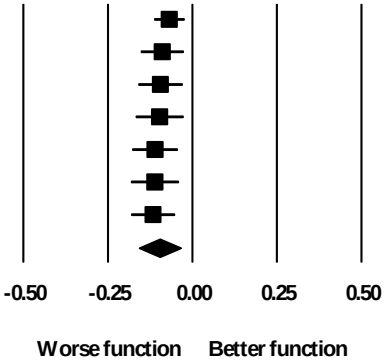

Figure 40: Delayed recall – cross-sectional (Influence analysis for changes in Fisher's Z)

Studyname	Subgroup within study	Statistics with studyremoved			
		Point	Standard error	Lower limit	Upper limit
Hofer et al. (2003)	None	-0.061	0.017	-0.095	-0.027
Valentijn et al. (2005)	None	-0.071	0.019	-0.108	-0.033
Era et al. (1986)	Young	-0.078	0.022	-0.121	-0.036
Era et al. (1986)	Middle	-0.079	0.022	-0.123	-0.036
Era et al. (1986)	Old	-0.082	0.022	-0.125	-0.038
Li et al. (1998)	None	-0.085	0.022	-0.128	-0.042
Baltes & Lindenberger (1997)	None	-0.086	0.023	-0.131	-0.042
Lin et al. (2011b)	None	-0.090	0.021	-0.131	-0.049
Bucks et al. (2016)	None	-0.097	0.022	-0.140	-0.053
		-0.081	0.020	-0.121	-0.041

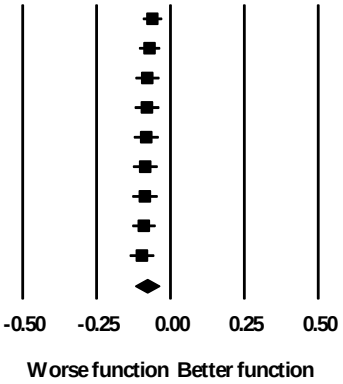

Figure 41: Fluency – cross-sectional (Influence analysis for changes in Fisher's Z)

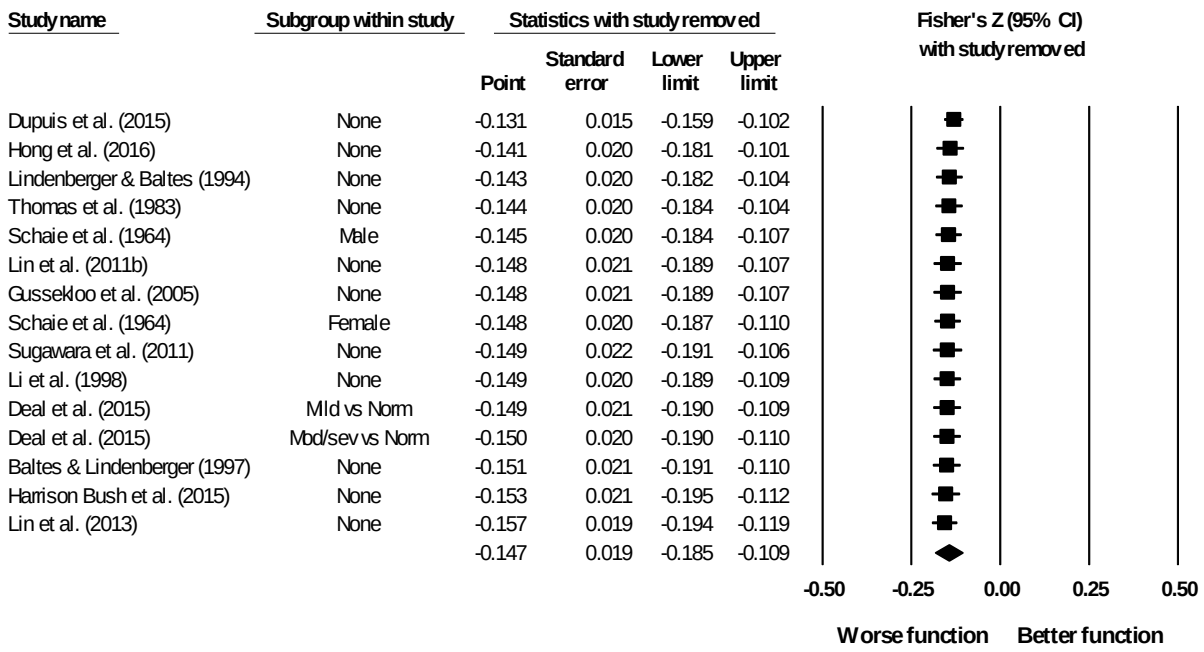

Figure 42: Global cognition – cross-sectional (Influence analysis for changes in Fisher's Z)

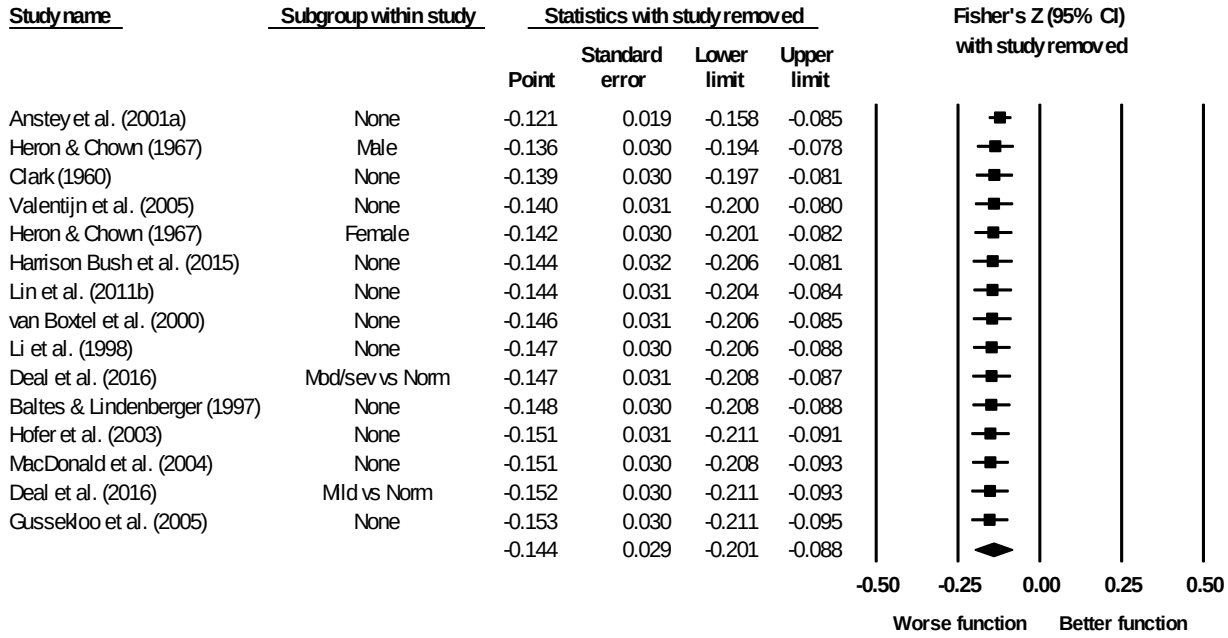

Figure 43: Immediate recall – cross-sectional (Influence analysis for changes in Fisher's Z)

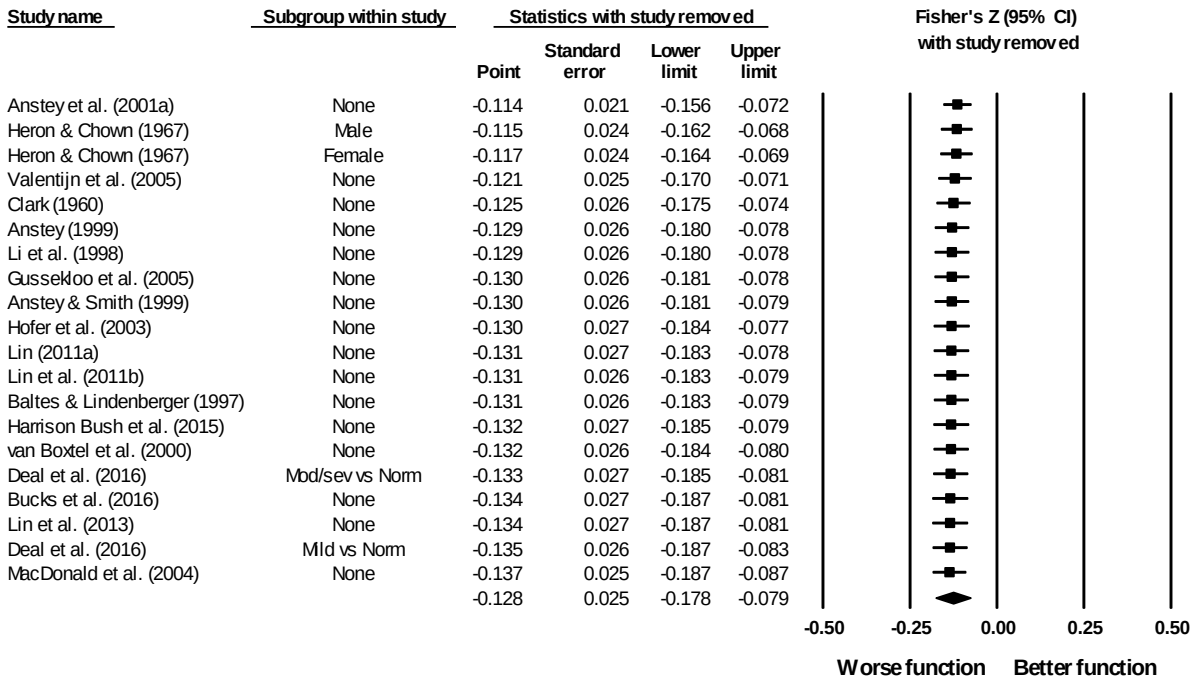

Figure 44: Processing speed – cross-sectional (Influence analysis for changes in Fisher's Z)

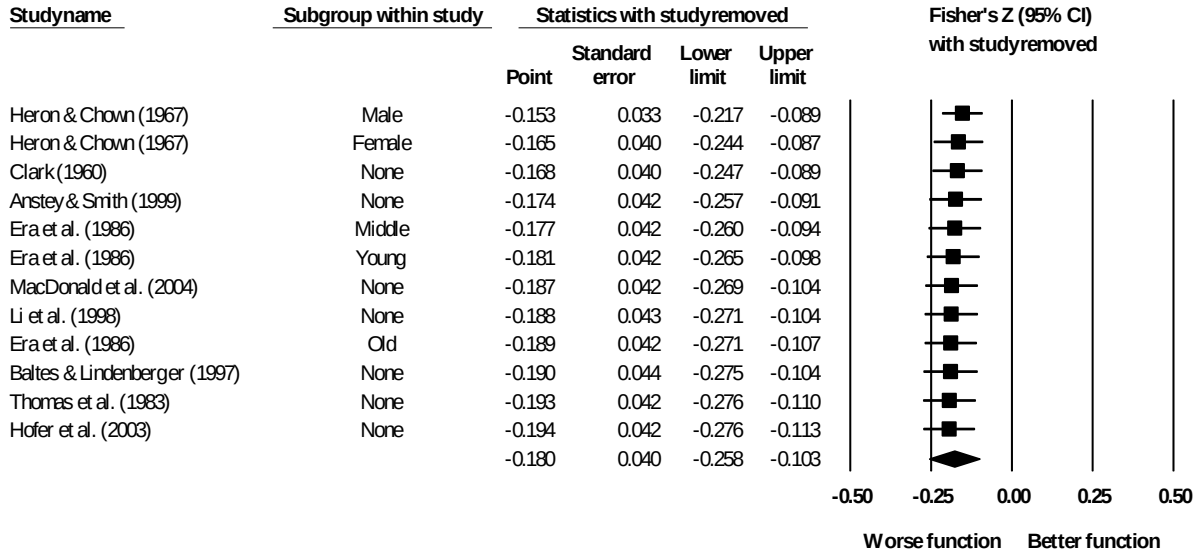

Figure 45: Reasoning – cross-sectional (Influence analysis for changes in Fisher's Z)

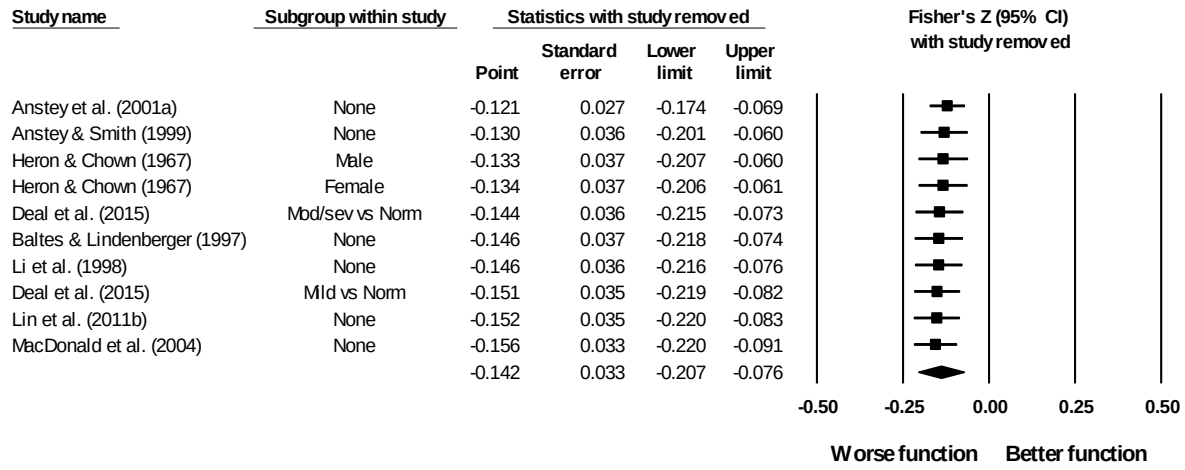

Figure 46: Semantic memory – cross-sectional (Influence analysis for changes in Fisher's Z)

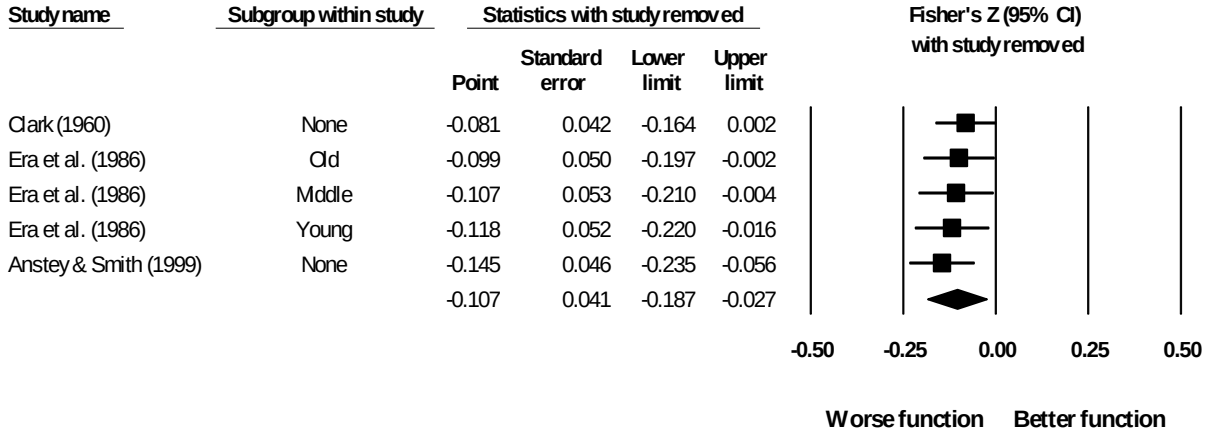

Figure 47: Visuospatial ability – cross-sectional (Influence analysis for changes in Fisher's Z)

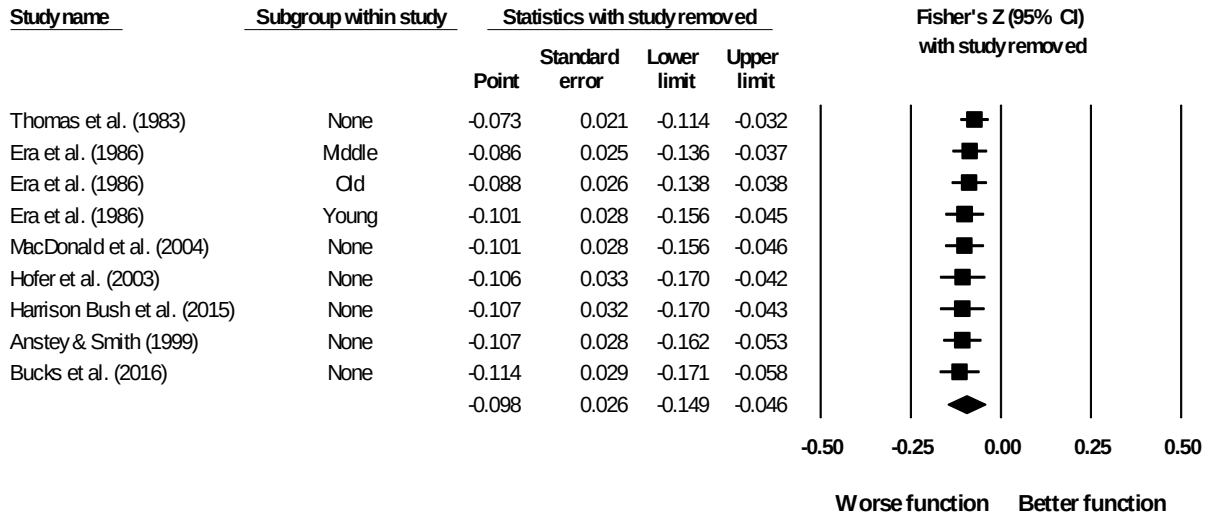

Figure 48: Working memory – cross-sectional (Influence analysis for changes in Fisher's Z)

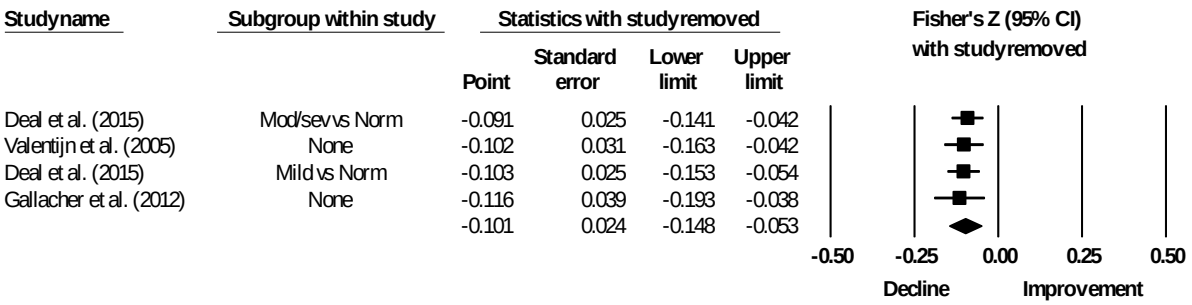

Figure 49: Delayed recall – cohort (Influence analysis for changes in Fisher's Z)

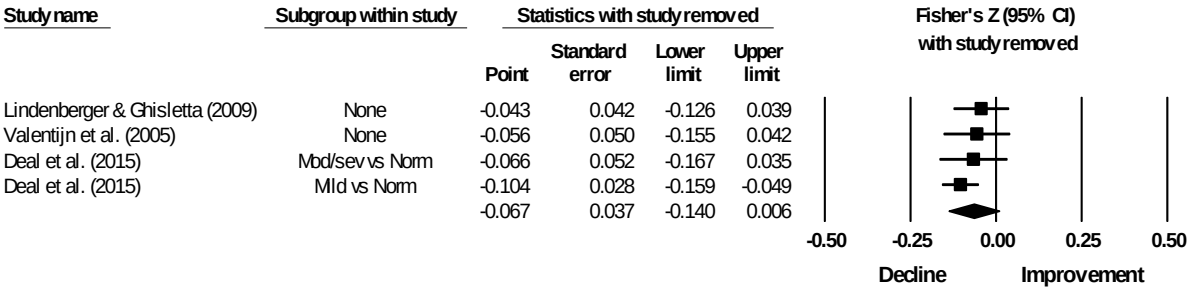

Figure 50: Fluency – cohort (Influence analysis for changes in Fisher's Z)

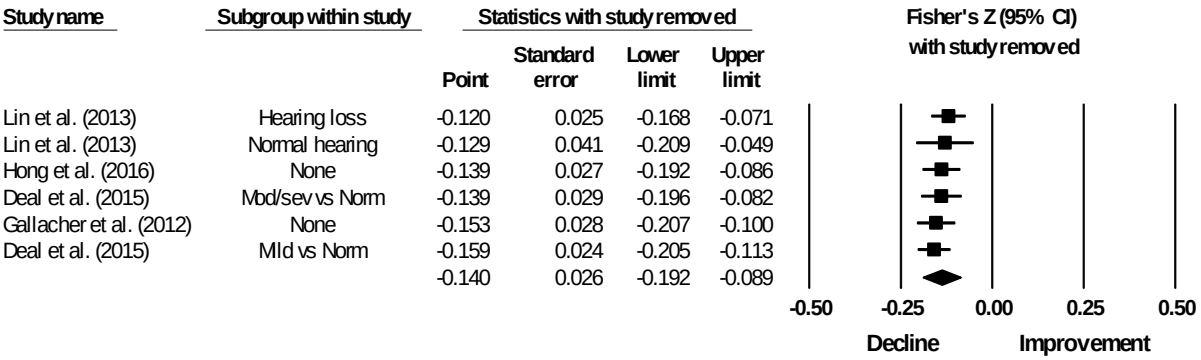

Figure 51: Global cognition – cohort (Influence analysis for changes in Fisher's Z)

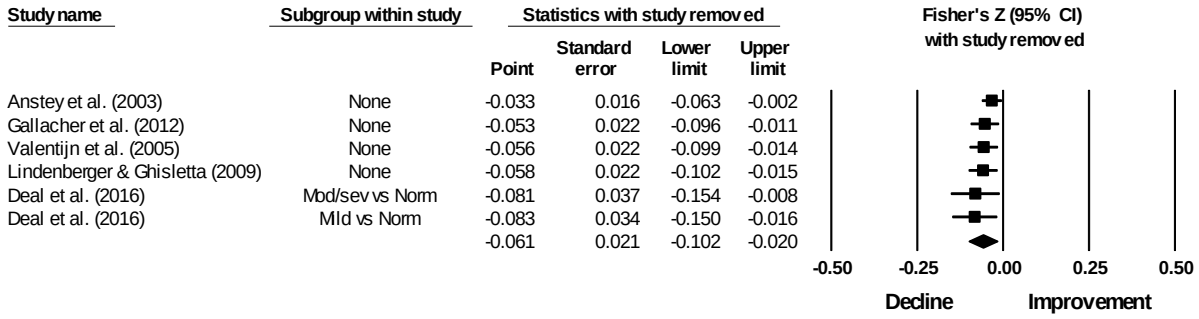

Figure 52: Immediate recall – cohort (Influence analysis for changes in Fisher's Z)

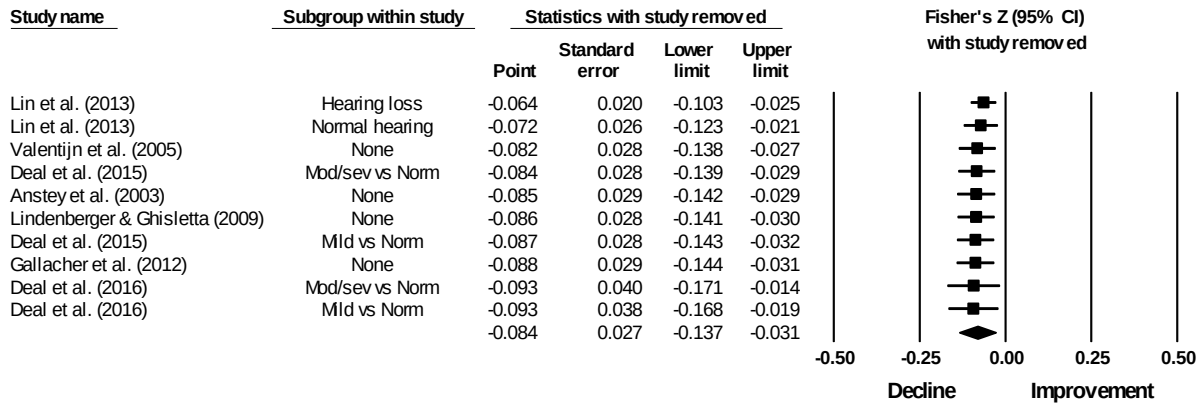

Figure 53: Processing speed – cohort (Influence analysis for changes in Fisher's Z)

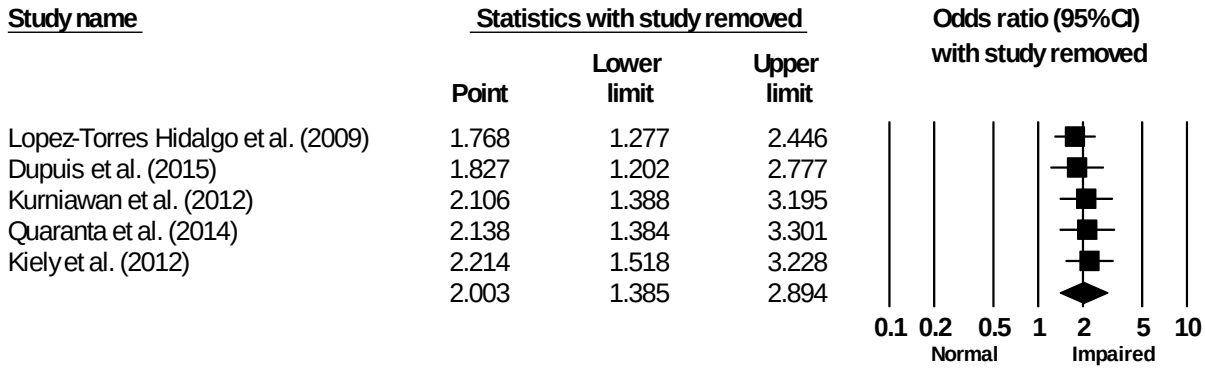

Figure 54: Cognitive impairment – cross-sectional (Influence analysis for changes in Odds Ratio)

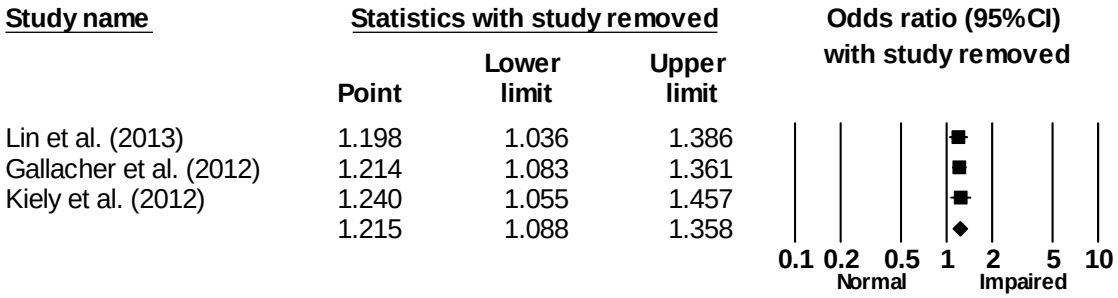

Figure 55: Cognitive impairment – cohort (Influence analysis for changes in Odds Ratio)

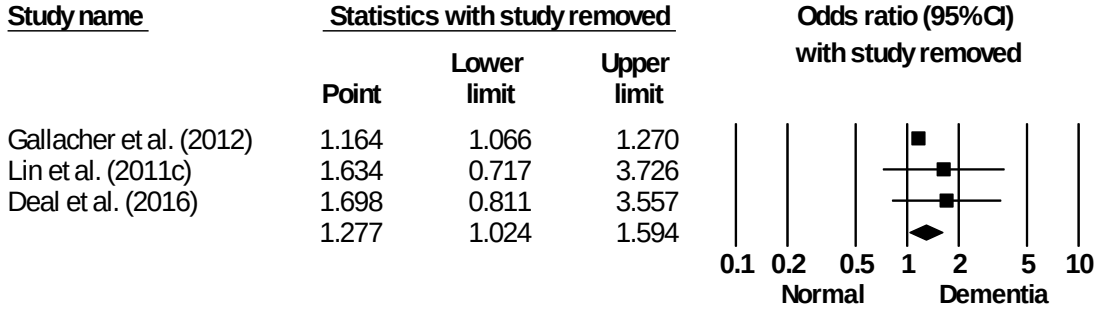

Figure 56: Dementia – cohort (Influence analysis for changes in Odds Ratio)

CUMULATIVE META-ANALYSIS

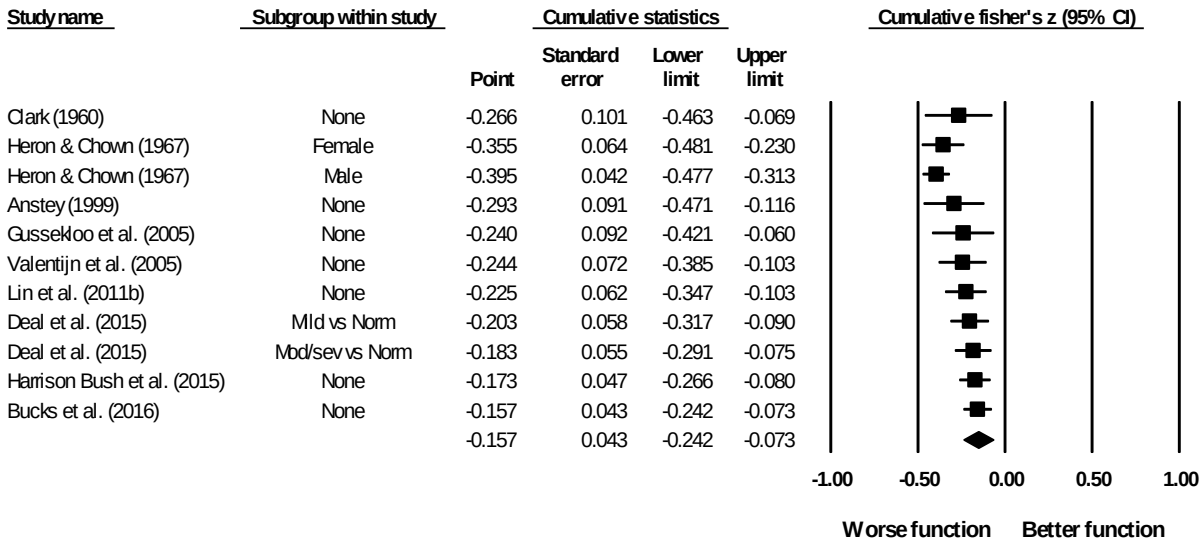

Figure 57: Attention – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

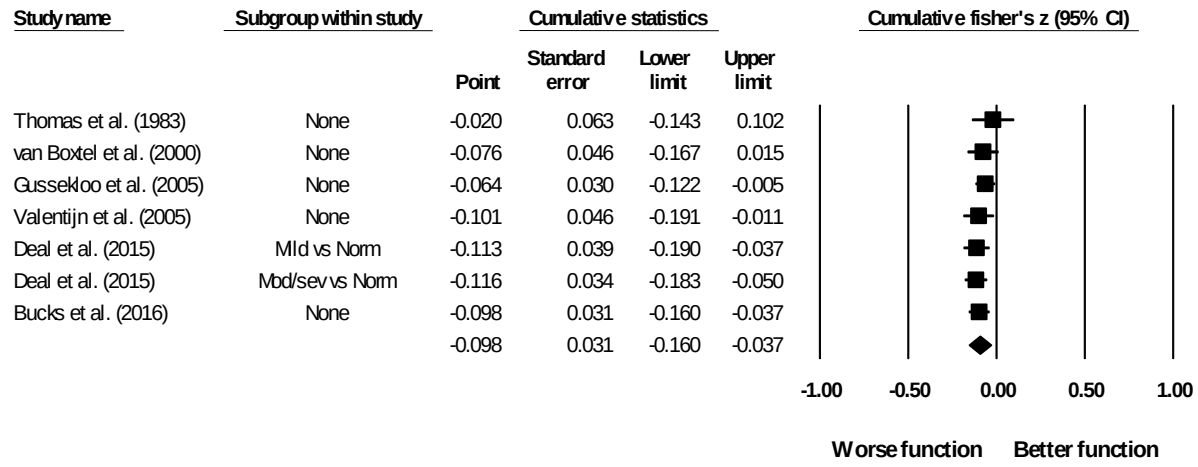

Figure 58: Delayed recall – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

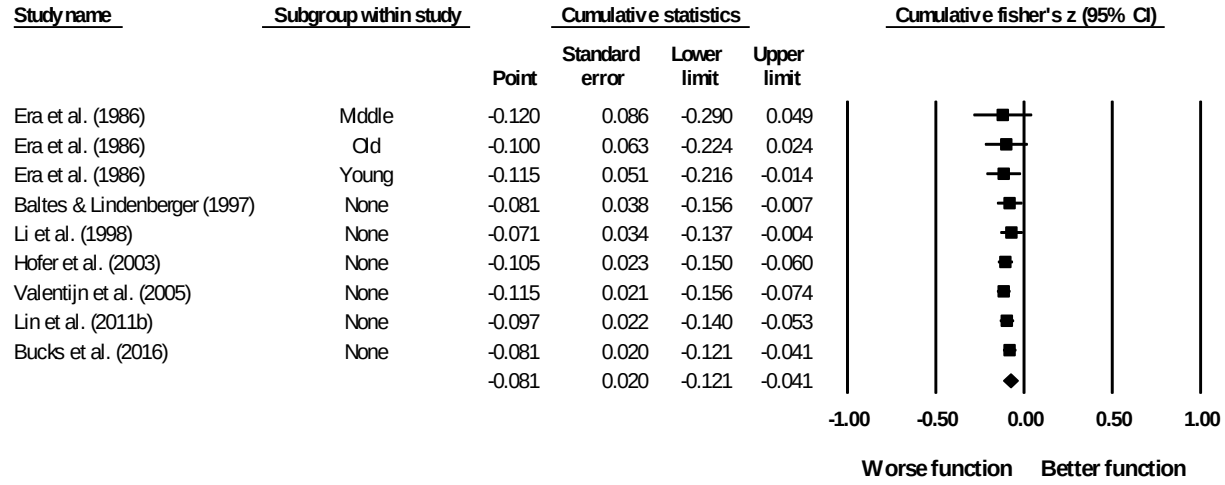

Figure 59: Fluency – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

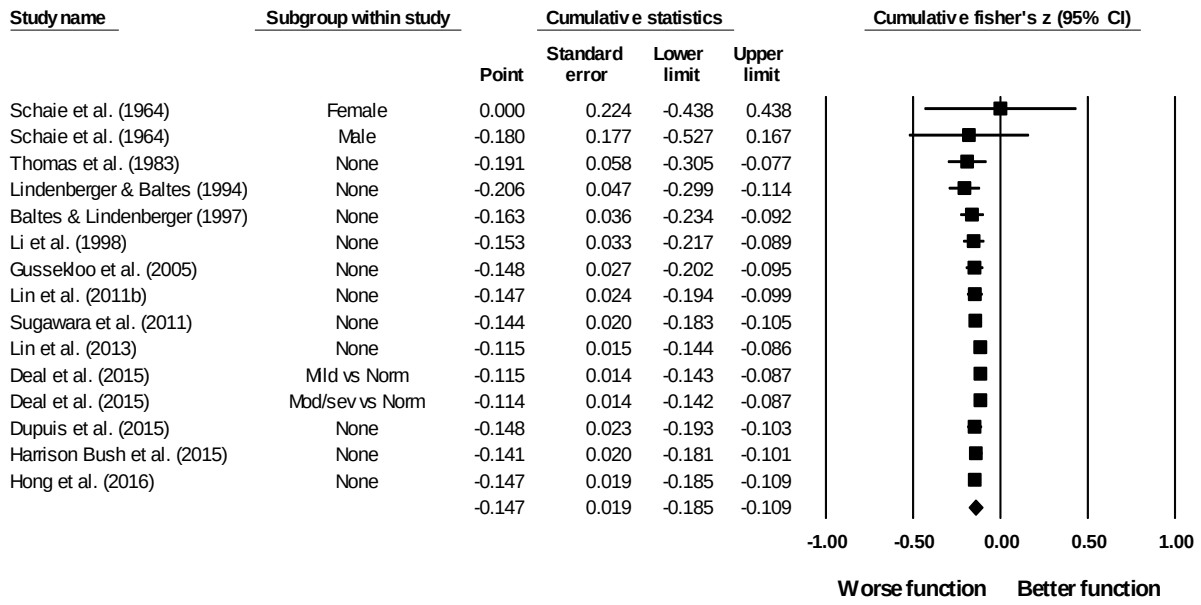

Figure 60: Global cognition – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

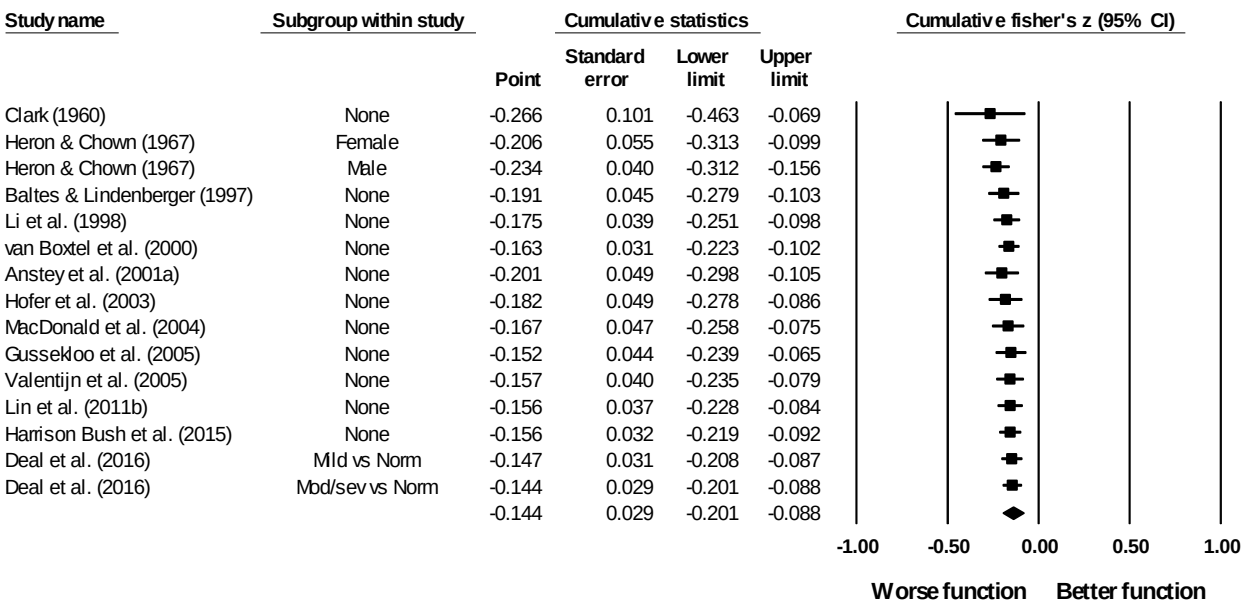

Figure 61: Immediate recall – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

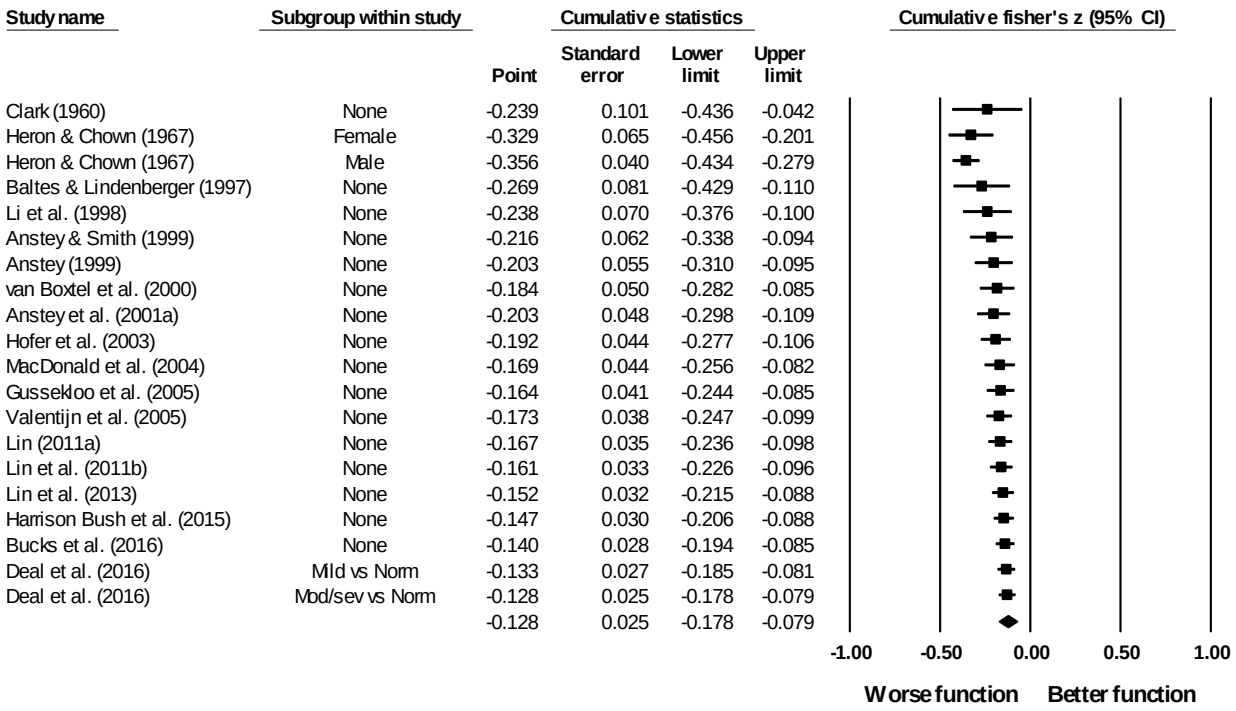

Figure 62: Processing speed – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

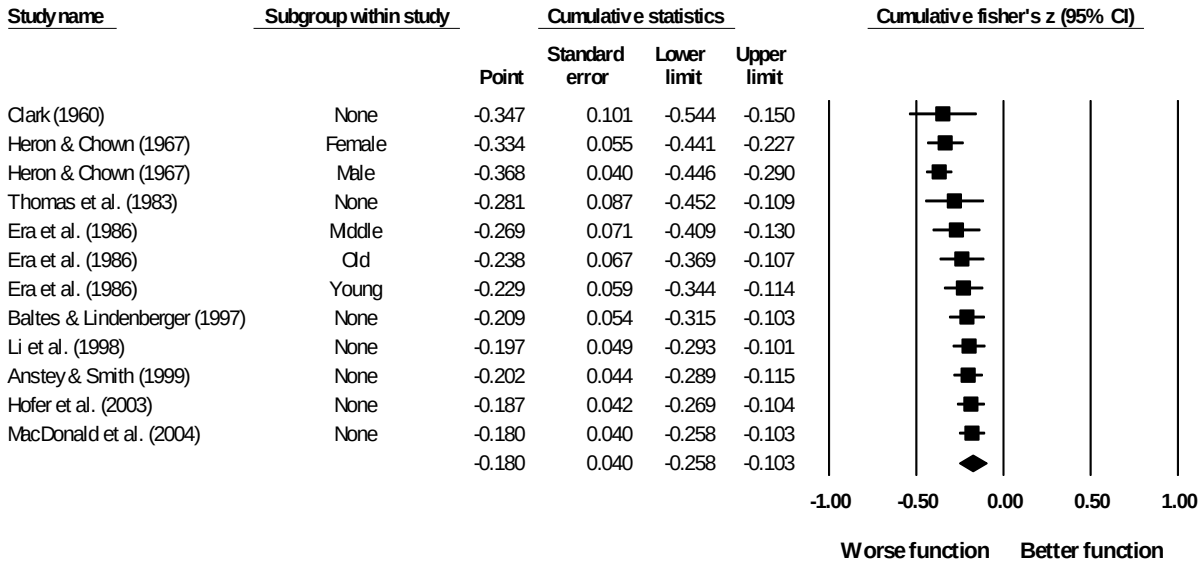

Figure 63: Reasoning – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

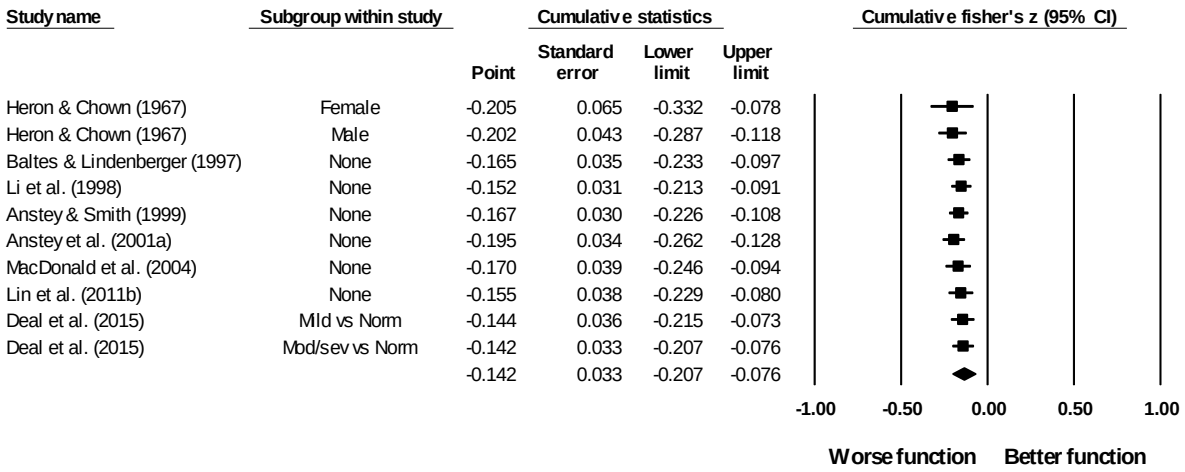

Figure 64: Semantic memory – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

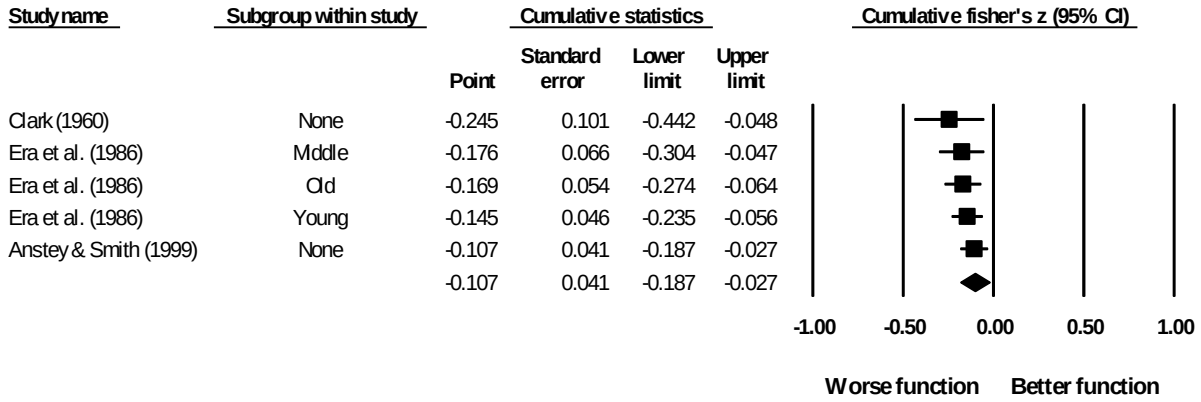

Figure 65: Visuospatial ability – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

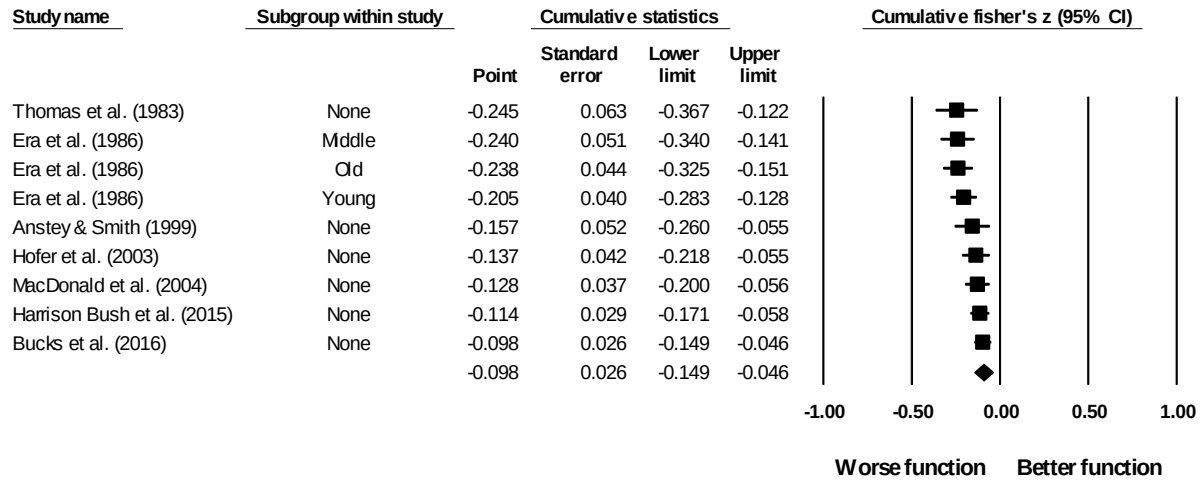

Figure 66: Working memory – cross-sectional (Cumulative meta-analysis for changes in Fisher's Z)

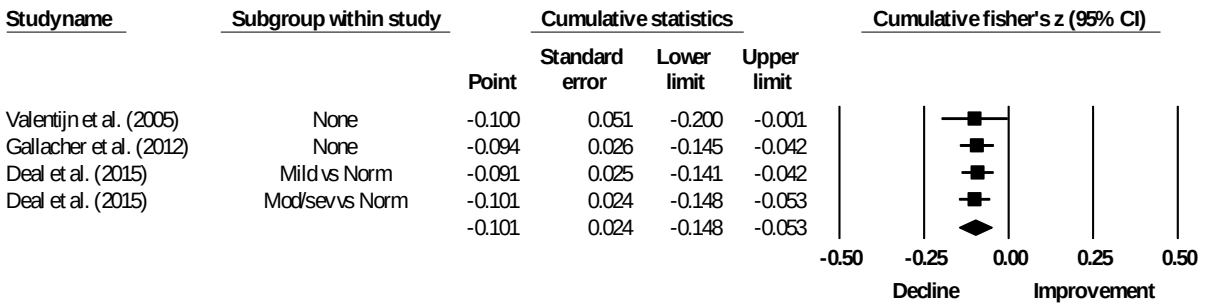

Figure 67: Delayed recall – cohort (Cumulative meta-analysis for changes in Fisher's Z)

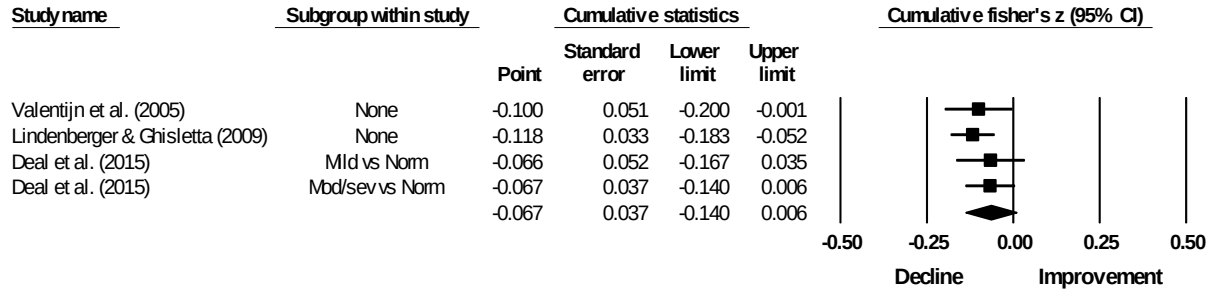

Figure 68: Fluency – cohort (Cumulative meta-analysis for changes in Fisher's Z)

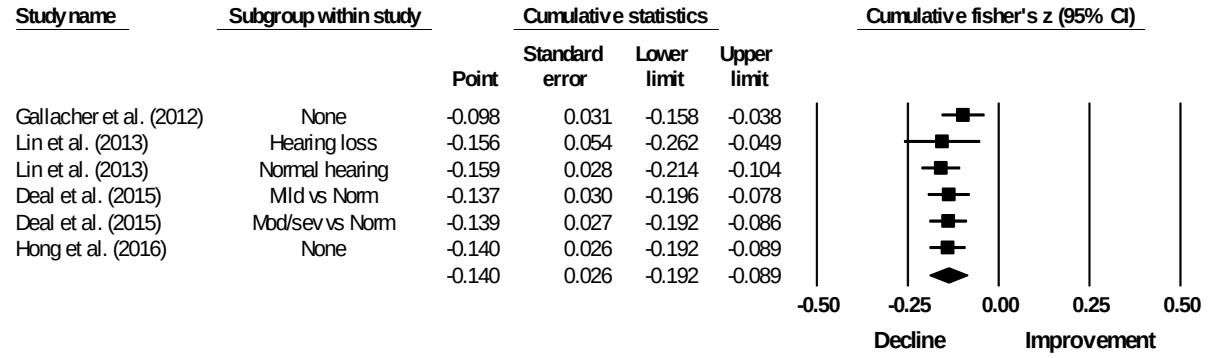

Figure 69: Global cognition – cohort (Cumulative meta-analysis for changes in Fisher's Z)

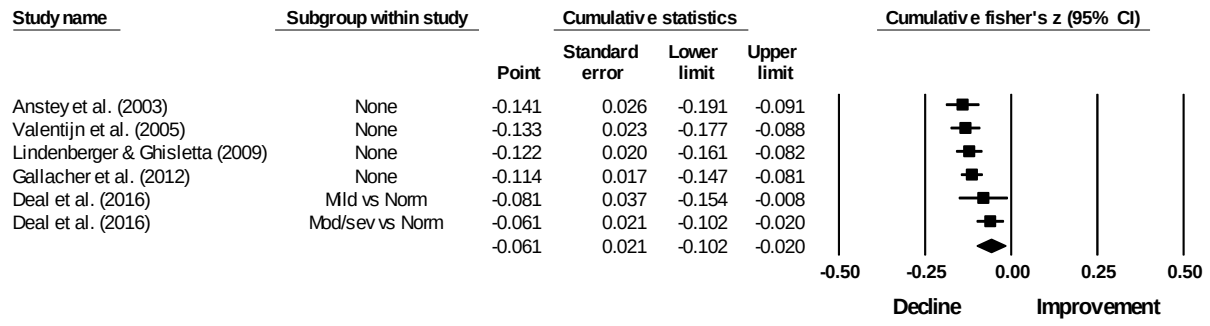

Figure 70: Immediate recall – cohort (Cumulative meta-analysis for changes in Fisher's Z)

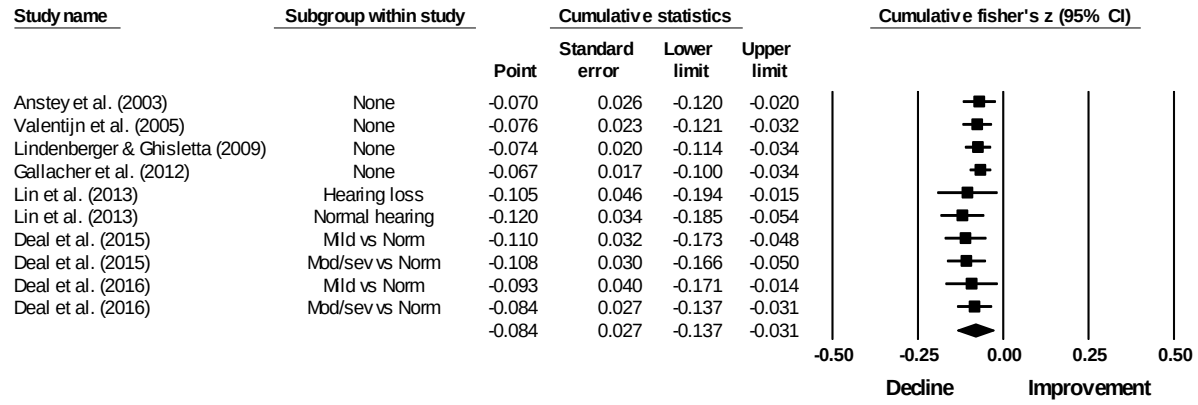

Figure 71: Processing speed – cohort (Cumulative meta-analysis for changes in Fisher's Z)

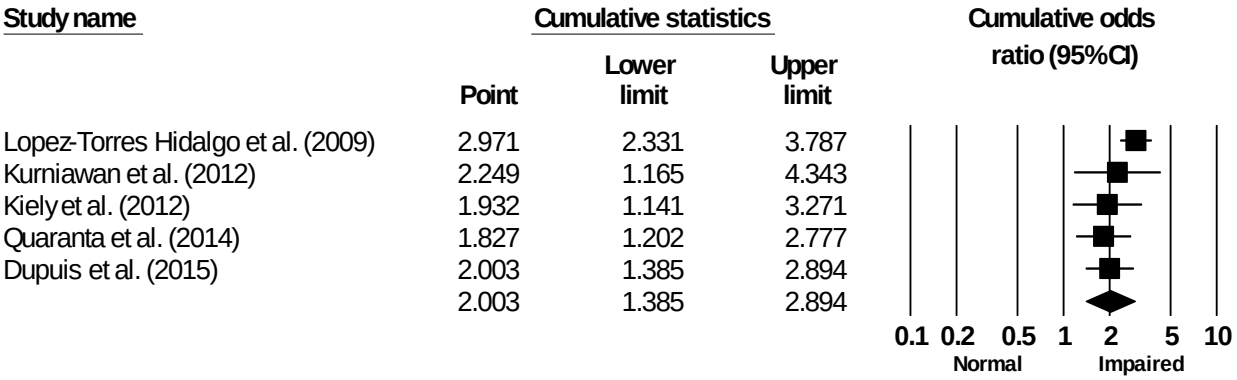

Figure 72: Cognitive impairment – cross-sectional (Cumulative meta-analysis for changes in Odds Ratio)

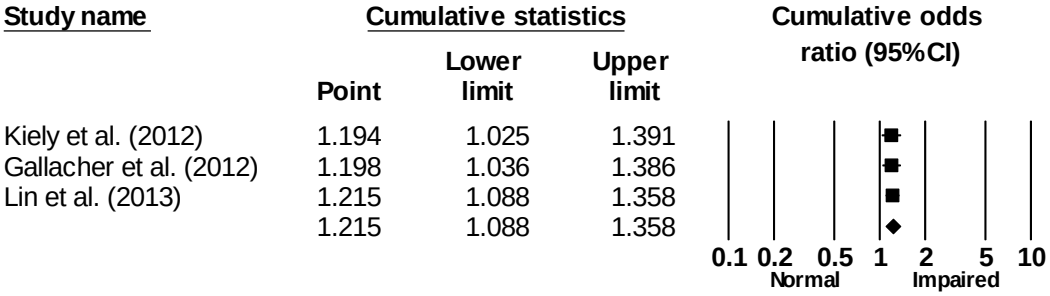

Figure 73: Cognitive impairment – cohort (Cumulative meta-analysis for changes in Odds Ratio)

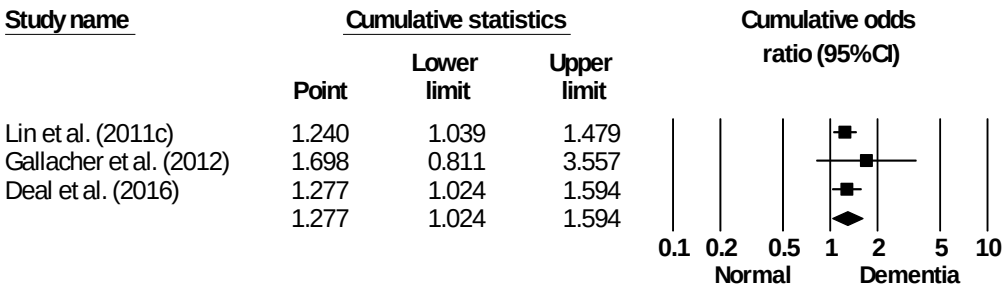

Figure 74: Dementia – cohort (Cumulative meta-analysis for changes in Odds Ratio)

MODERATOR ANALYSIS

Table 10: Cognitive function – Attention – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Country/Region					
- Europe	4	1341	-0.284 (0.091)	-0.462, -0.107	**4.02 (0.045)**
- USA	5	1669	-0.094 (0.028)	-0.149, -0.04	
Ear used					
- Better	6	3927	-0.095 (0.036)	-0.165, -0.025	2.15 (0.14)
- Both	5	1232	-0.24 (0.092)	-0.421, -0.06	
Sound-treated booth/room					
- No	7	2517	-0.22 (0.062)	-0.341, -0.099	**7.47 (0.01)**
- Yes	4	2642	-0.043 (0.019)	-0.081, -0.005	
Used WHO criteria					
- No	7	2517	-0.22 (0.062)	-0.341, -0.099	**7.47 (0.01)**
- Yes	4	2642	-0.043 (0.019)	-0.081, -0.005	
Hearing aid user removed					
- Not declared	5	1716	-0.249 (0.086)	-0.418, -0.079	2.87 (0.09)
- No	6	3443	-0.088 (0.039)	-0.164, -0.012	
Cognitive test accessible					
- No	3	506	-0.022 (0.042)	-0.105, 0.061	**6.59 (0.01)**
- Yes	9	4833	-0.189 (0.049)	-0.285, -0.092	
Analysis used					
- Correlation	4	1033	-0.347 (0.048)	-0.442, -0.252	**32.26 (<0.0001)**
- Linear regression	5	3800	-0.057 (0.016)	-0.088. -0.025	
Reported significant					
- No	6	3232	-0.043 (0.017)	-0.077, -0.009	**8.75 (0.003)**
- Yes	5	2172	-0.259 (0.071)	-0.398, -0.12	
Controlled for age					
- No	3	642	-0.395 (0.042)	-0.477, -0.313	**37.96 (<0.0001)**
- Yes	8	4517	-0.085 (0.028)	-0.14, -0.03	
Controlled for sex					
- No	3	642	-0.395 (0.042)	-0.477, -0.313	**37.96 (<0.0001)**
- Yes	8	4517	-0.085 (0.028)	-0.14, -0.03	
Controlled for race					
- No	7	3592	-0.21 (0.07)	-0.347, -0.074	2.94 (0.09)
- Yes	4	1567	-0.083 (0.025)	-0.133, -0.034	
Controlled for education (level or years)					
- No	4	822	-0.293 (0.091)	-0.471, -0.116	**4.58 (0.03)**
- Yes	7	4337	-0.089 (0.031)	-0.149, -0.029	
Controlled for vascular risk factors					
- No	7	3592	-0.21 (0.07)	-0.347, -0.074	2.94 (0.09)
- Yes	4	1567	-0.083 (0.025)	-0.133, -0.034	
Controlled for hypertension					
- No	7	3592	-0.21 (0.07)	-0.347, -0.074	2.94 (0.09)
- Yes	4	1567	-0.083 (0.025)	-0.133, -0.034	
Controlled for current smokers					
- No	8	4486	-0.193 (0.056)	-0.302, -0.084	3.27 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Controlled for previous smokers					
- No	8	4486	-0.193 (0.056)	-0.302, -0.084	3.27 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Controlled for depression					
- No	7	1970	-0.225 (0.062)	-0.347, -0.103	**7.42 (0.01)**
- Yes	4	3189	-0.049 (0.018)	-0.083, -0.014	
Controlled for pre-morbid IQ					
- No	7	2473	-0.198 (0.062)	-0.319, -0.078	1.53 (0.22)
- Yes	4	2686	-0.091 (0.061)	-0.211, 0.029	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. $Q_b(p)$, Between-group differences and alpha value for between-group differences; WHO, World Health Organisation; IQ, intelligence quotient.

Table 11: Cognitive function – Delayed recall – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Country/Region					
- Europe	3	1254	-0.124 (0.054)	-0.229, -0.019	0.06 (0.8)
- USA	3	585	-0.106 (0.049)	-0.202, -0.01	
Sound-treated booth/room					
- No	4	1513	-0.101 (0.046)	-0.191, -0.011	0.01 (0.94)
- Yes	3	2295	-0.096 (0.051)	-0.195, 0.003	
Used WHO criteria					
- No	4	1513	-0.101 (0.046)	-0.191, -0.011	0.01 (0.94)
- Yes	3	2295	-0.096 (0.051)	-0.195, 0.003	
Cognitive test accessible					
- No	4	1038	-0.108 (0.031)	-0.168, -0.047	0.06 (0.81)
- Yes	3	2770	-0.092 (0.058)	-0.205, 0.021	
Reported significant					
- No	4	2796	-0.038 (0.019)	-0.075, -0.001	**10.75 (0.001)**
- Yes	3	1012	-0.167 (0.035)	-0.236, -0.099	
Controlled for vascular risk factors					
- No	4	3029	-0.076 (0.045)	-0.164, 0.012	1.07 (0.3)
- Yes	3	779	-0.135 (0.035)	-0.202, -0.067	
Controlled for depression					
- No	4	1513	-0.101 (0.046)	-0.191, -0.011	0.01 (0.94)
- Yes	3	2295	-0.096 (0.051)	-0.195, 0.003	
Controlled for pre-morbid IQ					
- No	3	1122	-0.064 (0.03)	-0.122, -0.005	1.25 (0.26)
- Yes	4	2686	-0.135 (0.056)	-0.245, -0.025	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. $Q_b(p)$, Between-group differences and alpha value for between-group differences; WHO, World Health Organisation; IQ, intelligence quotient.

Table 12: Cognitive function – Fluency – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Dementia participants removed					
- Not declared	6	3576	-0.084 (0.023)	-0.13, -0.039	0.06 (0.8)
- Yes	3	1053	-0.071 (0.049)	-0.166, 0.025	
Ear used					
- Better	6	3094	-0.075 (0.026)	-0.126, -0.025	0.079 (0.78)
- Both	3	1535	-0.088 (0.037)	-0.16, -0.016	
Frequencies >4kHz included					
- No	7	4135	-0.09 (0.024)	-0.138, -0.043	0.001 (0.97)
- Yes	3	1535	-0.089 (0.04)	-0.167, -0.01	
Sound-treated booth/room					
- No	3	885	-0.086 (0.045)	-0.174, 0.002	0.02 (0.89)
- Yes	6	3744	-0.079 (0.025)	-0.128, -0.03	
Hearing aid user removed					
- Not declared	4	566	-0.088 (0.042)	-0.171, -0.005	0.03 (0.87)
- No	5	4063	-0.079 (0.028)	-0.135, -0.024	
Reported significant					
- No	8	3197	-0.044 (0.018)	-0.079, -0.009	**11.84 (0.001)**
- Yes	4	1700	-0.147 (0.024)	-0.195, -0.1	
Controlled for age					
- No	4	1428	-0.129 (0.027)	-0.181, -0.077	**4.01 (0.045)**
- Yes	5	3201	-0.057 (0.024)	-0.105, -0.009	
Controlled for education (level or years)					
- No	6	1922	-0.105 (0.023)	-0.15, -0.06	0.69 (0.41)
- Yes	3	2707	-0.067 (0.039)	-0.145, -0.01	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. $Q_b(p)$, Between-group differences and alpha value for between-group differences;

Table 13: Cognitive function – Global cognition – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Country/Region					
- Europe	4	1060	-0.136 (0.031)	-0.197, -0.076	1.15 (0.28)
- USA	8	3857	-0.099 (0.016)	-0.13, -0.068	
Cognitively impaired participants removed					
- Not declared	9	4758	-0.155 (0.025)	-0.203, -0.107	3.64 (0.06)
- Yes	5	2788	-0.096 (0.019)	-0.133, -0.059	
Dementia participants removed					
- Not declared	9	4853	-0.159 (0.024)	-0.205, -0.112	**5.02 (0.03)**
- Yes	5	2693	-0.09 (0.019)	-0128, -0.053	
Cardiovascular risks removed					
- Not declared	10	3407	-0.163 (0.028)	-0.218, -0.108	**5.28 (0.02)**
- No	3	2310	-0.084 (0.02)	-0.124, -0.044	
Race					
- Mixed	4	3484	-0.102 (0.02)	-0.141, -0.062	**5.17 (0.02)**
- Not declared	9	3892	-0.177 (0.027)	-0.229, -0.125	
Ear used					
- Better	7	4656	-0.105 (0.014)	-0.134, -0.077	2.82 (0.09)
- Both	7	1408	-0.185 (0.045)	-0.274, -0.097	
Frequencies >4kHz included					
- No	10	7005	-0.148 (0.023)	-0.193, -0.104	0.05 (0.82)
- Yes	5	697	-0.138 (0.038)	-0.213, -0.063	
Sound-treated booth/room					
- No	9	3106	-0.13 (0.018)	-0.166, -0.095	0.48 (0.49)
- Yes	6	4596	-0.159 (0.038)	-0.233, -0.085	
Used WHO criteria					
- No	11	5045	-0.166 (0.023)	-0.212, -0.121	**6.34 (0.01)**
- Yes	4	2657	-0.091 (0.019)	-0.128, -0.053	
Hearing loss criteria					
- >25dB	3	2453	-0.175 (0.083)	-0.338, -0.012	0.26 (0.61)
- Continuous	10	3453	-0.131 (0.017)	-0.165, -0.098	
Hearing aid user removed					
- Not declared	5	1966	-0.117 (0.023)	-0.162, -0.073	1.14 (0.29)
- No	9	5477	-0.156 (0.028)	-0.211, -0.101	
Cognitive test accessible					
- No	12	7340	-0.15 (0.021)	-0.192, -0.109	0.5 (0.48)
- Yes	3	362	-0.11 (0.053)	-0.214, -0.005	
Analysis used					
- Correlation	6	956	-0.153 (0.033)	-0.217, -0.089	3.82 (0.15)
- Linear mixed models	3	2310	-0.084 (0.02)	-0.124, -0.044	
- Linear regression	4	2497	-0.123 (0.02)	-0.162, -0.084	
Reported significant					
- No	6	2481	-0.158 (0.02)	-0.196, -0.119	0.004 (0.95)
- Yes	9	5221	-0.16 (0.028)	-0.215, -0.105	
Controlled for sex					
- No	6	2848	-0.196 (0.034)	-0.262, -0.13	**6.34 (0.01)**
- Yes	9	4854	-0.104 (0.014)	-0.132, -0.076	
Controlled for race					
- No	10	4151	-0.178 (0.024)	-0.225, -0.132	**8.96 (0.003)**
- Yes	5	3551	-0.092 (0.017)	-0.124, -0.059	
Controlled for education (level or years)					
- No	8	2895	-0.196 (0.032)	-0.258, -0.134	**7.03 (0.01)**
- Yes	7	4807	-0.104 (0.014)	-0.132, -0.076	
Controlled for education (years)					
- No	12	5615	-0.158 (0.026)	-0.209, -0.107	1.21 (0.27)
- Yes	3	2087	-0.12 (0.022)	-0.163, -0.077	
Controlled for education (level)					
- No	11	4982	-0.167 (0.023)	-0.213, -0.121	**6.25 (0.01)**
- Yes	4	2720	-0.092 (0.019)	-0.128, -0.055	
Controlled for vascular risk factors					
- No	10	4151	-0.178 (0.024)	-0.225, -0.132	**8.96 (0.003)**
- Yes	5	3551	-0.092 (0.017)	-0.124, -0.059	

Table 13 (Continued): Cognitive function – Global cognition – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Controlled for stroke					
- No	12	4477	-0.168 (0.021)	-0.21, -0.126	**8.08 (0.004)**
- Yes	3	3225	-0.09 (0.018)	-0.124, -0.055	
Controlled for hypertension					
- No	10	4151	-0.178 (0.024)	-0.225, -0.132	**8.96 (0.003)**
- Yes	5	3551	-0.092 (0.017)	-0.124, -0.059	
Controlled for diabetes					
- No	12	4477	-0.168 (0.021)	-0.21, -0.126	**8.08 (0.004)**
- Yes	3	3225	-0.09 (0.018)	-0.124, -0.055	
Controlled for current smokers					
- No	11	5045	-0.166 (0.023)	-0.212, -0.121	**6.34 (0.01)**
- Yes	4	2657	-0.091 (0.019)	-0.128, -0.053	
Controlled for previous smokers					
- No	11	5045	-0.166 (0.023)	-0.212, -0.121	**6.34 (0.01)**
- Yes	4	2657	-0.091 (0.019)	-0.128, -0.053	
Controlled for depression					
- No	12	6482	-0.161 (0.024)	-0.207, -0.114	2.84 (0.09)
- Yes	3	1220	-0.099 (0.027)	-0.153, -0.046	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. $Q_b(p)$, Between-group differences and alpha value for between-group differences; WHO, World Health Organisation.

Table 14: Cognitive function – Immediate recall – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Country/Region					
- Europe	8	3329	-0.128 (0.028)	-0.183, -0.074	0.04 (0.85)
- USA	5	2399	-0.121 (0.027)	-0.174, -0.069	
Dementia participants removed					
- Not declared	9	4185	-0.162 (0.046)	-0.252, -0.072	0.85 (0.36)
- Yes	6	2562	-0.115 (0.022)	-0.158, -0.072	
Ear used					
- Better	6	3141	-0.126 (0.021)	-0.167, -0.085	0.28 (0.59)
- Both	9	3606	-0.155 (0.05)	-0.253, -0.057	
Frequencies >4kHz included					
- No	11	5197	-0.166 (0.036)	-0.237, -0.095	**4.76 (0.03)**
- Yes	5	2591	-0.076 (0.19)	-0.114, -0.038	
Sound-treated booth/room					
- No	11	4303	-0.166 (0.037)	-0.238, -0.094	**4.04 (0.04)**
- Yes	4	2444	-0.082 (0.02)	-0.121, -0.043	
Used WHO criteria					
- No	12	5344	-0.157 (0.035)	-0.225, -0.088	2.15 (0.14)
- Yes	3	1403	-0.091 (0.027)	-0.145, -0.038	
Hearing aid user removed					
- Not declared	7	2734	-0.2 (0.049)	-0.296, -0.104	**3.99 (0.046)**
- No	7	3560	-0.093 (0.021)	-0.134, -0.052	
Cognitive test accessible					
- No	8	4316	-0.176 (0.044)	-0.262, -0.09	0.88 (0.35)
- Yes	9	2971	-0.127 (0.028)	-0.183, -0.072	
Analysis used					
- Correlation	9	3587	-0.176 (0.046)	-0.267, -0.085	1.21 (0.27)
- Linear regression	4	2104	-0.117 (0.027)	-0.17, -0.064	
Reported significant					
- No	6	2668	-0.061 (0.019)	-0.098, -0.023	**13.67 (<0.001)**
- Yes	7	3083	-0.159 (0.018)	-0.195, -0.123	
Controlled for age					
- No	6	2702	-0.197 (0.066)	-0.327, -0.067	1.54 (0.22)
- Yes	9	4045	-0.111 (0.018)	-0.147, -0.076	
Controlled for sex					
- No	7	2155	-0.19 (0.054)	-0.297, -0.084	2.11 (0.15)
- Yes	8	4592	-0.107 (0.019)	-0.145, -0.068	
Controlled for education (level or years)					
- No	8	3196	-0.172 (0.053)	-0.276, -0.068	1.0 (0.32)
- Yes	7	3551	-0.114 (0.022)	-0.158, -0.071	
Controlled for education (level)					
- No	10	4437	-0.167 (0.04)	-0.245, -0.089	1.85 (0.17)
- Yes	5	2310	-0.1 (0.029)	-0.158, -0.043	
Controlled for vascular risk factors					
- No	10	3997	-0.16 (0.044)	-0.247, -0.073	0.89 (0.35)
- Yes	5	2750	-0.114 (0.019)	-0.153, -0.076	
Controlled for stroke					
- No	10	3997	-0.16 (0.044)	-0.247, -0.073	0.89 (0.35)
- Yes	5	2750	-0.114 (0.019)	-0.153, -0.076	
Controlled for hypertension					
- No	11	4450	-0.157 (0.04)	-0.235, -0.079	0.94 (0.33)
- Yes	4	2297	-0.112 (0.025)	-0.16, -0.064	
Controlled for diabetes					
- No	11	4450	-0.157 (0.04)	-0.235, -0.079	0.94 (0.33)
- Yes	4	2297	-0.112 (0.025)	-0.16, -0.064	
Controlled for current smokers					
- No	12	5344	-0.157 (0.035)	-0.225, -0.088	2.15 (0.14)
- Yes	3	1403	-0.091 (0.027)	-0.145, -0.038	
Controlled for previous smokers					
- No	12	5344	-0.157 (0.035)	-0.225, -0.088	2.15 (0.14)
- Yes	3	1403	-0.091 (0.027)	-0.145, -0.038	
Controlled for study site					
- No	12	4650	-0.165 (0.034)	-0.231, -0.098	**5.34 (0.02)**
- Yes	3	2097	-0.072 (0.021)	-0.114, -0.03	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. $Q_b(p)$, Between-group differences and alpha value for between-group differences;

Table 15: Cognitive function – Processing speed – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Country/Region					
- Australia	5	3348	-0.107 (0.08)	-0.263, 0.05	**7.88 (0.02)**
- Europe	8	3329	-0.185 (0.043)	-0.27, -0.099	
- USA	7	4983	-0.058 (0.014)	-0.086, -0.031	
Cognitively impaired participants removed					
- Not declared	16	8466	-0.143 (0.032)	-0.206, -0.081	**5.52 (0.02)**
- Yes	3	2741	-0.056 (0.019)	-0.094, -0.018	
Dementia participants removed					
- Not declared	13	7114	-0.154 (0.037)	-0.225, -0.082	2.42 (0.12)
- Yes	7	4546	-0.083 (0.028)	-0.137, -0.028	
Race					
- Mixed	6	4881	-0.054 (0.014)	-0.082, -0.027	**7.47 (0.01)**
- Not declared	14	6779	-0.162 (0.037)	-0.234, -0.09	
Ear used					
- Better	9	7694	-0.075 (0.019)	-0.112, -0.038	**4.32 (0.04)**
- Both	11	3966	-0.174 (0.043)	-0.259, -0.088	
Frequencies >4kHz included					
- No	14	9750	-0.15 (0.033)	-0.214, -0.086	**4.59 (0.03)**
- Yes	7	2951	-0.07 (0.017)	-0.104, -0.036	
Sound-treated booth/room					
- No	13	4663	-0.171 (0.039)	-0.247, -0.094	**8.04 (0.01)**
- Yes	7	6997	-0.056 (0.012)	-0.078, -0.033	
Used WHO criteria					
- No	14	5704	-0.166 (0.035)	-0.234, -0.097	**10.02 (0.002)**
- Yes	6	5956	-0.047 (0.013)	-0.072, -0.023	
Hearing aid user removed					
- Not declared	9	3094	-0.188 (0.054)	-0.293, -0.083	3.5 (0.06)
- No	10	8113	-0.082 (0.019)	-0.118, -0.045	
Analysis used					
- Correlation	9	3587	-0.205 (0.049)	-0.302, -0.108	**10.67 (0.01)**
- Linear mixed models	3	3040	-0.038 (0.017)	-0.072, -0.005	
- Linear regression	8	5033	-0.071 (0.014)	-0.099, -0.043	
Reported significant					
- No	14	9133	-0.053 (0.01)	-0.073, -0.032	**10.12 (0.001)**
- Yes	6	3466	-0.213 (0.049)	-0.309, -0.116	
Controlled for age					
- No	6	2702	-0.229 (0.068)	-0.362, -0.095	**4.57 (0.03)**
- Yes	14	8958	-0.079 (0.015)	-0.108, -0.05	
Controlled for sex					
- No	7	2155	-0.211 (0.062)	-0.332, -0.089	**4.09 (0.04)**
- Yes	13	9505	-0.081 (0.015)	-0.111, -0.052	
Controlled for race					
- No	14	6779	-0.162 (0.037)	-0.234, -0.09	**7.47 (0.01)**
- Yes	6	4881	-0.054 (0.014)	-0.082, -0.027	
Controlled for education (level or years)					
- No	10	3556	-0.18 (0.048)	-0.273, -0.087	**4.06 (0.04)**
- Yes	10	8104	-0.077 (0.018)	-0.112, -0.042	
Controlled for education (level)					
- No	12	4797	-0.162 (0.04)	-0.241, -0.084	3.38 (0.07)
- Yes	8	6863	-0.078 (0.022)	-0.121, -0.035	
Controlled for vascular risk factors					
- No	13	6326	-0.169 (0.039)	-0.247, -0.092	**7.45 (0.01)**
- Yes	7	5334	-0.056 (0.013)	-0.082, -0.03	
Controlled for stroke					
- No	13	6326	-0.169 (0.039)	-0.247, -0.092	**7.45 (0.01)**
- Yes	7	5334	-0.056 (0.013)	-0.082, -0.03	
Controlled for hypertension					
- No	14	6779	-0.162 (0.037)	-0.234, -0.09	**7.47 (0.01)**
- Yes	6	4881	-0.054 (0.014)	-0.082, -0.027	
Controlled for diabetes					
- No	14	6779	-0.162 (0.037)	-0.234, -0.09	**7.47 (0.01)**
- Yes	6	4881	-0.054 (0.014)	-0.082, -0.027	
Controlled for current smokers					
- No	15	7673	-0.156 (0.034)	-0.222, -0.09	**8.33 (0.004)**
- Yes	5	3987	-0.049 (0.015)	-0.079, -0.019	
Controlled for previous smokers					
- No	15	7673	-0.156 (0.034)	-0.222, -0.09	**8.33 (0.004)**
- Yes	5	3987	-0.049 (0.015)	-0.079, -0.019	
Controlled for study site					

- No	15	7399	-0.15 (0.033)	-0.214, -0.086	**6.7 (0.01)**
- Yes	4	4081	-0.055 (0.017)	-0.089, -0.021	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. Q_b(p), Between-group differences and alpha value for between-group differences; WHO, World Health Organisation.

Table 16: Cognitive function – Reasoning – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	Q_b(*p*)
Ear used					
- Better	4	646	-0.114 (0.041)	-0.195, -0.032	1.92 (0.17)
- Both	8	2482	-0.207 (0.054)	-0.313, -0.102	
Frequencies >4kHz included					
- No	9	2454	-0.194 (0.051)	-0.294, -0.095	1.87 (0.17)
- Yes	4	1715	-0.106 (0.04)	-0.184, -0.027	
Sound-treated booth/room					
- No	8	1700	-0.208 (0.053)	-0.312, -0.104	2.78 (0.1)
- Yes	4	1428	-0.102 (0.035)	-0.171, -0.033	
Cognitive test accessible					
- No	3	387	-0.154 (0.051)	-0.255, -0.053	0.24 (0.62)
- Yes	9	2741	-0.189 (0.049)	-0.285, -0.093	
Reported significant					
- No	7	2169	-0.075 (0.022)	-0.117, -0.033	**27.59 (<0.001)**
- Yes	5	988	-0.304 (0.038)	-0.378, -0.23	
Controlled for age					
- No	8	2195	-0.213 (0.057)	-0.325, -0.1	1.92 (0.17)
- Yes	4	933	-0.115 (0.041)	-0.195, -0.035	
Controlled for sex					
- No	7	1520	-0.202 (0.06)	-0.32, -0.084	0.69 (0.41)
- Yes	5	1608	-0.141 (0.043)	-0.225, -0.056	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. Q_b(p), Between-group differences and alpha value for between-group differences;

Table 17: Cognitive function – Semantic memory – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Country/Region					
- Australia	3	1199	-0.183 (0.083)	-0.345, -0.02	3.23 (0.2)
- Europe	4	1034	-0.152 (0.031)	-0.213, -0.091	
- USA	3	673	-0.072 (0.037)	-0.145, 0.001	
Ear used					
- Better	3	673	-0.072 (0.037)	-0.145, 0.001	3.29 (0.07)
- Both	7	2233	-0.17 (0.039)	-0.246, -0.094	
Frequencies >4kHz included					
- No	7	2232	-0.138 (0.044)	-0.224, -0.053	0.002 (0.96)
- Yes	3	674	-0.141 (0.049)	-0.237, -0.045	
Sound-treated booth/room					
- No	7	2233	-0.17 (0.039)	-0.246, -0.094	3.29 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Used WHO criteria					
- No	7	2233	-0.17 (0.039)	-0.246, -0.094	3.29 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Hearing aid user removed					
- Not declared	6	1918	-0.183 (0.042)	-0.265, -0.102	**3.88 (0.049)**
- No	4	988	-0.081 (0.031)	-0.142, -0.02	
Controlled for age					
- No	4	1559	-0.186 (0.054)	-0.291, -0.08	1.86 (0.17)
- Yes	6	1347	-0.104 (0.027)	-0.156, -0.051	
Controlled for sex					
- No	6	2053	-0.157 (0.044)	-0.243, -0.07	0.52 (0.47)
- Yes	4	853	-0.112 (0.043)	-0.197, -0.028	
Controlled for race					
- No	7	2233	-0.17 (0.039)	-0.246, -0.094	3.29 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Controlled for education (level or years)					
- No	7	2233	-0.17 (0.039)	-0.246, -0.094	3.29 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Controlled for vascular risk factors					
- No	7	2233	-0.17 (0.039)	-0.246, -0.094	3.29 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Controlled for hypertension					
- No	7	2233	-0.17 (0.039)	-0.246, -0.094	3.29 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Controlled for current smokers					
- No	7	2233	-0.17 (0.039)	-0.246, -0.094	3.29 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	
Controlled for previous smokers					
- No	7	2233	-0.17 (0.039)	-0.246, -0.094	3.29 (0.07)
- Yes	3	673	-0.072 (0.037)	-0.145, 0.001	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. $Q_b(p)$, Between-group differences and alpha value for between-group differences; WHO, World Health Organisation.

Table 18: Cognitive function – Working memory – cross-sectional

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Country/Region					
- Australia	3	2274	-0.032 (0.021)	-0.073, 0.01	**4.33 (0.04)**
- Europe	4	1428	-0.131 (0.043)	-0.215, -0.047	
Ear used					
- Better	6	3509	-0.128 (0.04)	-0.206, -0.05	1.51 (0.22)
- Both	3	1346	-0.069 (0.027)	-0.122, -0.015	
Sound-treated booth/room					
- No	4	1458	-0.101 (0.05)	-0.198, -0.003	0.01 (0.93)
- Yes	5	3397	-0.095 (0.034)	-0.163, -0.028	
Analysis used					
- Correlation	6	1812	-0.148 (0.038)	-0.223, -0.072	**6.16 (0.01)**
- Linear regression	3	3043	-0.042 (0.018)	-0.078, -0.007	
Reported significant					
- No	6	3565	-0.046 (0.017)	-0.079, -0.013	**8.13 (0.004)**
- Yes	6	2581	-0.159 (0.036)	-0.23, -0.088	
Controlled for age					
- No	5	1553	-0.115 (0.033)	-0.179, -0.05	0.4 (0.53)
- Yes	4	3302	-0.082 (0.041)	-0.161, -0.002	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. Q_b(p), Between-group differences and alpha value for between-group differences;

Table 19: Cognitive function – Global cognition – cohort

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	Q_b(*p*)
Reported significant					
- No	3	1186	-0.087 (0.045)	-0.174, 0.001	1.89 (0.17)
- Yes	3	3041	-0.159 (0.028)	-0.214, -0.104	
Controlled for pre-morbid IQ					
- No	3	2844	-0.183 (0.022)	-0.225, -0.14	**7.53 (0.006)**
- Yes	3	1383	-0.091 (0.025)	-0.141, -0.041	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. Q_b(p), Between-group differences and alpha value for between-group differences;

Table 20: Cognitive function – Immediate recall – cohort

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	Q_b(*p*)
Hearing aid user removed					
- Not declared	3	3113	-0.116 (0.018)	-0.151, -0.08	**27.12 (<0.001)**
- No	3	1447	-0.008 (0.01)	-0.028, 0.012	
Controlled for education (level)					
- No	3	3113	-0.116 (0.018)	-0.151, -0.08	**27.12 (<0.001)**
- Yes	3	1447	-0.008 (0.01)	-0.028, 0.012	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. Q_b(p), Between-group differences and alpha value for between-group differences;

Table 21: Cognitive function – Processing speed – cohort

Variable	ES (#)	Participants (#)	Fisher's Z (SE)	CI (95%)	$Q_b(p)$
Country/Region					
- Europe	3	1964	-0.064 (0.023)	-0.108, -0.02	0.44 (0.51)
- USA	6	3366	-0.092 (0.036)	-0.162, -0.022	
Cognitively impaired participants removed at baseline					
- Not declared	6	2830	-0.014 (0.008)	-0.03, 0.003	**12.6 (<0.001)**
- Yes	3	3524	-0.161 (0.041)	-0.24, -0.081	
Dementia participants removed at baseline					
- Not declared	3	1383	-0.055 (0.023)	-0.101, -0.009	1.06 (0.3)
- Yes	5	3431	-0.102 (0.039)	-0.178, -0.026	
Sound-treated booth/room					
- No	4	3504	-0.067 (0.017)	-0.1, -0.034	0.41 (0.52)
- Yes	6	3366	-0.092 (0.036)	-0.162, -0.022	
Used WHO criteria					
- No	4	3504	-0.067 (0.017)	-0.1, -0.034	0.41 (0.52)
- Yes	6	3366	-0.092 (0.036)	-0.162, -0.022	
Hearing loss criteria					
- >25dB	4	2750	-0.114 (0.07)	-0.251, 0.023	0.44 (0.51)
- Continuous	4	3504	-0.067 (0.017)	-0.1, -0.034	
Hearing aid user removed					
- Not declared	3	3113	-0.062 (0.018)	-0.098, -0.027	0.65 (0.42)
- No	7	3757	-0.093 (0.033)	-0.159, -0.027	
Reported significant					
- No	7	4728	-0.024 (0.01)	-0.043, -0.004	**28.32 (<0.001)**
- Yes	3	2142	-0.182 (0.028)	-0.237, -0.127	
Cognitively impaired participants removed in analysis					
- Not declared	6	2830	-0.014 (0.008)	-0.03, 0.003	**20.9 (<0.001)**
- No	3	2500	-0.17 (0.033)	-0.234, -0.105	
Dementia participants removed in analysis					
- Not declared	4	1774	-0.063 (0.021)	-0.105, -0.021	**23.63 (<0.001)**
- No	3	2500	-0.17 (0.033)	-0.234, -0.105	
- Yes	3	2596	-0.013 (0.009)	-0.031, 0.006	
Controlled for race					
- No	4	3504	-0.067 (0.017)	-0.1, -0.034	0.41 (0.52)
- Yes	6	3366	-0.092 (0.036)	-0.162, -0.022	
Controlled for education (level)					
- No	3	3113	-0.062 (0.018)	-0.027, -0.098	0.65 (0.42)
- Yes	7	3757	-0.093 (0.033)	-0.027, -0.159	
Controlled for vascular risk factors					
- No	4	3504	-0.067 (0.017)	-0.1, -0.034	0.41 (0.52)
- Yes	6	3366	-0.092 (0.036)	-0.162, -0.022	
Controlled for stroke					
- No	6	3830	-0.066 (0.015)	-0.096, -0.036	0.65 (0.42)
- Yes	4	3040	-0.102 (0.043)	-0.186, -0.019	
Controlled for hypertension					
- No	4	3504	-0.067 (0.017)	-0.1, -0.034	0.41 (0.52)
- Yes	6	3366	-0.092 (0.036)	-0.162, -0.022	
Controlled for diabetes					
- No	6	3830	-0.066 (0.015)	-0.096, -0.036	0.65 (0.42)
- Yes	4	3040	-0.102 (0.043)	-0.186, -0.019	
Controlled for current smokers					
- No	4	3504	-0.067 (0.017)	-0.1, -0.034	0.41 (0.52)
- Yes	6	3366	-0.092 (0.036)	-0.162, -0.022	
Controlled for previous smokers					
- No	4	3504	-0.067 (0.017)	-0.1, -0.034	0.41 (0.52)
- Yes	6	3366	-0.092 (0.036)	-0.162, -0.022	
Controlled for depression					
- No	7	5004	-0.09 (0.032)	-0.154, -0.027	0.34 (0.56)
- Yes	3	1866	-0.068 (0.021)	-0.109, -0.027	
Controlled for pre-morbid IQ					
- No	6	5096	-0.092 (0.034)	-0.159, -0.024	0.5 (0.48)
- Yes	4	1774	-0.063 (0.021)	-0.105, -0.021	
Controlled for study site					
- No	6	3830	-0.066 (0.015)	-0.096, -0.036	0.65 (0.42)
- Yes	4	3040	-0.102 (0.043)	-0.186, -0.019	

ES, effect sizes; SE, standard error; CI, Confidence Intervals. $Q_b(p)$, Between-group differences and alpha value for between-group differences; WHO, World Health Organisation.

META-REGRESSION ANALYSIS

Table 22: Cognitive Function – Attention – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	11	5159	0.0065 ±0.0012	0.0042, 0.0088	**5.47 (<0.001)**
Impact factor	8	4517	-0.0046 ±0.024	-0.0516, 0.0425	-0.19 (0.85)
STROBE	11	5159	-0.0048 ±0.0136	-0.0313, 0.0218	-0.35 (0.73)
Age (mean)	8	4517	0.0016 ±0.0037	-0.0058, 0.0089	0.42 (0.67)
Age (min)	9	4833	0.005 ±0.0021	0.0014, 0.0096	**2.63 (0.01)**
Age (max)	8	4486	0.0032 ±0.007	-0.0105, 0.0169	0.46 (0.65)
Sex (% female)	11	5159	0.0013 ±0.0016	-0.0019, 0.0045	0.8 (0.43)
Race (% white)	4	1567	0.005 ±0.0054	-0.0056, 0.0157	0.93 (0.35)
Race (% black)	4	1567	-0.005 ±0.0058	-0.0163, 0.0063	-0.86 (0.39)
Race (% other)	4	1567	-0.062 ±0.0527	-0.1652 , 0.0412	-1.18 (0.24)
Education (% tertiary)	4	866	0.0122 ±0.0021	0.008, 0.0164	**5.74 (<0.001)**
Sample PTA	6	2138	0.0091 ±0.0031	0.003, 0.0152	**2.93 (0.003)**
Hearing loss (%)	7	4337	0.0012 ±0.0013	-0.0013, 0.0038	0.93 (0.35)
Hearing aid user (%)	5	3275	0.0023 ±0.0057	-0.0088, 0.0135	0.41 (0.68)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 23: Cognitive Function – Delayed recall – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	7	3808	-0.0018 ±0.0034	-0.0084, 0.0048	-0.52 (0.6)
Impact factor	6	3549	-0.0242 ±0.0232	-0.0697, 0.0213	-1.04 (0.3)
STROBE	7	3808	-0.013 ±0.012	-0.0366, 0.0106	-1.08 (0.28)
Age (mean)	7	3808	0.0003 ±0.0031	-0.0057, 0.0063	0.09 (0.93)
Age (min)	5	3482	0.001 ±0.002	-0.003, 0.005	0.49 (0.62)
Age (max)	5	3482	-0.0018 ±0.0051	-0.0118, 0.0082	-0.36 (0.72)
Sex (% female)	7	3808	0.0021 ±0.0038	-0.0054, 0.0096	0.56 (0.58)
Sample PTA	4	1170	0.0001 ±0.0035	-0.0067, 0.0069	0.04 (0.97)
Hearing loss (%)	5	3096	0.0006 ±0.0017	-0.0027, 0.0039	0.33 (0.74)
Hearing aid user (%)	4	2928	-0.0001 ±0.0058	-0.0116, 0.0114	-0.02 (0.99)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 24: Cognitive Function – Fluency – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	9	4629	0.0023 ±0.0019	-0.0015, 0.0061	1.2 (0.23)
Impact factor	6	4242	-0.0286 ±0.0313	-0.09, 0.0327	-0.91 (0.36)
STROBE	9	4629	0.0057 ±0.0133	-0.0204, 0.0318	0.43 (0.67)
Age (mean)	5	4063	-0.003 ±0.0042	-0.0111, 0.0052	-0.71 (0.48)
Age (min)	9	4629	-0.0019 ±0.001	-0.0039, -0.0000	-1.93 (0.054)
Age (max)	8	4282	0.0000 ±0.0014	-0.0028, 0.0028	0.02 (0.98)
Sex (% female)	8	4314	0.0002 ±0.0012	-0.0021, 0.0025	0.19 (0.85)
Sample PTA	7	2345	-0.0005 ±0.0007	-0.0024, 0.0014	-0.53 (0.6)
Hearing loss (%)	6	3094	0.0016 ±0.0017	-0.0017, 0.0048	0.93 (0.35)
Hearing aid user (%)	5	3094	-0.0036 ±0.0077	-0.0188, 0.0115	-0.47 (0.64)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 25: Cognitive Function – Global cognition – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	15	7702	0.0006 ±0.0019	-0.003, 0.0043	0.34 (0.74)
Impact factor	12	7396	0.0081 ±0.005	-0.0018, 0.018	1.6 (0.11)
STROBE	15	7702	0.0048 ±0.0089	-0.0126, 0.0223	0.54 (0.59)
Age (mean)	14	7523	0.0009 ±0.0033	-0.0057, 0.0074	0.26 (0.8)
Age (min)	12	7075	0.0003 ±0.0011	-0.0019, 0.0025	0.24 (0.81)
Age (max)	9	4244	-0.001 ±0.0014	-0.0038, 0.0017	-0.74 (0.46)
Sex (% female)	14	7387	0.0006 ±0.0018	-0.0029, 0.0041	0.33 (0.74)
Race (% white)	5	3551	-0.0012 ±0.0013	-0.0037, 0.0014	-0.91 (0.37)
Race (% black)	5	3551	0.0011 ±0.0013	-0.0013, 0.0036	0.92 (0.36)
Race (% other)	5	3551	-0.0295 ±0.0342	-0.0965 , 0.0375	-0.86 (0.39)
Education (mean years)	4	2388	-0.0149 ±0.0255	-0.0648, 0.035	-0.59 (0.56)
Education (% primary)	5	2700	0.0000 ±0.0018	-0.0034, 0.0035	0.02 (0.98)
Education (% secondary)	4	2290	-0.0005 ±0.004	-0.0082, 0.0073	-0.12 (0.91)
Education (% tertiary)	6	2616	-0.0001 ±0.0027	-0.0055, 0.0052	-0.05 (0.96)
Sample PTA	10	4234	-0.0011 ±0.0039	-0.0087, 0.0066	-0.28 (0.78)
Hearing loss (%)	8	4762	0.0005 ±0.0014	-0.0023, 0.0033	0.35 (0.73)
Hearing aid user (%)	7	3629	0.0006 ±0.0027	-0.0047, 0.0058	-0.21 (0.83)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology

Table 26: Cognitive Function –Immediate recall – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	15	6747	0.0026 ±0.0017	-0.0007, 0.0059	1.57 (0.12)
Impact factor	12	6105	0.0158 ±0.0212	-0.0258, 0.0574	0.74 (0.46)
STROBE	15	6747	0.0043 ±0.0112	-0.0176, 0.0262	0.39 (0.7)
Age (mean)	11	5926	0.0013 ±0.0042	-0.0069, 0.0096	0.32 (0.75)
Age (min)	15	6747	0.0013 ±0.0013	-0.0012, 0.0038	0.99 (0.32)
Age (max)	14	6400	-0.0011 ±0.0025	-0.006, 0.0037	-0.46 (0.64)
Sex (% female)	14	6432	0.0017 ±0.0015	-0.0013, 0.0046	1.12 (0.26)
Race (% white)	4	2297	-0.0026 ±0.0013	-0.0051, -0.0000	**-2.0 (0.046)**
Race (% black)	4	2297	0.0025 ±0.0013	0.000, 0.005	**1.99 (0.047)**
Race (% other)	4	2297	-0.0649 ±0.0393	-0.142, 0.0122	-1.65 (0.1)
Education (% primary)	5	2006	-0.0016 ±0.0021	-0.0057, 0.0024	-0.79 (0.43)
Education (% secondary)	4	1596	0.0061 ±0.0175	-0.0282, 0.0404	0.35 (0.73)
Education (% tertiary)	4	1596	0.0041 ±0.0013	0.0015, 0.0066	**3.07 (0.002)**
Sample PTA	7	3430	0.0014 ±0.0007	0.0001, 0.0028	**2.05 (0.04)**
Hearing loss (%)	6	3098	0.0024 ±0.0009	0.0007, 0.0041	**2.74 (0.01)**
Hearing aid user (%)	8	4013	0.0015 ±0.0026	-0.0036, 0.0066	0.57 (0.57)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology

Table 27: Cognitive Function – Processing speed – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	20	11660	0.0057 ±0.0012	0.0033, 0.0081	**4.61 (<0.001)**
Impact factor	17	11018	0.0072 ±0.0078	-0.0081, 0.0225	0.92 (0.36)
STROBE	20	11660	0.0006 ±0.0097	-0.0184, 0.0197	0.07 (0.95)
Age (mean)	16	10839	-0.0006 ±0.0029	-0.0063, 0.0052	-0.19 (0.85)
Age (min)	20	11660	0.0023 ±0.0012	-0.0001, 0.0047	1.85 (0.06)
Age (max)	19	11313	-0.0003 ±0.0022	-0.0047, 0.004	-0.15 (0.88)
Sex (% female)	19	11345	0.0008 ±0.0012	-0.0016, 0.0032	0.65 (0.52)
Race (% white)	6	4881	-0.0007 ±0.001	-0.0026, 0.0013	-0.68 (0.5)
Race (% black)	6	4881	0.0017 ±0.0011	-0.0005, 0.0039	1.55 (0.12)
Race (% other)	6	4881	-0.0013 ±0.0014	-0.004, 0.0013	-0.98 (0.33)
Education (mean years)	5	1726	0.0071 ±0.0157	-0.0235, 0.0378	0.46 (0.65)
Education (% primary)	7	4590	-0.0052 ±0.0016	-0.0083, -0.002	**-3.23 (0.001)**
Education (% secondary)	6	4180	0.0056 ±0.0124	-0.0187, 0.0299	0.45 (0.65)
Education (% tertiary)	6	4180	0.0085 ±0.0012	0.0061, 0.0108	**7.18 (<0.001)**
Sample PTA	11	6374	0.0004 ±0.0013	-0.002, 0.0029	0.35 (0.72)
Hearing loss (%)	8	5667	0.0006 ±0.0011	-0.0016, 0.0027	0.51 (0.61)
Hearing aid user (%)	11	8566	-0.0023 ±0.0025	-0.0071, 0.0026	-0.92 (0.36)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology

Table 28: Cognitive Function – Reasoning – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	12	3128	0.0068 ±0.0017	0.0034, 0.0101	**3.97 (<0.001)**
Impact factor	5	1840	-0.001 ±0.0486	-0.0962, 0.0942	-0.02 (0.98)
STROBE	12	3128	-0.0165 ±0.0125	-0.041, 0.008	-1.32 (0.19)
Age (mean)	5	1920	-0.0026 ±0.008	-0.0129, 0.0182	0.33 (0.74)
Age (min)	12	3128	0.0037 ±0.0015	0.0008, 0.0065	**2.52 (0.01)**
Age (max)	12	3128	0.0006 ±0.0023	-0.0038, 0.005	0.26 (0.79)
Sex (% female)	11	2813	-0.0000 ±0.0012	-0.0025, 0.0024	-0.04 (0.97)
Sample PTA	7	1912	0.0016 ±0.0009	-0.0001, 0.0033	1.79 (0.07)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 29: Cognitive Function – Semantic memory – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	10	2906	0.0025 ±0.002	-0.0014, 0.0065	1.26 (0.21)
Impact factor	8	2366	0.0149 ±0.0263	-0.0367, 0.0665	0.57 (0.57)
STROBE	10	2906	0.0039 ±0.0151	-0.0257, 0.0335	0.26 (0.8)
Age (mean)	7	2187	0.0001 ±0.0104	-0.0203, 0.0204	0.01 (0.996)
Age (min)	8	2580	-0.0002 ±0.0019	-0.004, 0.0036	-0.13 (0.9)
Age (max)	7	2233	-0.0009 ±0.0026	-0.0061, 0.0042	-0.35 (0.73)
Sex (% female)	9	2591	-0.0004 ±0.0013	-0.0029, 0.0022	-0.29 (0.77)
Education (% tertiary)	4	866	0.0038 ±0.0021	-0.0004, 0.008	1.79 (0.07)
Sample PTA	6	1157	-0.0023 ±0.0044	-0.011, 0.0064	-0.52 (0.6)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 30: Cognitive Function – Visuospatial ability – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	8	669	0.0062 ±0.0032	-0.0001, 0.0125	1.93 (0.053)
STROBE	8	669	0.0273 ±0.0182	-0.0084, 0.0629	1.5 (0.13)
Age (min)	8	669	0.002 ±0.0024	-0.0026, 0.0067	0.85 (0.39)
Age (max)	8	669	0.0009 ±0.0024	-0.0037, 0.0055	0.39 (0.7)
Sex (% female)	8	669	0.001 ±0.0009	-0.0009, 0.0028	1.02 (0.31)
Sample PTA	7	567	0.0008 ±0.0028	-0.0047, 0.0064	0.3 (0.77)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 31: Cognitive Function – Working memory – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	9	4855	0.0046 ±0.0013	0.0019, 0.0072	**3.41 (0.001)**
Impact factor	5	4209	-0.0381 ±0.0339	-0.1045, 0.0283	-1.12 (0.26)
STROBE	9	4855	0.0211 ±0.0073	0.0068, 0.0355	**2.88 (0.004)**
Age (mean)	6	4468	-0.0031 ±0.0035	-0.01, 0.0038	-0.87 (0.38)
Age (min)	9	4855	-0.0011 ±0.0023	-0.0056, 0.0033	-0.5 (0.62)
Age (max)	9	4855	0.0002 ±0.0016	-0.003, 0.0034	0.13 (0.9)
Sex (% female)	9	4855	0.0018 ±0.0009	-0.0001, 0.0036	1.9 (0.06)
Sample PTA	7	2627	0.0004 ±0.0012	-0.0019, 0.0027	0.35 (0.73)
Hearing loss (%)	5	3250	-0.0017 ±0.0022	-0.0061, 0.0027	-0.75 (0.45)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 32: Cognitive Function – Delayed recall – cohort

Variable	ES (#)	Participants (#)	$\beta_1 \pm$SE	CI (95%)	*Z(p)*
Year of publication	4	1774	-0.0017 ±0.0074	-0.0162, 0.0128	-0.23 (0.82)
Impact factor	4	1774	0.0041 ±0.0119	-0.0192, 0.0274	0.35 (0.73)
STROBE	4	1774	-0.0156 ±0.0398	-0.0935, 0.0623	-0.39 (0.7)
Length to FU (years)	4	1774	-0.001 ±0.0044	-0.0095, 0.0076	-0.22 (0.82)
Age (mean BL)	4	1774	-0.0003 ±0.0068	-0.0136, 0.0129	-0.05 (0.96)
Age (min BL)	4	1774	0.0002 ±0.0062	-0.0119, 0.0123	0.03 (0.97)
Sex (% female FU)	4	1774	-0.0002 ±0.001	-0.0021, 0.0017	-0.21 (0.83)
Sample PTA	4	1774	-0.0044 ±0.0067	-0.0175, 0.0087	-0.66 (0.51)

BL, Baseline; ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; FU, follow-up; PTA, Pure-tone average. STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 33: Cognitive Function – Fluency – cohort

Variable	ES (#)	Participants (#)	$\beta_1 \pm$SE	CI (95%)	*Z(p)*
Year of publication	4	1233	0.0106 ±0.0077	-0.0046, 0.0258	1.37 (0.17)
Impact factor	4	1233	0.0479 ±0.0226	0.0036, 0.0922	**2.12 (0.03)**
STROBE	4	1233	0.0303 ±0.0156	-0.0003, 0.0608	1.94 (0.053)
Length to FU (years)	4	1233	0.0006 ±0.0049	-0.0035, 0.0155	1.24 (0.21)
Age (mean BL)	4	1233	-0.004 ±0.0023	-0.0085, 0.0005	-1.75 (0.08)
Age (min BL)	4	1233	-0.0047 ±0.0027	-0.0099, 0.0005	-1.78 (0.08)
Age (max BL)	4	1233	-0.0031 ±0.0016	-0.0063, 0.0001	-1.92 (0.054)

BL, baseline; ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; FU, follow-up; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 34: Cognitive Function – Global cognition – cohort

Variable	ES (#)	Participants (#)	$\beta_1 \pm$SE	CI (95%)	*Z(p)*
Year of publication	6	4227	0.0135 ±0.0246	-0.0347, 0.0618	0.55 (0.58)
Impact factor	6	4227	-0.0132 ±0.0056	-0.0242, -0.0022	**-2.35 (0.02)**
STROBE	6	4227	0.0567 ±0.0235	0.0107, 0.1027	**2.41 (0.02)**
Length to FU (years)	6	4227	0.0064, ±0.0024	0.0016, 0.0112	**2.61 (0.009)**
Age (mean BL)	5	3367	-0.0045 ±0.0017	-0.0077, -0.0012	**-2.69 (0.007)**
Age (min BL)	6	4227	-0.0036 ±0.0014	-0.0065, -0.0008	**-2.53 (0.01)**
Age (max BL)	4	2310	-0.0067 ±0.0036	-0.0138, 0.0003	-1.87 (0.06)
Sex (% female FU)	5	3367	-0.0001 ±0.0013	-0.0026, 0.0023	-0.11 (0.91)
Race (% white)	4	2310	0.0021 ±0.0021	-0.002, 0.0061	1.01 (0.31)
Race (% black)	4	2310	-0.0021 ±0.0021	-0.0061, 0.002	-1.01 (0.31)
Education (% tertiary)	4	2310	-0.0104 ±0.0087	-0.0275, 0.0068	-1.18 (0.24)
Sample PTA	5	3367	0.0025 ±0.0083	-0.0138, 0.0188	0.3 (0.76)

BL, baseline; ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; FU, follow-up; PTA, Pure-tone average. STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 35: Cognitive Function – Immediate recall – cohort

Variable	ES (#)	Participants (#)	$\beta_1 \pm$SE	CI (95%)	*Z(p)*
Year of publication	6	4225	0.0109 ±0.0018	0.0074, 0.0143	**6.12 (<0.001)**
Impact factor	6	4225	0.0097 ±0.0114	-0.0126, 0.032	0.86 (0.39)
STROBE	6	4225	0.0197 ±0.0042	0.0114, 0.028	**4.65 (<0.001)**
Length to FU (years)	6	4225	-0.0051 ±0.0045	-0.0139, 0.0037	-1.14 (0.25)
Age (mean BL)	6	4225	0.0013 ±0.0025	-0.0036, 0.0061	0.51 (0.61)
Age (min BL)	6	4225	0.0026 ±0.0019	-0.0011, 0.0062	1.37 (0.17)
Sex (% female FU)	5	3709	0.0008 ±0.0011	-0.0011, 0.0028	0.74 (0.46)

BL, baseline; ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; FU, follow-up; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 36: Cognitive Function – Processing speed – cohort

Variable	ES (#)	Participants (#)	β_1 ±SE	CI (95%)	*Z(p)*
Year of publication	10	6462	0.0026 ±0.0057	-0.0085, 0.0137	0.45 (0.65)
Impact factor	10	6462	-0.0169 ±0.0034	-0.0236, -0.0102	**-4.94 (<0.001)**
STROBE	10	6462	0.008 ±0.0107	-0.0131, 0.029	0.74 (0.46)
Length to FU (years)	10	6462	0.0031 ±0.0042	-0.0051, 0.0114	0.74 (0.46)
Age (mean BL)	10	6462	-0.0017 ±0.0027	-0.007, 0.0037	-0.62 (0.54)
Age (min BL)	10	6462	-0.0008 ±0.0024	-0.0055, 0.0038	-0.36 (0.72)
Age (max BL)	8	3865	0.0003 ±0.0029	-0.0054, 0.0059	0.09 (0.92)
Sex (% female FU)	9	5946	-0.0002 ±0.0016	-0.0033, 0.0028	-0.15 (0.88)
Race (% white)	6	2958	0.0001 ±0.0025	-0.0048, 0.005	0.05 (0.96)
Race (% black)	6	2958	0.0001 ±0.0025	-0.005, 0.0048	-0.05 (0.96)
Education (% primary)	4	2705	0.0039 ±0.054	-0.1019, 0.1097	0.07 (0.94)
Education (% secondary)	4	2705	-0.0554 ±0.0741	-0.2006, 0.0898	-0.75 (0.45)
Education (% tertiary)	6	2958	-0.0017 ±0.0103	-0.0218, 0.0184	-0.16 (0.87)
Current smoker (%)	5	3762	0.0021 ±0.0034	-0.0047, 0.0088	0.6 (0.55)
Previous smoker (%)	4	2705	-0.022 ±0.0062	-0.0341, -0.0099	**-3.56 (<0.001)**
Never smoked (%)	4	2705	0.0198 ±0.0085	0.0031, 0.0365	**2.32 (0.02)**
Sample PTA	7	5298	0.003 ±0.0054	-0.0076, 0.0136	0.56 (0.58)
Hearing aid user (%)	6	3254	-0.0037 ±0.0069	-0.0172, 0.0098	-0.54 (0.59)

BL, baseline; ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; FU, follow-up; PTA, Pure-tone average. STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Table 37: Cognitive Impairment – cross-sectional

Variable	ES (#)	Participants (#)	$\beta_1 \pm$ SE	CI (95%)	*Z(p)*
Year of publication	5	6553	-0.0353 ±0.0937	-0.219, 0.1484	-0.38 (0.71)
Age (mean years)	5	6553	-0.0332 ±0.0428	-0.117, 0.0507	-0.78 (0.44)
Age (min)	4	6252	0.0002 ±0.0207	-0.0402, 0.0407	0.01 (0.99)
Sex (% female)	5	6553	0.0144 ±0.0205	-0.0257, 0.0546	0.7 (0.48)
PTA (mean)	4	6119	-0.0224 ±0.0241	-0.0697, 0.025	-0.93 (0.35)
Hearing loss (%)	4	2332	0.0025 ±0.0048	-0.0068, 0.0119	0.53 (0.59)
Cognitive impairment (%)	4	6118	0.0003 ±0.0131	-0.0254, 0.0259	0.02 (0.98)
Impact factor	5	6553	-0.139 ±0.0784	-0.2926, 0.0146	-1.77 (0.08)
STROBE	5	6553	0.155 ±0.172	-0.1822, 0.4922	0.9 (0.37)

ES, effect size; $\beta_1 \pm$ SE, slope and standard error; CI, confidence interval; PTA, Pure-tone average. STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

Appendix B: Health Screen

Participant ID:_____ Date:_____

Age:_____

	Question	Response	Exclude
1.	Have you ever had a stroke or T.I.A.? (Probe: T.I.A. Stands for transient ischemic attack)	Yes / No	**Yes**
2.	Do you have trouble with your vision that prevents you from reading ordinary print even when you have glasses on?	Yes / No	
3.	Have you had heart surgery?	Yes / No	
4.	Have you ever had a problem due to abuse of drugs or medications?	Yes / No	**Yes**
5.	Have you ever been treated for alcohol or drug abuse?	Yes / No	**Yes**
6.	Do you have diabetes that requires insulin to control?	Yes / No	
7.	Do you have hypertension that is not well controlled?	Yes / No	
8.	Have you ever had a heart attack?	Yes / No	
9.	Are you currently taking medication for a psychiatric condition?	Yes / No	**If Yes Consult medications for exclusions.**
10.	Have you been hospitalised for mental or emotional problems in the past 5 years?	Yes / No	**Yes**
11.	Do you have epilepsy?	Yes / No	**Yes**
12.	Do you have Parkinson's disease?	Yes / No	**Yes**
13.	Have you ever had brain surgery?	Yes / No	
14.	Have you ever undergone surgery to clear arteries to the brain?	Yes / No	
15.	Have you ever had any illness/injury (such as a brain injury) that caused a permanent decrease in memory or other mental functions?	Yes / No	**Yes**
16.	Have you ever been diagnosed as having a brain tumour?	Yes / No	**Yes**
17.	Do you currently or have you recently had, an injury, swelling, inflammation or pain in either of your hands or wrists?	Yes / No	**Yes**
18.	Do you have multiple sclerosis, cerebral palsy, or Huntington's disease?	Yes / No	**Yes**
19.	A: Are you aware if any of your immediate biological relatives (your biological parents, brothers or sisters, or children) have been told by a doctor that they have Alzheimer's disease or any other form of dementia?'	Yes/No	

	If yes:		
	B: What is the relationship of that relative to you?		

Medication Name

List of excluded medications:

Generic Name	*Trade Name(s)*
Amisulpiride	Solian
Aripiprazole	Abilify
Chlorpromazine	Thorazine; Largactil
Clozapine	Clozaril
Fluphenazine	Fluphenazine
Haloperidol	Haldol
Iloperidone	Fanapt
Olanzapine	Olanzapine Apotex
Olanzapine	Olanzapine Glenmark
Olanzapine	Olanzapine Mylan
Olanzapine	Olanzapine Neopharma
Olanzapine	Olanzapine Teva
Olanzapine	Olazax
Olanzapine	Olazax Disperzi
Olanzapine	Zalasta
Olanzapine Pamoate	Zypadhera
Olanzapine	Zyprexa
Paliperidone	Invega
Paliperidone Palmitate	Xeplion
Perphenazine (generic)	Perphenazine
Pimozide	Orap
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine (generic)	Thioridazine

Thiothixene	Navane
Trifluoperazine	Stelazine
Sertindole	Serdolect
Sulperide	Dolmatil
Ziprasidone	Geodon
Zotepine	Zoleptil
Haloperidol decanoate	Haldol
Flupenthixol decanoate	Depixol
Fluphenazine decanoate	Modecate
Pipothiazine palmitate	Piportil
Zuclopenthixol decanoate	Clopixol
Risperidone	Risperdal Consta
Carbamazepine	Tegretol
Divalproex sodium (valproic acid)	Depakote
Gabapentin	Neurontin
Lamotrigine	Lamictal
lithium carbonate	Eskalith, Lithobid
lithium citrate	Lithium citrate
Oxcarbazepine	Trileptal
Topiramate	Topamax
Levetiracetam	Keppra
Levetiracetam	Levetiracetam Accord
Levetiracetam	Levetiracetam Activas
Levetiracetam	Levetiracetam Ratiopharm
Levetiracetam	Levetiracetam Sun
Levetiracetam	Levetiracetam Teva
Levetiracetam	Matever
Retigabine	Trobalt
Lacosamide	Vimpat

Appendix C: Information sheet for main study

Hearing ability, Cognitive Function and Lifestyle in Older Adults

What is this project about?
This is a project being carried out by Trinity College Dublin and DeafHear examining the relationship between hearing ability, mental processes such as memory and attention, and other aspects such as lifestyle and mood. We would like to invite you to participate in this project. Your participation will help to build scientific knowledge in this important area of research.

Who can take part?
Anyone over the age of 50.

If I agree to take part what happens?
If you agree to take part you will be contacted and asked some questions about your health. If you are eligible you will then be asked to complete some questionnaires at home – to provide us with some background information about your life (for example, your education, your mood and your memory).

You will then be invited to DeafHear on 35 North Frederick Street, Dublin 1, to complete some more questionnaires and some tasks that provide us with information about your mental processes like memory and attention. You will be asked to sign a consent form giving your consent to take part in this study before beginning this session. Some of these are paper and pen tests, and a few are computer based tests. You do not need to be familiar with a computer to complete the tasks; they only involve pressing one or two buttons in response to instructions. We will also measure your grip strength and hearing acuity. This assessment should take no longer than two hours and there will be regular breaks during the session.

What are my rights?
Participation in this project is entirely voluntary and you are free to decline to complete some or all of the questionnaires or tasks. You are free to withdraw from the project, or your data from the project, at any time even after signing the consent form. This project is covered by standard institutional indemnity insurance and has been given approval by the Research Ethics Committee in Trinity College Dublin and has been approved by DeafHear. Nothing in this document restricts or curtails your rights. There are no risks with taking part.

What happens to my data?
The data collected during this project will be treated as strictly confidential and will be stored securely under a unique project ID code to protect your anonymity. Only the project team will be

able to link your name to the information you provide during the project, your name or other identifying information will not be published and will not be disclosed to anyone outside the project team.

You are entitled to request access to information we store about you, as per the terms of the Freedom of Information Act.

We will aim to publish the results of the project, but only as group results and no identifying information will be released about any participant. The data may also be used in future related studies, but identities will be again confidential.

Your contact information will only be used to contact you for future projects provided you give us your permission to do so.

For queries related to this project, please contact David Loughrey

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Appendix D: Consent form for main study

Consent Form

Hearing ability, Cognitive Function and Lifestyle in Older Adults

What does the project involve?

If you give your consent to take part in this testing session, you will be asked to complete some pen and paper tasks and some computerised tasks to assess cognitive function. We will also measure your grip strength. You will also be asked to complete an audiometric session to measure your hearing ability. This assessment should take no longer than two hours and there will be regular breaks during the session. This consent form is also to give us permission to collect the questionnaire we asked you to complete.

You are free to withdraw your participation from the project at any time and you can decline to provide some or all of the information requested.

The information we collect will never be made available to anyone other than members of the project team or their assistants. Your participation in our project will be very helpful to us and much appreciated.

What happens to the data I provide?

The data collected during this project will be treated as strictly confidential and will be stored securely under a unique ID code, separately from your name and other identifiable information, in order to protect your anonymity. Only the project team will be able to link your name to the information you provide during the project. The information we collect will never be made available to anyone other than members of the NEIL research team or their assistants.

You are free to withdraw any data you provide from the project at a later date if you wish. You are entitled to request access to information we store about you as per the terms of the Data Protection Act. We will aim to publish the results of this project in scientific journals, but only as group results and without any information that could potentially identify a participant. The data may also be used in future related studies, but identities will again remain confidential.

Statement of Consent

By signing this consent form, I indicate that:

- I am confirming that I have read and understood this form and the project information sheet.
- I have had the opportunity to ask questions and any questions have been answered to my satisfaction.
- I freely agree to take part in this research project.
- I understand that participation is voluntary, and that I can withdraw my participation or my data from the project at any time.
- I understand that my data will be stored under a unique ID code, and not linked to my name or other identifying information. Any data obtained through my participation will be confidential, processed in accordance with the Data Protection Act, published in a group format and used only for the purposes of research.
- I understand that this data may also be used in future related studies, but identities will again remain confidential.
- I understand that this project is covered by standard institutional indemnity insurance and has been granted Research Ethics Committee approval from all institutions involved.

Please sign here

Full Name: _____

Signed: _____ **Date:** _____

Thank you for your consent. Your participation is very helpful to us.

Researcher Statement: To be signed by researcher

I have explained the nature and purpose of this research project, the procedures to be undertaken and any risks that may be involved. I have offered to answer any questions and fully answered these questions. I believe the participant understands my explanation and has freely given informed consent.

Full Name: _____

Signed: _____ **Date:** _____

Participant ID: _____

Appendix E: Audiological background questionnaire

Participant ID: _____

Audiological background

1. Do you feel you have a hearing loss?
No ☐ **skip to Q8** Yes ☐ Don't know ☐

2. Which is your better ear?
Right ☐ Left ☐ No Difference ☐
Don't know ☐

3. Was your hearing loss sudden or gradual?
Sudden ☐ Gradual ☐ Don't know ☐

4. Do you wear a hearing aid of any type?
No ☐ Yes ☐ Don't know ☐

If yes, for how long?
_____

5. Does your hearing loss fluctuate (i.e. get better and worse)?
No ☐ Yes ☐ Don't know ☐

6. How old were you when your hearing loss developed?

<30	☐	50-59	☐	80-89	☐
30-39	☐	60-69	☐	90+	☐
40-49	☐	70-79	☐	Don't know	☐

7. Do you know what caused it?

From birth	☐	Noise exposure	☐	Other	☐
Age-related	☐	Chemical exposure	☐	Don't know	☐
Accident	☐	Disease	☐	Head injury	☐ Surgery ☐

If other, please list below:
_____

8. Are you currently being treated or followed by any doctor for any hearing or ear problems?
No ☐ Yes ☐

If yes, what for?
_____

9. Are you aware if any of your immediate biological relatives (your biological parents, brothers or sisters, or children) have had hearing loss?
No ☐ Yes ☐ Don't know ☐

10. In the past year have you had buzzing, ringing or noise (tinnitus) in your ears that lasts longer than 5 minutes?
No ☐ Yes, past week ☐ Yes, not past week ☐ Unknown ☐

Appendix F: Information sheet for sub-study

Hearing ability and Memory in Older Adults

What is this project about?
This is a project being carried out by Trinity College Dublin to examine the relationship between hearing ability and memory.

Who can take part?
We are inviting all eligible adults who participated in our previous study on hearing ability and cognitive function.

If I agree to take part what happens?
If you agree to take part you will be contacted and invited to DeafHear on 35 North Frederick Street, Dublin 1 or to Trinity College Dublin.

When you come in for your appointment you will be asked to sign a consent form giving your consent to take part in this study before beginning the testing session.

The test consists of viewing and remembering some simple colours and shapes on a screen and you will be asked a simple question regards their similarity. This assessment should take no longer than 15 minutes.

What are my rights?
Participation in this project is entirely voluntary and you are free to decline to complete some or all of the questionnaires or tasks. You are free to withdraw from the project, or your data from the project, at any time even after signing the consent form. This project is covered by standard institutional indemnity insurance and has been approval by the Research Ethics Committee in Trinity College Dublin. Nothing in this document restricts or curtails your rights. There are no risks with taking part.

What happens to my data?
The data collected during this project will be treated as strictly confidential and will be stored securely under a unique project ID code to protect your anonymity. Only the project team will be able to link your name to the information you provide during the project, your name or other identifying information will not be published and will not be disclosed to anyone outside the project team.

You are entitled to request access to information we store about you, as per the terms of the Freedom of Information Act. We will aim to publish the results of the project, but only as group results and no identifying information will be released about any participant. The data may also be used in future related studies, but identities will be again confidential.
Your contact information will only be used to contact you for future projects provided you give us your permission to do so.

For queries related to this project, please contact David Loughrey

Email: loughred@tcd.ie
Phone: 087-4210320

David Loughrey TCIN Lloyd building Trinity College Dublin Dublin 2 loughred@tcd.ie (01) 896 4506	Dr Sabina Brennan TCIN Lloyd Building Trinity College Dublin Dublin 2 brennas1@tcd.ie (01) 896 8414	Dr Robert Coen Dept. of Medical Gerontology, Trinity College Dublin Dublin 2 rcoen@stjames.ie (01) 4162640	Prof Brian Lawlor TCIN Lloyd Building Trinity College Dublin Dublin 2 lawlorba@tcd.ie (01) 896 8576

Appendix G: Consent form for sub-study

Consent Form

Hearing ability, Cognitive Function and Lifestyle in Older Adults

David Loughrey	Email: loughred@tcd.ie	Phone: 087-432 7986
Dr Sabina Brennan	Email: brennas1@tcd.ie	Phone: (01) 896 8414
Dr Robert Coen	Email: rcoen@stjames.ie	Phone: (01) 416 2640
Prof Brian Lawlor	Email: lawlorba@tcd.ie	Phone: (01) 896 8576

What does the project involve?

If you give your consent to take part in this testing session, you will be asked to complete a short memory test. This assessment should take no longer than 15 minutes. You are free to withdraw your participation from the project at any time.

The information we collect will never be made available to anyone other than members of the project team or their assistants. Your participation in our project will be very helpful to us and much appreciated.

What happens to the data I provide?

The data collected during this project will be treated as strictly confidential and will be stored securely under a unique ID code, separately from your name and other identifiable information, in order to protect your anonymity. Only the project team will be able to link your name to the information you provide during the project. The information we collect will never be made available to anyone other than members of the NEIL research team or their assistants.

You are free to withdraw any data you provide from the project at a later date if you wish. You are entitled to request access to information we store about you as per the terms of the Data Protection Act. We will aim to publish the results of this project in scientific journals, but only as group results and without any information that could potentially identify a participant. The data may also be used in future related studies, but identities will again remain confidential.

Statement of Consent

By signing this consent form, I indicate that:

- I am confirming that I have read and understood this form and the project information sheet.
- I have had the opportunity to ask questions and any questions have been answered to my satisfaction.
- I freely agree to take part in this research project.
- I understand that participation is voluntary, and that I can withdraw my participation or my data from the project at any time.
- I understand that my data will be stored under a unique ID code, and not linked to my name or other identifying information. Any data obtained through my participation will be confidential, processed in accordance with the Data Protection Act, published in a group format and used only for the purposes of research.
- I understand that this data may also be used in future related studies, but identities will again remain confidential.
- I understand that this project is covered by standard institutional indemnity insurance and has been granted Research Ethics Committee approval from all institutions involved.

Please sign here

Full Name: _____

Signed: _____ **Date:** _____

Thank you for your consent. Your participation is very helpful to us.

Researcher Statement: To be signed by researcher

I have explained the nature and purpose of this research project, the procedures to be undertaken and any risks that may be involved. I have offered to answer any questions and fully answered these questions. I believe the participant understands my explanation and has freely given informed consent.

Full Name: _____

Signed: _____ **Date:** _____

Participant ID: _____

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

The association of age-related hearing loss with cognition function, cognitive impairment and dementia: a systematic review with meta-analysis

David Loughrey, Michelle Kelly, George Kelley, Brian Lawlor, Sabina Brennan

Citation

David Loughrey, Michelle Kelly, George Kelley, Brian Lawlor, Sabina Brennan. The association of age-related hearing loss with cognition function, cognitive impairment and dementia: a systematic review with meta-analysis. PROSPERO 2015 CRD42015026052 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015026052

Review question

To evaluate the available evidence regarding the relationship between peripheral age-related hearing loss and cognitive function, cognitive impairment and dementia.

Searches

Sources to be searched include:
(1) electronic searches in multiple databases: PubMed (MEDLINE), Cochrane Library, EMBASE and Scopus.
(2) cross-referencing from retrieved studies, including those in personal files.
(3) citation tracking.
The restrictions include:
(1) grey literature search.

Types of study to be included

Study designs to be included:(1) cross-sectional studies,(2) longitudinal or cohort studies,(3) published studies up to September, 2015,(4) minimum age in sample - =18 years of age,(5) baseline sample includes general community-dwelling population rather than special groups at risk (e.g. coronary heart disease patients or nursing home),(6) main exposure variable is the individual's peripheral hearing status (as assessed by audiometric assessment),(7) full inclusion of hearing loss sample, i.e. no exclusion of those with more moderate-severe hearing loss,(8) assessment of one or more of the following outcomes:(a) standardised or adapted cognitive tests;(b) standardised assessment of cognitive impairment;(c) standardised assessment of dementia. (9) outcome measurements taken by health professionals or trained investigators but not based on self-report data, and(10) hearing loss assessed by health professionals, trained investigators but not based on self-report data. Exclusion criteria include the following:(1) review articles,(2) case-cohort studies,(3) case-control study designs,(4) case reports,(5) comments,(6) letters,(7) animal studies,(8) presentations from conference meetings,(9) unpublished studies (abstracts, master theses, dissertations, etc.), and(10) studies in which the outcome(s) were self-reported.

Condition or domain being studied

Peripheral acquired hearing loss and cognitive function, cognitive impairment and dementia

Participants/population

Adults with peripheral acquired hearing loss and cognitive or neuropsychological assessment of cognitive function, cognitive impairment or dementia.

Intervention(s), exposure(s)

The main exposure variable is the individual's peripheral hearing status. Only hearing assessment that reports the measured or average decibel threshold for one or more frequencies will be included. Self-report measures or other measures such as the whispered voice test will not be included. Studies diagnosing hearing loss by administering a pure-tone at a fixed decibel level will not be included, i.e. screening measures.

Comparator(s)/control
The non-exposed control group includes adults who have normal hearing status.

Context

Primary outcome(s)
The primary outcomes include:
(1) Cognitive function (cognitive tests will be allocated to one of several cognitive domains)
(2) Cognitive impairment
(3) Dementia

Secondary outcome(s)
None.

Data extraction (selection and coding)
Study Selection: Two researchers will independently screen studies for eligibility by reviewing the titles and abstracts of articles based on the pre-defined eligibility criteria. If the inclusion or exclusion criteria cannot be decided based on the title and abstract, full articles will be retrieved and the decision will be made accordingly. After independent study selection is performed, reviewers will review every selection for agreement and discrepancies will be resolved by consensus. If a decision cannot be achieved, a content area and clinical expert (Dr. B.A. Lawlor) will resolve any disagreement(s). A flow chart illustrating all included and excluded studies will be created. In addition, a list of all included and excluded studies will be provided as well as the reason(s) for exclusion.
Study coding: Using Microsoft Excel software (version 2011) we will develop a comprehensive codebook that can hold more than 200 items per study. We will code continuous variables, categorical variables and free text information. The codebook developed will be pilot-tested and revised as necessary. The lead author (D. Loughrey) will code or extract data from each selected article. The second author (Dr. M.E. Kelly) will independently check every data point for accuracy and consistency. Any disagreement will be discussed and resolved until 100% agreement is reached. If consensus cannot be reached, the content area and clinical specialist (Dr. B.A. Lawlor) will be consulted.

Risk of bias (quality) assessment
We will use the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) instrument to assess the quality of reporting of our included observational studies. Two researchers (D. Loughrey and Dr. M.E. Kelly) will conduct all assessments independent of each other. They will then compare their selections for accuracy and consistency. Inter-rater agreement will be assessed using Cohen's kappa statistic. Any disagreements will be discussed and resolved until 100% agreement is reached. If consensus cannot be reached, the content area and clinical expert (Dr. B.A. Lawlor) will be consulted to resolve the discrepancy.

Strategy for data synthesis
This is a meta-analysis using the aggregate data approach. There will be 6 meta-analyses - one for cross-sectional studies and one for longitudinal studies across three categories of outcomes – cognitive function, cognitive impairment and dementia.
Statistical Analysis: Descriptive Statistics will be generated for continuous [sample sizes, means, medians, standard deviations, standard errors, 95% confidence intervals (CI)] and categorical (frequencies and percentages) variables. For cognitive function we plan to allocate each cognitive test into a cognitive domain. These domains will be decided a priori in consultation with content area research and clinical specialists (B.A. Lawlor, and S. Brennan). We plan to use correlation coefficients (r) to examine the association of hearing loss with each cognitive domain. We planned to use risk ratios (RR), also known as relative risks as our effect size (ES) to examine the association between hearing loss and cognitive impairment and dementia. An ad hoc decision was made to use Odds Ratios instead. All ES will be converted to r or OR and

calculated using Comprehensive Meta-Analysis, version 3.0. We will use random-effects, method-of-moments models for pooling of the ESs. All the Fisher's Z or log ORs from individual studies will be summed together, which will give us the summary Fisher's Z or log OR. The summary Fisher's Z or logs OR will be used for all analyses and then converted back to the original metric, i.e., r and OR respectively. Forest plots will be used to visually display the estimated ES of each study and their corresponding 95% CI's. In addition, an overall pooled effect as well as 95% CI's will be calculated for each outcome. Furthermore, for cognitive impairment and dementia, 95% prediction intervals (PI's) will be used to estimate the RR boundaries in a new trial. Small-study effects (publication bias, etc.) will be assessed using a funnel plot and Egger's linear regression test. Influence analysis (sensitivity analysis) will be used to examine the effects of each study on the overall results. Cumulative meta-analysis, ranked by year, will be used to examine the accumulation of findings over time. Between-study heterogeneity will be assessed using I-squared statistics. Simple weighted least squares meta-regression (random-effects, method of moments approach) will be used to examine the relationship between each outcome and selected covariates. Planned covariates to examine a priori will include:
(1) country in which the study was conducted (USA, other),
(2) subject characteristics (age, sex, education, race/ethnicity),
(3) type of analysis,
(4) audiometric factors (frequencies and ear used),
(5) studies that examined the association between hearing loss and outcomes while controlling for demographic, vascular and psychosocial factors (e.g. depression),
(6) bias due to loss to follow up (longitudinal studies),
(7) time to follow up (longitudinal studies),
(8) test used to assess outcomes,
(9) test used to assess outcome accessible to a hearing loss population (visual, other),
(10) type of dementia (AD, other),
(11) smoking status/alcohol use,
(12) socio-economic status related variables.
(13) impact factor of journal in which study was published.

Analysis of subgroups or subsets

If a lack of data (fewer than 3 results for moderator analysis or 4 results for meta-regression analysis) exists for some of our predictor variables, for example, an insufficient number of studies that controlled for a vascular factor such as diabetes, we will examine our results with the few studies that did control for such things as diabetes deleted from the model to see if it has an effect on our overall findings. For categorical variables, less than three results for any one category will warrant such analysis. For continuous variables less than four results for any one category will warrant such analysis.

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Details of any existing review of the same topic by the same authors
There is no earlier version of this systematic review with meta-analysis.

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

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