HAVE YOU HEARD ABOUT HEARING LOSS, HEARING AID USE, AND COGNITIVE DECLINE: RELATIONSHIPS, MECHANISMS, AND A PROPOSED INVESTIGATION USING EVENT-RELATED POTENTIALS

by

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To my family: da chi sempre vi ama.

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ABSTRACT

This thesis summarizes and analyses the literature surrounding hearing loss (HL), hearing aid (HA) use, and cognition. While the literature investigating human cognition shows a clear relationship between HL and dementia the nature of this relationship is unclear. In animal research, there is a clear link between HL and hippocampal neurogenesis. This study details a proposed electrophysiology study investigating the Late-Positive Component (LPC). The LPC has been associated with the hippocampus, which degenerates early in the dementia disease process. Results from this study will show the importance of hearing health for overall cognitive health.

LIST OF ABBREVIATIONS USED

AD	Alzheimer's Dementia
ANOVA	Analysis of Variance
CAMCOG	The Cambridge Cognitive Examination
CES-D	Center for Epidemiological Studies Depression Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
DTI	Diffusion Tensor Imaging
ERP	Event-Related Potentials
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging
FUEL	Framework for Understanding Effortful Listening
HA	Hearing aid
HHIE-S	The Hearing Handicap Inventory for the Elderly Screening
HL	Hearing loss
LPC	Late-Positive Component
MMSE	Mini-Mental State Exam
MoCA	Montreal – Cognitive Assessment
MRI	Magnetic Resonance Imaging
MWM	Morris Water Maze
NIHL	Noise Induced Hearing Loss
RAM	Radial-Arm Maze
SADL	Satisfaction with Amplification in Daily Life
SMMSE	Short Mini-Mental State Exam
S-LP	Speech-Language Pathology
WMHs	White Matter Hyperintensities

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CHAPTER 1 INTRODUCTION

Canada's aging population is increasing, especially so in the province of Nova Scotia. It is estimated that by 2030, 1 in 4 Nova Scotians will be over the age of 65 (Nova Scotia Department of Seniors, 2017). The rates of both HL and dementia increase with age (World Health Organization, 2020, 2021). In 2016, an estimated 564 000 Canadians were living with dementia, but in 2031 that number is estimated to climb to 937 000 (*Prevalence and Monetary Costs of Dementia in Canada*, 2016). A staggering 1 500 000 adults between 45 and 85 in Canada were estimated to have some level of HL in 2016 (Mick et al., 2021). As our aging population continues to increase, both cognitive decline and HL will continue to have a great impact on Canadian society.

Research has shown that HL and dementia are not just increasingly common in aging populations, they are related. Researchers have found an independent association between HL and dementia (F. R. Lin, 2011). Furthermore, HL has been identified as the largest potentially modifiable risk factor for dementia (Livingston et al., 2020). Given the significant implications of these disorders, prevention is an important investment.

While the relationship between hearing and cognition has been well-studied, the mechanisms that underly this relationship are largely unclear in humans. There are several theories for this relationship. Some hypothesize that hearing and cognitive changes are caused by the same underlying factor, like vascular changes (F. R. Lin, 2011). Others hypothesize that sensory degradation, due to a decrease in input from the auditory system is causing neurological and cognitive changes (Desjardins, 2016). Some research has argued that a social factors may mediate the relationship between HL and

cognitive decline, but recent research has shown social factors have a limited impact on this relationship (Hämäläinen et al., 2019).

Animal research points to another possible explanation for the relationship between memory and hearing loss. Studies have shown that mice with HL have reduced hippocampal neurogenesis compared to mice with no HL (Liu et al., 2016, 2018; Zhuang et al., 2020). These hippocampal changes are accompanied by cognitive changes in learning and memory, as evidenced by worse performance on tasks like the Morris Water Maze (MWM) task (Liu et al., 2016, 2018). In humans, the hippocampus is also associated with various functions, including memory, and is one of the first structures to degenerate in dementia (den Heijer et al., 2010).

Hearing loss and cognition have been investigated using cognitive screening measures like the Mini-Mental State Exam (MMSE) (Acar et al., 2011; Dawes et al., 2015), or behavioral measures of cognition (Amieva et al., 2018; Desjardins, 2016; F. R. Lin, 2011). However, a wide variety of cognitive measures are used, and it is still mostly unclear how HL and cognition are related in humans.

One additional important factor in the relationship between HL and dementia is the use of HAs. Although the relationship between HL and cognitive decline has been well documented, the research examining HAs as a possible mitigating factor points to a less straightforward relationship.

In a study by Desjardins (2016) examining the effects of HAs on cognitive test measures. Researchers provided individuals with HL with HAs, and observed changes in their performance on various tasks from baseline. there were robust improvements with HA use for cognitive measures presented auditorily. However, visual task performance

did not tend to improve significantly. The author concluded that this could mean the potential transfer of cognitive benefits from HA use to non-auditory domains may be limited, and cognitive benefits may only be present for auditory measures.

Furthermore, a scoping review examining visual and hearing interventions to improve outcomes for individuals with dementia found that the evidence of HA use improving cognitive decline was limited (Dawes et al., 2019). This review concluded that more research examining the effects of HA use on cognition is necessary. If HAs can reduce the impact of HL on cognition, they are a potential preventative measure against cognitive decline.

Neuroimaging research can provide insight into how behavioural changes can be associated with functional neurological changes. Event-related potentials (ERPs) are a measure of the electrophysiological activity of the brain in response to a specific event or stimulus (Kolb, 2003). Individual responses to a specific stimulus are averaged over multiple participants and trials, until specific patterns called components are revealed. These components can be related to specific cognitive functions like memory. ERPs give excellent temporal resolution for functional neurological responses, but do not on their own reveal information about specific neurological structures implicated in particular cognitive processes. However, pairing functional magnetic resonance imaging (fMRI) with ERPs can link structural and functional neurological information (Luck, 2014).

One study where simultaneous ERP and fMRI were conducted revealed interesting information about recognition memory, the late-positive component (LPC), and hippocampal activity (Hoppstädter et al., 2015). The researchers observed an increase in positive electrical activity 580 – 750ms after presentation of a word that participants

recognized. Furthermore, the LPC was associated with an increase in hippocampal activity on the fMRI. Therefore, the LPC component is an electrophysiological response that is associated with the hippocampus.

This thesis will detail the relationship between HL, HA use, and cognition. Potential mechanisms underlying this relationship, from both animal and human models, will be discussed. A potential experiment using the LPC to investigate the changes in recognition memory due to HL and HA use will be outlined. This ERP research would further our understanding of a specific neurological change associated with hearing loss. It would also provide evidence that hippocampal changes, similar to those observed in mice, underly the relationship between HL and cognition in dementia. Potential implications of this proposed research, including clinical implications, will be discussed.

CHAPTER 2 AN OVERVIEW OF HL, HA USE, AND COGNITION

Research has shown HL and HA use have an influence on cognition. Epidemiology studies have shown HL to be independently associated with cognition (F. R. Lin, 2011; F. R. Lin, Ferrucci, et al., 2011). These studies have investigated the relationship between HL and various other related factors, including multisensory impairment (Brenowitz et al., 2019), and depression (Amieva et al., 2018). Furthermore, HL has been identified as the largest potentially modifiable risk factor for dementia(Livingston et al., 2020). There is some evidence supporting HL as a preventative measure for cognitive decline.

Another area of research involves if HL treatment can affect cognitive decline. Various considerations are important in this relationship, such as dosage of HA use (Doherty & Desjardins, 2015). The modality of the tasks used to measure cognitive abilities may also have an impact (Desjardins, 2016).

2.1 The Relationship Between HL and Cognition

2.1.1 Literature Summary

The relationship between HL and cognition has been proven in many large-scale epidemiological studies. This association has been shown to be independent of other risk factors such as cardiovascular disease, or age. While HL is often present with these other risk factors, research has shown that HL itself has a significant effect on cognitive decline.

A seminal study showed HL is independently associated with dementia (F. R. Lin, Metter, et al., 2011). This study of 639 participants without dementia aged 36 to 90 measured hearing levels in participants, and examined their dementia diagnoses an

average of 11.9 years later. Hearing was measured using pure-tone audiometry at 0.5, 1, 2, and 4 kHz, and was classified as normal (<25dB), mild HL (25-40dB), moderate HL (41-70dB), and severe (>70dB). Dementia diagnoses was determined using neurological and neuropsychological assessments, and guidelines from the DSM-3 (Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition). The analyses used cox proportional hazard models and analyses of variance to examine the relationship between of dementia diagnoses and HL. In this study, hazard ratios analyzed the time to dementia diagnosis in relation to the severity of hearing loss, adjusting for a variety of potential confounds like age, race, and hypertension.

The results showed that HL was independently associated with incident dementia. Furthermore, greater levels of HL were linearly associated with higher hazard ratios of incident dementia. In comparison with normal hearing thresholds, mild HL had a hazard ratio of 1.89 for incident dementia, moderate had a higher hazard ratio of 3.00 and severe HL had the highest hazard ratio of 4.94.

Another study that used cox proportional hazard models to identify risk of dementia diagnosis with HL found similar results. This French study followed 3 777 participants 65 years and older for a period of 25 years (Amieva et al., 2018). In this study, both HL and HA use were self reported. Cognitive status determined using MMSE, as well as dementia diagnoses. Other factors like depression, and disability were measured in this study by using the Center for Epidemiological Studies Depression Scale (CES-D), and activities of daily living.

This study found that dementia and disability risk were increased with self-reported HL, with adjustments for sociodemographic factors. In male participants, there

was also an increased risk of depression with self-reported HL. Therefore, even self-reported measures of HL are associated with an increased risk of dementia.

Self-reported hearing difficulties, objective measures of HL and physician diagnoses of dementia were investigated using data from the English Longitudinal Study of Ageing (Davies et al., 2017). This study of 7 865 adults examined self-reported HL using a questionnaire, and a hearing screening to objectively investigate HL. Using these measures, hearing was classified as moderate or poor (severe to profound HL).

The results showed both objective and subjective measures of HL were related to increased dementia diagnoses in participants. Severity of HL impacted rate of dementia diagnoses. Participants with moderate self-reported hearing had a 39% higher increase in dementia diagnosis, and those with poor hearing had a 57% higher rate of dementia diagnoses over an 11-year period than participants with normal hearing thresholds.

Self-reported hearing loss can also be related to subjective measures of cognitive function. An 8 year longitudinal study of 10 107 men aged 62 or older investigated subjective cognitive function and self-reported hearing loss (Curhan et al., 2019). This study used questionnaires to determine subjective cognitive function and HL. This measure of cognitive decline was subjective, therefore it could be variable between individuals as a result of variables such as self-monitoring, or comfort reporting health issues. However, Curhan and colleagues (2019) stated that it may reflect subtle early cognitive changes noticed by the participants that may be undetected on standardized cognitive tests.

The results of this study showed that HL was associated with increased risk of subjective cognitive decline. The multivariable adjusted relative risk increased with

greater levels of HL, with mild HL at 1.3, moderate at 1.42, and severe HL at 1.54. This analysis did show a significant relationship between subjective HL and cognitive difficulties. However, limitations of this study include the subjective nature of the measurements, as well as the sample which only included white male healthcare professionals.

In addition to diagnoses of dementia, and self-reported cognition there is also a relationship between HL and individual cognitive abilities. A study of 605 adults aged 60 to 69 investigated hearing loss, as measured through pure-tone audiometry, and the Digit Symbol Substitution Test (DSST), a nonverbal measure of executive function and processing (F. R. Lin, 2011). The analyses used regression models to determine the relationship between HL, cognition, and confounding factors like demographics.The results of this study showed that HL was associated with significantly lower scores on the DSST. Furthermore, a hearing loss of 25 dB HL was equivalent to the effects of 7 years of aging on cognition.

The influence of HL on incident dementia as well as cognitive changes to memory, perceptual speed and processing speed has also been investigated. A study of 929 participants aged 70 – 79 investigated HL using pure-tone audiometry, and incident dementia diagnoses (Deal et al., 2017). Perceptual speed was measured using The Pattern Comparison Test and Letter Comparison Test. Verbal memory was examined using the Buschke Selective Reminding Test. The Boxes Test and Digit Copying Test measured psychomotor speed.

A relationship between HL and increased of incident dementia diagnosis was found for a 9 year follow-up period. However, only working memory and HL had a

relationship during 7 years of follow-up cognitive testing. While there appears to be a clear relationship between risk for and diagnosis of cognitive decline and HL, the impacts of HL on individual cognitive domains are more complex.

The impact of HL on cognitive decline is further impacted by the presence of other sensory disorders. One study of 1 810 participants without dementia tested vision, hearing, smell, and touch and investigated the role impact of sensory impairment dementia diagnosis 10 years later (Brenowitz et al., 2019). Results were adjusted for demographics, and other comorbid health conditions (e.g. cardiovascular disease). The most common sensory impairment was HL, with 35% of participants having HL. Multisensory impairment involving two impairments was present in 26% of participants, and three or more impairments was present in 5.6% of participants.

The results showed that dementia was most strongly associated with smell, and moderately associated with hearing and touch impairments. The risk of dementia showed a graded increase with multiple sensory impairments. In patients with 3-4 sensory impairments, the risk of dementia was nearly 3 times higher than participants with no sensory impairment, and 2 times higher than participants with a single sensory impairment. Therefore, HL on its own is associated with an increased risk of dementia, but other sensory impairments can compound the risk.

Data from the Canadian Longitudinal Study on Aging has shown that the prevalence of HL and vision loss in Canadians increases significantly with age (Mick et al., 2021). When their data is scaled to the entire Canadian population aged 45-85, 4 000 000 Canadians had at least mild vision loss, 2 700 000 had at least mild HL (pure-tone average >25 dB HL), and 1 100 000 had a minimum of mild impairment in both senses.

The high incidence of single and dual sensory impairments in Canadian adults has a significant implication on the cognitive function of older Canadian adults.

2.1.2 Hearing Health and Prevention

Given the relationship between HL and cognition, there is a significant potential impact of hearing health on cognitive health. A report from The Lancet Commissions discussing significant factors in dementia prevention and treatment highlighted the importance of hearing health (Livingston et al., 2020). The report directly addresses the misconception that dementia is an inevitable consequence of getting older. Instead, dementia risk can change with various risk factors, including lifestyle factors that are modifiable. This report modelled different risk factors for dementia, as well as the estimated effect that modifying these risk factors would have on dementia. One measure, the population attributable fraction, is an estimate of the percentage of new cases that would be reduced if a risk factor was eliminated.

Hearing loss was identified as the largest potentially modifiable risk factor for dementia. Furthermore, population attributable fraction calculation of hearing loss was 8%. For comparison, the population attributable fraction for obesity was 1%, depression was 4%, and social isolation was 4%. These results of this model have significant implications for the role of hearing health in cognitive health, as HL has not been widely recognized as a risk factor for cognitive decline. This report was the first time HL was included in calculations of the population attributable fraction of dementia risk factors. Hearing health must be a priority in the prevention of cognitive decline.

One way to include hearing health in preventative efforts to improve cognitive health is through hearing screenings. A study of 123 adults with hearing loss, and 20

controls investigated a potential audiological screening to identify individuals at risk for cognitive decline (Castiglione et al., 2019). Hearing was measured using pure-tone audiometry, the Italian Matrix Sentence Task, and speech audiometry including speech-in noise ratios. Cognition was assessed by neurologists and geriatricians using various measures like the MoCA (Montreal – Cognitive Assessment), and DSM-5 guidelines. Participants with a family history of cognitive decline were excluded to avoid a confound of genetics.

The results of this study showed a significant correlation between cognitive measures, like the MoCA, and speech-in noise ratios. Overall, hearing screenings for individuals with mild to moderate HL would complement cognitive screenings for individuals at risk of cognitive decline. Comprehensive audiological assessments after the age of 55 may also help identify patients at risk of cognitive decline. In summary, audiological assessment, through screenings or full evaluations as indicated, is one step in identifying risk for cognitive impairment. Given HL is a risk factor for dementia, identifying HL is an important step in understanding the auditory and cognitive profiles of individuals.

2.1.3 Summary

Research has demonstrated that HL and dementia are independently associated (F. R. Lin, Metter, et al., 2011). The relationship between HL and cognition is present in studies that use various methods of measuring both HL and cognition (Amieva et al., 2018; Curhan et al., 2019; Deal et al., 2017; F. R. Lin, Ferrucci, et al., 2011). Many of these analyses have also adjusted for demographics, and other confounding factors such as cardiovascular disease (Amieva et al., 2018; F. R. Lin, Ferrucci, et al., 2011).

Furthermore, HL is a large but underrecognized area of dementia prevention (Livingston et al., 2020). In addition to being preventable, HL is treatable, and that may impact cognition.

2.2 The Relationship Between HAs on Cognition

While HA companies are advertising the potential benefits of HAs for auditory health and cognitive health (Starkey, 2020), the research examining the effects of HA use on cognition indicates there is a complex relationship between these two factors. The association between HL and cognition has implications for our treatment of hearing loss, the impact of HA use on cognition also has implications on the nature of the relationship between HL and dementia. If HL is impacting cognition due to understimulation, which some call the sensory deprivation, HA use would impact cognition because it is increasing sensory input, and thus cognitive stimulation (Kalluri & Humes, 2012; Tesch-Römer, 1997). However, if HL and cognitive changes are due to age-related physiological changes in neural structures, simply increasing sensory input may not necessarily have an impact on cognitive outcomes.

Cognition is complex, and encompasses mental activities like attention, memory, and executive function. Section 2.2.1 summarizes the types of cognitive abilities that are measured in investigations of HA use and cognition. It also includes the various procedures that are used to assess these aspects of cognition. The measure of cognition, as well as the modality of the measure (i.e. visual or auditory), are key variables to consider in studies of HA use and cognition.

This section also discusses whether the current evidence for improved cognition with HA use is related to short-term or long-term effects. The length of the effects of HAs

on cognition has implications on HA use as a preventative strategy for cognitive decline. While short-term gains in cognition or even stable cognitive levels are more favourable than cognitive decline, they may not be as significant in a long-term preventative dementia strategy. In addition, this section will also discuss the implications of the lasting effects of these cognitive changes on the nature of the relationship between HA use and cognition.

In the next section of this chapter, a discussion of relevant factors that may affect the relationship between HA use and cognition. This includes factors specific to the participant's HA use including hours of wear, and HA satisfaction. Other factors outside of the domain of HA use, like physical health status, mental health status, and social determinants of health will be discussed. In addition, the directionality of the relationship between HA use and cognition will be discussed. This chapter will conclude with a summary of key findings, and a discussion of HA use and cognition.

2.2.1 A Summary of How Cognitive Abilities are Studied in Research Examining HAs and Cognition

The research examining HL and cognition includes a variety of different measures of cognition. In general, these can be divided into three categories. The first category includes measures of different cognitive domains or components of cognition. Most commonly, these include the following cognitive areas: working memory (Desjardins, 2016; Doherty & Desjardins, 2015; Lunner, 2003; Lunner et al., 2009), executive function (van Hooren et al., 2005), selective attention (Desjardins, 2016; van Hooren et al., 2005) processing speed (Desjardins, 2016; Lunner, 2003; Lunner et al., 2009; van Hooren et al., 2005), and learning (Choi et al., 2011; Dawes et al., 2015; van Hooren et

al., 2005). The second way researchers measure cognition is by using clinical screenings of cognitive function. This most often is the Mini-Mental State Exam (MMSE) (Acar et al., 2011; Dawes et al., 2015; Tesch-Römer, 1997). Finally, researchers can examine if HA use is related to later-diagnoses of dementia (Amieva et al., 2018; Dawes et al., 2015; F. R. Lin, Metter, et al., 2011; Mahmoudi et al., 2019).

While there are different ways of measuring cognition, it is important to consider that this is a source of variability in the findings surrounding HL and cognition. For example, in a review by Kalluri & Humes (2012) they found that of the 7 studies examining the long-term effects of HAs on cognition, 3 of the studies that found a significant effect of HL on cognition measured cognition using clinical dementia screening tools. The studies of tasks that examine more discrete cognitive abilities, like individual measures of memory or attention tended not to show a statistically significant effect of HA use on cognition.

A wide variety of cognitive tasks have been used in studies of HL and individual cognitive components. This has included a variety of tests of memory. The Auditory Verbal Learning Test (Schmidt, 1996), an auditory measure of short-term verbal memory and learning, has shown no effect of HA use on participant's scores (Dawes et al., 2015). Results for the Visual Verbal Learning Test (Brand & Jolles, 1985), a visual measure of short-term verbal memory and learning, have had mixed results. While one study showed no effect of HA use on test scores (van Hooren et al., 2005), a more recent study has shown improvement on measures of short term memory, but not latency (a measure of efficiency), in participants who used HAs (Choi et al., 2011).

Studies examining working memory have found mixed results. The Listening Span Test (Daneman & Carpenter, 1980) is an auditory measure of working memory. In a single-subject design conducted by Desjardins (2016) 4/6 participants had a high or moderate increase in their scores after several weeks of HA use. Another study found that participants who completed a Listening Span Test in a background noise condition had improved scores after a period of HA use (Doherty & Desjardins, 2015). However, participants who completed the visual Reading Span Test (Rönnberg et al., 1989) had no significant changes in their scores after HA use (Desjardins, 2016).

The Auditory N-Back (Monk et al., 2011) is a cognitive task that examines the executive component of working memory. There was a significant improvement in performance on this task in older adults (63 – 74 years of age) with HAs, but not in middle-aged adults (50 – 60 years of age) with HAs in one study (Doherty & Desjardins, 2015). Therefore, working memory tasks have shown variable improvement with HA use. In general, visual tasks have been the least sensitive to improvement with hearing aid use. Factors such as age, as well as listening condition, have affected participant performance.

The next series of cognitive tasks are processing tasks which examine cognitive speed, flexibility, and visual-perceptual processing. The Trail Making Test (Bowie & Harvey, 2006) is one visual-motor processing test that has been used in the literature. A study by Dawes and colleagues (2015) has shown no significant benefit of HA use. The Concept Shifting Task (Vink & Jolles, 1985) is a modified version of the Trail Making Test. Participant scores on this task also did not improve with HA use (van Hooren et al., 2005).

The DSST (Wechsler, 1991) is a perceptual processing task that has been used in several studies of the cognitive effects of HA use. However, most studies not have found that HA use had an effect on participant performance on this task (Dawes et al., 2015; Desjardins, 2016; Tesch-Römer, 1997; van Hooren et al., 2005). One study showed an increased in DSST scores with hearing aid use (F. R. Lin, 2011). In summary, these processing tasks, presented in the visual modality, have shown mixed improvements with HA use.

Selective attention is another area of cognition that has been examined in the research on HL and cognition. The Coordinate Response Measure Corpus (Bolia et al., 2000) has been used in one study to examine auditory selective attention. This single-subject design found a moderate to high improvement in this task for all participants after 2 to 4 weeks of HA use (Desjardins, 2016).

The Stroop Task (Stroop, 1992) is a measure of visual selective attention and executive functioning. In two studies, there was no improvement on this task with HA use (Desjardins, 2016; van Hooren et al., 2005). Similar to working memory, it appears that the modality of the selective attention task has been an important factor. Improvement on selective attention tasks after HA use has only been present in auditory, not visual measures of selective attention.

Finally, the research has also included some language-based measures of cognition. A Spot-the-Word Task (Lehrl, 1977) had German participants choose a which word was a real-German word in the presence of four distractor non-words. A study by Tesch-Römer (1997) showed no significant differences in performance on this task in

HA users compared to age-matched hearing-impaired participants without HAs, and a control group.

Verbal Fluency Tasks (Lindenberger et al., 1993; Strauss et al., 2006) require participants to name as many words in a category as they can in 60 seconds. This task has been used in a various studies of HA use and cognition, all of which showed no effect of HA use on participant scores (Dawes et al., 2015; Tesch-Römer, 1997; van Hooren et al., 2005). Therefore, none of these linguistically-based measures of cognition have shown an improvement in participant scores with HA use.

The literature examining HA use and cognition using clinical screening tools has shown mixed results. The MMSE is a cognitive screening tool for cognitive impairment (Folstein et al., 1975). One study with 34 participants reported an increase in MMSE scores from an average of 20.3 to 23.0 after 3 months of HA use (Acar et al., 2011) . However, a much larger study which investigated cognition in 666 adults with hearing impairment found no difference in MMSE scores at follow-up after 5 and 11 years of HA use (Dawes et al., 2015). These findings are in line with a study by Tesch-Romer (1997) that showed no effect of HA use on MMSE after 6 month hearing use.

Finally, the effects of HA use on cognition has been studied by examining if HA use delays or mitigates the risk of dementia diagnosis. If HAs can be used as preventative measures for cognitive decline, HA use would ideally delay or prevent dementia diagnosis. In the previously described studies by Lin and colleagues, self-reported HA use was not associated with any reduction in dementia risk (F. R. Lin, Metter, et al., 2011). In contrast, research by Amieva and colleagues also used self-reported hearing aid use and found a that while there was an relationship between HL and dementia, this risk

was not present in individuals who wore HAs (Amieva et al., 2018). Therefore, the effects of HA use on reduction of dementia risk is unclear.

Although HA use may not reduce risk of dementia, perhaps the use of HAs could delay dementia diagnoses. A study of 666 adults by Dawes and colleagues (2015) did not find that HA use delayed dementia diagnosis. However, an even larger study with over 100 000 participants showed that the use of HAs delayed diagnosis of dementia and other age-related conditions like falls and depression (Mahmoudi et al., 2019). As Mahmoudi and colleagues (2019) state in their analysis, their study was retrospective in nature so causality cannot be inferred. Therefore, while there is some indication that HA use may somewhat delay dementia diagnoses, the nature of the relationship unclear.

In addition to considering what aspects of cognition improve with HA use, and how cognition is measured, it is important to consider if the effects of HA use improve cognition over the long-term or the short-term. Short-term benefits could indicate that HA use simply benefits the auditory sensory system, as opposed to the overall cognitive system (van Hooren et al., 2005).

A review by Kalluri & Humes (2012) examined this exact question, and defined long-term studies as those examining HA use from 3 – 24 months, while short-term studies generally examined hearing aid use for a period equal to or less than 2 months. In their review, they found that the short-term effects of HA use were more clearly beneficial. While just under half of the studies examining long-term effects of HA use on cognition have shown an effect of HA use on cognition, these studies had used gross-dementia measures of cognition instead of more rigorous examinations of cognition.

Long-term studies have shown variable results. The two studies that have been previously discussed examining HA use over a period of several years had significantly different results (Dawes et al., 2015; Mahmoudi et al., 2019). It does appear from the literature review conducted for this thesis that many studies examining hearing-aid for a time period of less than 1 year have shown some effect of HA use on cognition (Acar et al., 2011; Choi et al., 2011; Desjardins, 2016; Doherty & Desjardins, 2015). However, other studies examining HA use over similar time periods have shown no effect of HA use on cognition (Tesch-Römer, 1997; van Hooren et al., 2005). Some studies had investigated HA use over the same time period, for example 6 months, but had found different results (Choi et al., 2011; Tesch-Römer, 1997).

Therefore, while the research does generally support some short-term cognitive gains after HA use, this is one of many other complex variables to consider in analyzing these studies. Factors like the type of cognitive tasks used, as well as study and participant characteristics must also be considered.

2.2.2 Other Influential Factors: HA Characteristics and Participant Characteristics

Adding to the complexity of interpreting these studies is that HA use can be variable, and this variability has often not been described in the literature. Factors like hours of daily HA use, and HA fit could be responsible for the variations seen in the literature. In addition, the characteristics of the person wearing the HA must be considered.

As will be discussed in this section, factors like an individual's baseline cognitive ability can affect their ability to use certain HA features like noise-reduction (Lunner et

al., 2009). This is a crucial consideration, because it is another potential source of variability in research examining the impacts of HA use on cognition. . If participants require a certain cognitive capacity to fully use various HA features, it is possible that to benefit from HA use participants must have a baseline level of cognitive abilities.

Variables related to HA use include daily HA use, HA care skills, HA fit, HA satisfaction, and hearing handicap. Not all studies have reported these factors, but of those that did there has been relationship between these HA factors and cognitive outcomes. Considering the variable of HA use, studies that have reported HA use of 6.6 to 8 hours daily have shown no cognitive effect of HA use (Tesch-Römer, 1997; van Hooren et al., 2005). While a study that reported an average of 12 hours of daily HA use has found increases in auditory working memory as a result of HA use (Doherty & Desjardins, 2015).

HA care and maintenance is another important variable, as participants likely will not benefit from their HAs if they are unable to properly care for them. One measure of HA skills is the Practical HA Skills Test – Revised (Doherty & Desjardins, 2012). In two studies that have used this test to ensure participants were properly maintaining their HAs, positive effects of HA use on auditory cognitive tasks have been found (Desjardins, 2016; Doherty & Desjardins, 2015).

HA fit is another variable that is often not reported in studies examining HA use and cognition. HA fit determines if the participant's HA amplifies sound sufficiently across a range of frequencies to result in acceptable audibility. In studies where HA fit has been measured, there has been positive effects of HA use on certain cognitive measures (Desjardins, 2016; Doherty & Desjardins, 2015).

In addition to HA fit, which is measured by quantitative audiological standards, there are functional measures of everyday communication improvement as a result of HA use. For example, The Hearing Handicap Inventory for the Elderly Screening (HHIE-S) is a functional measure of hearing-related disability (Ventry & Weinstein, 1983). The HHIE-S had a greater predictive value for quality of life than pure-tone audiometry when measured 10 years after assessment (Gopinath et al., 2012). In addition, increased HA use has been related to reduced hearing handicap scores and increased HA satisfaction (Gopinath et al., 2012; Tesch-Römer, 1997). However, two studies that reported HHIE-S scores did not find a link between HA use and improved cognitive performance (Dawes et al., 2015; Tesch-Römer, 1997)

In summary, HA use is not a binary variable, and there are several characteristics like hours of daily use, HA fit, HA maintenance, and HA handicap which must be considered. While it is not standard to report these variables in the literature, research that has reported these variables has shown their potential impact on the relationship between HA use and cognition. Studies that reported HA use, HA fit, and HA maintenance have shown improvements on some cognitive tasks with HA use. However, the research that has quantified HA handicap has generally not shown a relationship between HA use and cognition.

In addition to the variety of factors related to HA use, HAs have been shown to affect a variety of areas in addition to cognition. One study by Acar and colleagues (2011) found that HA use improved participant's scores on the Geriatric Depression Scale – Short Form. HAs also delayed diagnoses of depression and anxiety, as well as reducing falls in the elderly (Mahmoudi et al., 2019). These relationships are complex as

depression, falls, and anxiety are also related to cognitive decline (Acar et al., 2011; Mahmoudi et al., 2019). However, one retrospective study (Mahmoudi et al., 2019) did not control for other factors like income, which could have confounded the results given that socio-economic status and income are a significant social determinant of health.

Another interesting consideration is that a person's cognitive abilities could impact their ability to successfully use various features of a HA. A detailed review by Lunner and colleagues (2009) described various HA features like microphone directionality and noise reduction in terms of the benefits they provide, but also the cognitive skills required for them to be beneficial. For example, a person with high working memory may tolerate more distortions and aggressive noise reduction.

A study by Desjardins & Doherty (2014) found that participants with faster information processing used less effort when noise reduction was activated automatically by their HA in a difficult listening condition. A similar study showed that cognitive function correlated with performance in difficult listening conditions, and concluded that cognitive function may affect an individual's ability to adjust to different settings and listening changes (Lunner, 2003). Therefore, an individual's baseline cognition may impact their ability to successfully use the various features of a HA, which could lead to differences in cognitive outcomes with HA use.

2.2.3 Summary

This section has discussed the literature surrounding HA use and cognition, as well as highlighted various factors that may influence this relationship. Overall, studies that have used clinical measures like the MMSE or time of dementia diagnosis have shown mixed results of HA use on cognition. However, the nature of this relationship, as

well as the causality, is unclear. Measures of individual cognitive abilities like working memory, processing time, or selective attention have helped determine what specific impacts HAs have on cognition. In general, auditory measures of cognition have been more sensitive to the effects of HA use.

When interpreting these results, it is important to consider HA as well as participant characteristics. While often not reported in the literature, quantitative and qualitative measures of HA use such as daily HA use, HA skills, hearing handicap, and HA fit have been associated with different outcomes. Specifically, studies where participants have a higher number of hours of daily HA use, have demonstrated skillful HA maintenance, and have measured HA fit also show some cognitive benefit of HA use. HA use has also been shown to reduce other conditions associated with dementia like depression, and falls, however the directionality of this relationship is unclear and confounds like income complicate these findings. Finally, successful use of HAs may rely on certain cognitive skills, mainly in the area of processing, which further complicates measuring the impact of HAs on cognition.

CHAPTER 3 POTENTIAL MECHANISMS

The previous chapter discussed the relationship between HL, HA use, and cognition. While these factors have a relationship, the nature of the relationship is mostly unknown. This section aims to discuss possible explanations of why HL and cognition may be related.

This chapter will discuss the animal research that examines the relationship between HL and cognition. Firstly, section 3.1.1 will summarize how the cognitive function was changed as evidenced in the measures like the Morris Water Maze (MWM) (Cheng et al., 2011; Liu et al., 2016, 2018; Tao et al., 2015), the radial-arm maze (RAM) (Kim et al., 2006; Park et al., 2018), and novel object recognition (Park et al., 2018) tasks in mice with hearing loss. Secondly in section 3.1.2, the associated neurological changes in the hippocampus after noise exposure and/or HL will be discussed. This will include a discussion of why a decrease in hippocampal neurogenesis related to hearing loss, as opposed to oxidative stress, is likely the key factor causing these hippocampal changes (Liu et al., 2016, 2018). Lastly, the key points relating to the mechanisms behind HL and cognitive changes will be summarized.

In section 3.2, the various mechanisms that have been investigated in the human research on HL and cognition will be discussed. This includes various hypotheses such as the common-cause hypothesis, the role of social factors, the information-degradation hypothesis, and the sensory-deprivation hypothesis. Neurological changes associated with HL and cognition will be discussed. These changes were investigated using various

methods, like functional and structural neuroimaging (Mudar & Husain, 2016), and neuropathology (Parker et al., 2020).

Section 3.3 will link the animal and human models of hearing loss, through the potential influence of HL on the human hippocampus.

3.1 Animal Mechanisms Research

3.1.1 Behavioural Research

Investigations of HL and cognition in humans use a variety of tasks that measure different aspects of cognition like memory, processing, and attention. In the animal research that investigates HL and cognition, three tasks have been used: the MWM, the RAM, and an object recognition task. While this section will focus mostly on neurological mechanisms, not behavioural results, the effects of HL on animal performance on each of these tasks will briefly be discussed to connect changes in cognitive to neurological changes.

The most used task in the research of related topic is the MWM task, a task that is used to measure learning and spatial memory (Vorhees & Williams, 2006). In this task, rodents swim in a pool with four quadrants to find the target quadrant with a hidden platform so they can escape from the water. In cued versions of the MWM task, signs are placed around the pool as spatial cues. Through the training, the animal learns how to use signs around the pool to locate the platform. While there are various methodologies and variations of the MWM task, the key variables for measuring spatial learning and memory are as follows. Learning is usually measured with three key variables: latency (the time from the start of the task to the end), path length (distance from the start to end

of the task), and cumulative distance (path length over latency) (Vorhees & Williams, 2006).

Spatial memory is typically measured by a spatial orientation test after the cued session. In this test the escape platform is removed. Then some measure of preference for the target quadrant where the platform was previously located is measured as an indicator of memory. These measures can include number of swims across the target quadrant, total distance swam in the target quadrant, and total amount of time spent swimming in the target quadrant (Vorhees & Williams, 2006). This measure is an indication of preference for the previous location of the escape platform, and thus interpreted as an index of memory (Vorhees & Williams, 2006).

The majority of animal studies showing cognitive changes due to noise exposure and/or Noise-Induced Hearing Loss (NIHL) [1] used the MWM task. Furthermore, NIHL and/or noise exposure was associated with decreased performance on both the learning and memory variables of the MWM task.

Learning was generally related to the variables of latency and path. Researchers found an increase in latency (Liu et al., 2016, 2018; Tao et al., 2015), and a longer path (Liu et al., 2016) for mice with NIHL compared to control groups. Mice exposed to moderate noise for 2 hours daily also had a longer latency and path compared to mice in a control group (Cheng et al., 2011). Therefore, these results indicate that learning, as measured by the MWM learning-related variables of latency and path, is impaired in mice with NIHL and noise-exposure.

[1] In some studies, noise-exposure was a key variable but hearing level after noise exposure was not measured. To maintain accuracy during this analysis those studies will refer to 'noise exposure'. Studies where hearing level was a measured variables will refer to 'NIHL '.

Memory measures in the MWM task were also impacted by NIHL and/or noise exposure. Mice exposed to impulse noise had fewer swims across the quadrant where the platform was previously located compared to mice in the control groups (Cui et al., 2011). Mice with NIHL also had fewer crossings of the target quadrant than controls (Liu et al., 2016, 2018; Tao et al., 2015). Furthermore, mice in the NIHL group swam less distance in the target platform quadrants than mice in control groups (Liu et al., 2018). The time mice exposed to impulse noise spent in the target quadrant was significantly less in some studies (Cui et al., 2011). Therefore, the mice with NIHL and/noise exposure spent less time in the target quadrant, had fewer swims across the target quadrant, and swam less distance in the target quadrants than controls. These results indicate that spatial memory measures of the MWM task are also impaired in mice with NIHL and/or noise exposed mice.

The decrease in performance of mice with HL on the MWM task is also seen in mice with age-related hearing loss, or presbycusis—not just NIHL. A study by Yu and colleagues (2011) used two strains of mice, with the most significant difference between the strains being their hearing ability. The study examined groups of two types of mice, C57BL/6J and CBA/CaJ, at three time periods: 6-8 weeks, 24-26 weeks, and 42-44 weeks. The C57BL/6J mice had elevated hearing thresholds starting at 24-26 weeks, and by 42-44 weeks profound HL had developed. The other type of mice were CBA/CaJ mice, who had only slightly elevated hearing thresholds at 24-26 weeks, and mild HL at 42-44 weeks.

The behavioral results of the MWM task showed the C57BL/6J had worse learning and memory performance in the MWM task, at the 42-44 week time period. The

CBA/CaJ mice had a shorter latency, indicating better learning. At 43-44 weeks, the CBA/CaJ mice also had more crossings in the target quadrants compared to the C57BL/67 mice. Therefore, the behavioral results of the MWM task appear to vary between these two strains of mice, with the most significant difference between these strains being their hearing levels. Since differences in genetic background exists between the two strains of mice, this research provides limited evidence how presbycusis impacts learning and memory. Ideally, the comparison should be made between mice in the same strain but with and without presbycusis. Given that the deficient gene for presbycusis in C57 mice has been identified, and a version of this mouse with this gene corrected has been available, such a design is practically doable.

Another spatial learning task that is used in research investigating the relationship between HL and cognition in mice is the Radial-Arm Maze (RAM). This task involves animals locating food pellets or water at the end of a platform with 8 arms (Fujioka et al., 2001). The studies in this review used working-memory error (entry into an incorrect arm that was previously visited) (Kim et al., 2006; Park et al., 2018), correct entry ratio (the number of correct entries into the target arm divided by the number of total entries) (Park et al., 2018), and the number of correct choices before the first error was recorded (Kim et al., 2006) as the key measures for this task. Park and colleagues (2018) indicated that RAM performance was specifically related to working memory.

One study investigated the performance of three groups of mice with different prenatal auditory stimulus exposures on the RAM task, which was conducted 21 days after birth (Kim et al., 2006). The noise group was exposed to 95 dB[2] of noise daily for

[2] The decibel scale used was not specified by researchers.

one hour from the 15th day of pregnancy to delivery, the music group was exposed to 65 dB of music for 1 hour daily, and a control group was raised in a quiet environment. Mice with noise exposure in utero made more errors and took longer to find the target arm than rats exposed to music in utero, and a control group, when tested 21 days after birth. Hearing levels were not reported in this study, however the researchers compared the rats exposed to noise, music, and the control group. The noise exposure group of rats had the most errors, and had the highest number of errors compared to the control and music-exposed group. The researchers concluded that the noise exposure in utero caused deficits in spatial learning in the rats, as evidenced by their reduced performance on the RAM task.

In another study the performance on the RAM was found to be related with the HL and developed slowly after NIHL was established. In this study, poorer performance was not seen in the NIHL group immediately after noise exposure. Instead, a significant decline was seen in the NIHL group 9 months after the noise exposure, when the threshold shift in this group was significantly higher than the control group on all measures (Park et al., 2018). Twelve months after noise exposure, the hearing thresholds of the NIHL mice had improved to the point of full recovery as measured in ABR by clicks and 32 kHz tone bursts. At this 12-month time point, no difference was seen between the groups in the RAM task. Therefore, the deterioration of the NIHL group on the RAM task was not permanent.

In the same study by Park and colleagues (2018), an object recognition task was used to assess episodic recognition memory. Interestingly, performance on the object recognition task was poorer in the NIHL group 12 months after noise-exposure. Authors

concluded that the effect of HL on recognition memory was permanent, while the working memory impairments tested in the RAM task were reversible. Working memory impairment, as measured using the object recognition task, was less 'reversible' than spatial memory effects, as measured by the RAM. Therefore, the type of memory being measured in experimental tasks is an important factor when studying cognition.

The research reviewed above supports the idea that NIHL and presbycusis can lead to a deterioration in cognitive functions, many of which are related to the function of hippocampus. The next section will discuss the hippocampal changes related to noise exposure and NIHL, with a focus on neurogenesis.

3.1.2 The Impact of Noise Exposure and NIHL on Hippocampal Neurogenesis

The cognitive changes in spatial learning and memory described in section 3.1.1 are accompanied by changes to hippocampal neurogenesis, which is the process of producing new neurons associated with learning and memory formation (Apple et al., 2017). As reviewed by Epp and colleagues (2013), the mammalian hippocampus is one of the two brain areas with continuous neurogenesis throughout the lifespan. Specifically, new cells are proliferated mainly in the C3 region of the hippocampus. Learning activity promotes these new cells to differentiate into neurons and migrated to the dentate gyrus where they integrate in the existent neural network. These neurogenesis processes are critical for the formation of new memories (Epp et al., 2013; Rodríguez & Verkhratsky, 2011).

The hypothesis that HL impacts hippocampal neurogenesis is supported by neurological connections between the hippocampus and auditory system. In animals the

hippocampus and auditory system are connected structurally and functionally via a lemniscal and a non-lemniscal pathway (Moxon et al., 1999).

Noise exposure appears to reduce neurogenesis in the hippocampus, which has been considered as the reason why noise exposure leads to poorer cognitive function. In most previous studies, the focus was placed on the oxidative stress induced by the noise exposure, which is a transient phenomenon. Therefore, the effect in cognitive function and hippocampus neurogenesis was observed shortly after the noise exposure when the oxidative stress was high. In many of these studies, the noise-induced HL was undocumented. In one study, for example, researchers exposed mice to moderate noise for 2 hours daily for six weeks, and found an increased oxidative stress in the inferior colliculus, auditory cortex, and hippocampus (Cheng et al., 2011) as tested by markers such as malondialdehyde (MDA) and superoxide dismutase (SOD). In this study, an increase in hyperphosphorylation of the tau protein was also reported. However, while noise exposure was the key variable reported, hearing loss was not quantified or reported. After 6 weeks of noise exposure, there was significant oxidative stress in the inferior colliculus, auditory cortex, and hippocampus. The most significant oxidative stress was found in the hippocampus. Furthermore, the results showed hyperphosphorylation of tau in hippocampus after 6 weeks exposure to moderate intensity white noise. Therefore, oxidative stress can be caused by noise exposure in the hippocampus, which researchers have suggested as a cause of reduced learning and memory abilities.

In another study, Cui and colleagues (2011) examined the effects of high intensity impulse noise (165 dB) on cognition, tau phosphorylation in the hippocampus, and the (Glu)–N-methyl-D-aspartic acid receptor (NMDAR) signaling system. A significant

increase in glutamate and aspirate as well as hyperphosphorylation were found in the hippocampus 30 and 40 minutes after the noise exposure, suggesting the disruption of NMDAR signaling, which may be associated with the poorer performance in MWM performance. Furthermore, these changes in glutamate levels, aspirate levels, and NMDAR signaling leading to cell death are consistent pathological changes in Alzheimer's Disease (AD). However, hearing levels were not reported in this study, meaning the impact of hearing level on these factors cannot be ascertained from this research.

Further research associated noise related stress responses with hippocampal neurogenesis. One study examined the effects of noise on the stress response and hippocampal neurogenesis of rats (Jáuregui-Huerta et al., 2011). The rats were exposed to noise daily from postnatal day 21 to 35. The periods of noise were random in a 12 hour period and lasted for 18 – 39 seconds, in alternation with 20 – 165 seconds of silence. The noise consisted of 70 dB[3] of background acoustic sounds and 85 – 103 dB for the noisy events, which was a rat-specific adaptation of human environmental noise. Again, researchers treated noise as a key variable but did not report hearing loss. Researchers found elevated corticosterone levels, which are related to stress responses, when evaluated 1 day after noise exposure but not at post-natal day 90, which was almost two months after noise exposure. In addition to corticosterone levels, the researchers examined the number of cells marked by Bromodeoxiuridine (BrdU), which is an exogenous marker that can be taken from cells under mitosis, and therefore a measure of cell proliferation. The study reported significantly less BrdU-positive cells in mice

[3] Again, decibel scale not specified in this research.

exposed to the noise. The researchers concluded that the long-term exposure to environmental noise lead to the reduction in hippocampal cell proliferation.

Further research examined the effects of environmental noise exposure on astrocyte morphology in the hippocampus (Huet-Bello et al., 2017). The noise exposure was similar to the method described above (Jáuregui-Huerta et al., 2011), however instead of random exposure for a period of 12 hours, the potential noise exposure period was 24 hours (Huet-Bello et al., 2017). Again corticosterone levels were measured, however, neuronal structure was examined through measures of glial fibrillary and astrocyte process length. Noise also was found to increase the astrocyte arborization of rats, which researchers concluded was related to a hippocampal stress response. Once again, immediately after noise exposure corticosterone levels were elevated, indicating a stress response in the rats. The results for glial fibrillary did not reach statistical significance, however, there were significantly greater astrocyte process lengths in the noise-exposed rats. The researchers concluded that the effects of stressful responses to noise had changed the structure of neurons in the hippocampus.

Kraus and colleagues (2010) examined the effects of noise exposure on hippocampal neurogenesis. In this study 9 rats were exposed to high-intensity noise (12 kHz at 126 dB SPL) unilaterally, which caused NIHL [4] and damage to the inner and outer hair cells of the cochlea (Kraus et al., 2010). Hippocampal neurogenesis was examined using DCX immunolabeling, measuring neuronal precursor cells, and Ki67 immunolabeling, measuring proliferating cells in the dorsal dentate gyrus of the hippocampus. This study found that 10 weeks after noise exposure, there was an average

[4] Level of HL not reported in this study, but based on intensity of noise exposure likely moderate to severe.

of 30% reduction in DCX positive cells and an average 40% reduction in Ki67 cells. The researchers posited that the high-intensity noise was causing hyperactivity in the hippocampus, which was leading to the decrease in hippocampal neurogenesis. Since the observation was done 10 weeks after the noise exposure, it is unlikely that the decreased neurogenesis was directly caused by the noise-induced stress. Unfortunately, no data was reported dynamically to show the potential change in earlier time.

While the early research points to noise causing an oxidative stress response, leading to various changes in the hippocampus, this research examines short-term and transient effects of noise on the hippocampus. Furthermore, while oxidative stress is examined, the studies reviewed thus far have focused on noise exposure, but have not examined the impact of this noise. Specifically, only one study discussed the potential impact of NIHL caused by the noise exposure on the hippocampus (Kraus et al., 2010). However, more recent research points to longer-term effects of noise, related specifically to hearing loss, that outlast a short-term oxidative stress response (Liu et al., 2016, 2018; Tao et al., 2015).

A study by Liu and colleagues (2016) examined the long-term effects of NIHL on hippocampal neurogenesis. Mice were exposed to 123dB SPL of noise for two hours, leading to permanent NIHL (Liu et al., 2016). Oxidative stress was measured with various measures including corticosterone level, SOD, MDA, and DCF levels and the only statistically significant difference between these levels in the NIHL group and control group was present immediately after noise exposure. No long-term effects of oxidative stress were observed at 1 month or 3 months after noise exposure, indicating that it is transient. Hippocampal neurogenesis was measured using DCX and Ki67

markers. Both markers were less in the noise group, indicating a decrease in hippocampal neurogenesis related to NIHL. Furthermore, MWM performance was also correlated with NIHL , indicating that the observed reduction in learning and memory is also associated with reduced hippocampal neurogenesis in mice with NIHL. In summary, this study was the first research to link NIHL , in lieu of oxidative stress, to reduced hippocampal neurogenesis in the hippocampus.

Liu and colleagues (2018) further examined the hippocampal mechanisms related to NIHL and cognitive changes in mice in a follow-up study. A control group of mice was compared to mice with NIHL caused by a range of frequencies (1 to 20 kHz) at a level of 123 dB for a 2 hour period. Neurogenesis was measured using various markers including BrdU, EdU, and NeuN. As well, the complexity of neural fibres was measured by examining dendritic branching. The results showed that mice with NIHL had a reduced level of hippocampal neurogenesis, and fewer hippocampal dendrites branches. Researchers argued that the effects of hippocampal neurogenesis were likely not due to stress, as there were no changes in the stem cell bank in hippocampus, 3 and 7 days after noise exposure. Furthermore, the researchers hypothesize that HL may result in a reduction in general learning-like cognitive activities. This study clearly shows that NIHL is a key factor in changing the structure and function of the hippocampus of mice.

In addition to the research examining NIHL alone, a recent study examined the effects of NIHL on aging mice (Zhuang et al., 2020). Mice were exposed to 120 dB SPL of noise for 2 hours to cause NIHL. Hippocampal neurogenesis was measured using Ki67 and DCX cells, and microglial morphology including soma area, process length, and process endpoints were assessed. The results of this research showed that HL increased

age-related decline in hippocampal neurogenesis. The authors concluded that this reduction in hippocampal neurogenesis is likely related to microglial morphology, and this may be a potential mechanism. Results showed that NIHL increased age-related decline in hippocampal neurogenesis. Hippocampal neurogenesis was also significantly correlated with dystrophic microglial morphology, and NIHL. In summary, this study shows the compounding effects of NIHL on age-related cognitive decline, as well as the relationship between microglial degeneration and hippocampal neurogenesis.

These recent research studies show that hippocampal neurogenesis is clearly related to hearing loss. While earlier studies linked noise related stress to various hippocampal changes, including neurogenesis, the effects of NIHL on hippocampal neurogenesis is a key factor that has long been ignored. Furthermore, the effects of permanent NIHL on the structure and function of the hippocampus are long term.

3.1.3 Summary: Mechanisms of NIHL on Cognitive Function and the Relationship with Hippocampal Neurogenesis

The relationship between HL and cognition in animals has been associated with various behavioral and neurological changes. Rodents with a history of noise-exposure, NIHL , and age-related HL have reduced behavioral performance on cognitive tasks including the MWM (Cheng et al., 2011; Liu et al., 2016, 2018; Tao et al., 2015), the RAM (Kim et al., 2006; Park et al., 2018), and an object recognition task (Park et al., 2018).

These behavioral changes are associated with neurological changes in the hippocampi of rodents. Earlier research argued these changes were due to oxidative stress responses from noise exposure and resulting cell toxicity (Cheng et al., 2011; Cui et al.,

2011; Huet-Bello et al., 2017; Jáuregui-Huerta et al., 2011). However, due to the lasting-nature of HL caused by this noise and the more transient effects of oxidative stress, it is more likely that HL itself is resulting in reduced hippocampal neurogenesis (Liu et al., 2016, 2018). Furthermore, the effects of age-related HL and NIHL are cumulative, with noise exposure accelerating age-related reductions in hippocampal neurogenesis (Zhuang et al., 2020). A potential mechanism for these hippocampal changes is changes to microglial morphology resulting from HL (Zhuang et al., 2020).

These animal findings show that age-related HL is related not only to cognitive changes, but to neurological changes in the hippocampus. Further research will determine the exact mechanism, but the research does indicate that HL is likely a causal factor in hippocampal changes.

3.2 Human Mechanisms Research

This section will discuss the proposed mechanisms that underly the relationship between HL and cognition, as investigated in human research. The literature has generally investigated four different hypotheses in an attempt to determine the causality, and directionality of the relationship between HL and dementia. These hypotheses include the common-cause, social factors, information-degradation, and sensory-deprivation hypotheses, which will be discussed in section 3.2.1.

Another avenue for investigating HL and cognition is through investigating neurological structures and function, which will be discussed in 3.2.2. This is predominantly done through neuroimaging research, such as Magnetic Resonance Imaging (MRI), and ERP. There is also some limited research investigating genetic and biological factors in humans. This section briefly discusses a wide range of structural and

functional neurological changes associated with the impacts of HL on cognition. Following the general discussion, results specific to hippocampal changes will be summarized, as these results are related to both the animal models of HL and cognition, and the proposed LPC investigation.

3.2.1 Hypothesized Mechanisms: Common-Cause, Social Factors, Information-Degradation, and Sensory-Deprivation Hypotheses

HL and cognition are undoubtedly related, but the nature of that relationship in human research has several proposed mechanisms. The mechanisms underlying this relationship are less straightforward in human research for several reasons. Specifically, there is variability in the way in which both HL and cognition are measured, as well as the mostly correlational methods used to investigate this relationship has made finding a causal link between HL and cognitive decline challenging (Chern & Golub, 2019).

A review by Chern and Golub (2019), provides an overview of the various mechanisms that have been investigated to explain the relationship between HL and cognitive decline. These mechanisms can be divided into two main categories: causal mechanisms and common mechanisms.

A causal mechanism is a mechanism where HL directly causes the cognitive decline. Most of the proposed mechanisms in the literature are causal in nature. For example, hearing loss could increase cognitive load for auditory stimuli, leaving less cognitive capacity for other cognitive tasks. Social isolation due to HL could cause cognitive decline, as there is an association between social isolation and cognition. It is also possible that HL changes neurological structure and function, leading to cognitive

decline. Perhaps these changes would be related to a reduction in hippocampal neurogenesis, as has been shown in the animal models (Liu et al., 2016, 2018).

In contrast, common mechanisms are a third confounding factor that explains the relationship between HL and cognitive decline (Chern & Golub, 2019). For example, hearing loss and cognitive decline could be caused by shared cardiovascular or neuropathological disease processes.

It is also possible that the relationship between HL and cognitive decline is multifactorial. For example, individuals with cardiovascular disease and social isolation due to their hearing loss could be at a greater risk of cognitive decline than individuals who are socially isolated but in good cardiovascular health. The presence of one factor does not negate the influence of other factors.

An example of this is the relationship between hearing loss and social isolation. One study of 3 777 French adults aged 65 and older investigated the relationship between self-reported HL, depression, disability and dementia for a 25 year follow-up period (Amieva et al., 2018). The self report of HL was a questionnaire that asked about HL and hearing aid use. Depression was measured using the CES-D. Activities of daily living, as well as instrumental activities of daily living were measured to reflect disability. Dementia diagnoses were made by neurologists, and any participant who already had a diagnosis at their initial visit was excluded from the study.

The results showed an increase in risk of disability and dementia with self-reported hearing loss. Men with HL were at a significantly greater risk of depression. In the discussion, the authors argue that social isolation is a key factor in the relationship between HL and depression. While HL increases the risk of dementia, disability and

depression, it is important to consider if any of these outcomes are necessarily related through the influence of social isolation.

An investigation using data 30 029 adults in the Canadian Longitudinal Study on Aging provides insight into the mediating effects of social factors on HL (Hämäläinen et al., 2019). HL was measured using a pure-tone average of 100, 2000, 3000 and 4000 kHz in the better ear. Cognition, specifically memory and executive function, was measured using the following tests: Mental Alternation Test, Animal Fluency test, Controlled Oral Word Association Test, Stroop Test, and Rey Auditory Verbal Learning Test. Social engagement was a self-report measure that included the number of activities and frequency of activities a participant engaged in with others, as well as the social network index, which counts social interactions with family, friends, and peers weekly to biweekly in the past year. The study also examined other relevant factors like retirement status, income, and education.

The results showed a correlation between the social variables, HL, and cognitive function. Furthermore, higher memory scores were related to better hearing. The moderating effects model showed a weak but significant effect of retirement on hearing loss predictors of cognitive function, and social network index. However, when examining the mediation of social factors on cognition and HL, the effects of social variables had a weak effect on these factors. Specifically, the variance attributed to social variables was negligible in model. Therefore, while the evidence showed that cognition is related to both HL and social variables, social factors did not significantly mediate the relationship between HL and cognition. This study has significant implications for the proposal that HL effects cognition due to social factors, as it shows that there is a

relationship between both HL and social factors on cognition. Nevertheless, in this large-scale study the social factors overall did not appear to have a large effect on the relationship between hearing loss and cognition.

Similarly, it is important to consider the analyses used and effects of the common-cause hypothesis. Studies have shown that participants with HL are more likely to be older male white smokers (F. R. Lin et al., 2014). Certain risk factors, like hypertension and diabetes, can damage both auditory and cognitive systems (Davis et al., 2016). The presence of these factors may increase the risk of both cognitive decline and HL, but is the relationship between the two due to a confounding third factor like age or cardiovascular issues? When these additional factors like diabetes, hypertension, and smoking are analysed as covariates, there is still a strong independent association between dementia and HL (F. R. Lin, Ferrucci, et al., 2011). Therefore, while HL and dementia may have common risk factors it is not likely that these are confounds, as analyses have adjusted for these factors and still shown an independent relationship between HL and dementia.

Another proposed mechanism that has been proposed to explain the relationship between HL and cognition is the information degradation hypothesis. In this model, HL increases cognitive load, which results in fewer resources for other cognitive activities (Pichora-Fuller, 2003; Pichora-Fuller et al., 2016). Listening effort is the term used to describe a purposeful allocation of cognitive resources to listening (Pichora-Fuller et al., 2016). In contrast, listening fatigue results from a high amount of effort being used in the listening tasks.

This model is well-supported by the subjective reports of individuals with HL, who report particular difficulties with cognitively demanding situations such as discourse, and speech processing (Pichora-Fuller, 2003). The processing of speech and language requires more cognitive capacity than perception of single tones, or single words in quiet. Being an active participant in a conversation requires skills like storing and remembering new information, which may tax the cognitive resources of an individual with HL who is using a significant amount of effort to process speech. Researchers have found that participants with HL who focused on identifying words had a reduced memory for those heard words, and comprehension of discourse.

Models like the Framework for Understanding Effortful Listening (FUEL) recognizes the individual as well as situational impact of motivation, demands, and effort on listening activities (Pichora-Fuller et al., 2016). An example of a conversation at a party can illustrate the influence of these factors. Demands would increase if more guests arrive at the party, and background noise increases, which would require increasing effort from the individual with HL. If a conversation turns from an interesting subject to an uninteresting (or unfamiliar) one for the individual with HL, they may be less interested and thus the individual would likely dedicate less effort to listening.

The FUEL framework also suggests that cognitive abilities have an impact on the impact of HL. For example, measures of listening span, the maximum amount of items a person can recall in a set of memory stimuli, can be used with manipulations of listening environment (e.g. background noise) to measure an individuals cognitive listening capacity. While this model reflects a wide range of individual and situational differences, future directions include structural and functional neuroimaging to determine how

effortful listening changes neurological activity in the long-term and short-term. It is possible that effortful listening could result in changes to neurological structure that may cause or worsen cognitive decline over time (Chern & Golub, 2019).

The auditory deprivation hypothesis can be summarized with the phrase "use it or lose it", meaning HL may cause a decrease in auditory input in the auditory/cognitive system (Gallacher et al., 2012). This was a proposed potential factor in a study investigating HL and dementia using interview based cognitive tasks (The Cambridge Cognitive Examination – CAMCOG), and non-interview based cognitive tasks (MMSE, delayed and immediate recall). Gallacher and colleagues (2012) found some support for this hypothesis, as their results for cognitive tasks that were administered by interview were most sensitive to HL. However, other researchers have shown impacts of HL on cognition outside of the auditory domain, such as on cognitive tasks requiring spatial navigation (Belkhiria et al., 2019). This hypothesis is discussed as one of several options in the literature (Gallacher et al., 2012).

While the cognitive load hypothesis and auditory deprivation are potential explanations for the findings, the same results might be taken as evidence for both of these hypotheses. For example, in an interviewing task, participants may perform worse due to auditory deprivation affecting their auditory cognitive abilities. However, worse performance could also be due to difficulties processing discourse increasing cognitive load. If HL is changing cognition in measurable ways, it would be more measurable to examine if these changes are having an effect on neurological structure and function.

3.2.2 Neurological Relationships Between HL and Cognition

The final causal mechanism to discuss is neurological changes that may be responsible for the relationship between HL and cognitive decline. The neuroimaging methods used to investigate these changes are diverse and include MRI, fMRI, and ERP. Special analyses like functional connectivity (FC), to measure connections between different brain areas, and diffusion tensor imaging (DTI), which shows neurological tracts of the brain, can provide additional information about neurological structures. Biological methods, such as measures of tau-proteins and β-amyloid levels, can also be used to investigate pathophysiological markers of this relationship.

A review of functional and structural changes related to HL and cognition showed various neurological changes that were related to HL and cognitive decline (Mudar & Husain, 2016). Most of the changes summarized in the review related to structural and functional changes related to auditory cognitive abilities like sound processing. Structural changes in gray and white matter due to hearing loss, as measured using MRI, have included various areas like the auditory cortex, prefrontal cortex, anterior cingulate, medial frontal gyrus, superior temporal cortex and overall cortical volume. DTI research has shown changes in the orientation of tracts connecting the inferior colliculus and the primary auditory cortex in aging individuals. fMRI studies showed an increase in temporal lobe activity in adults with mild hearing loss, when exposed to pink noise. In studies with linguistic based auditory stimuli, HL was associated with reduced activation of the auditory and limbic systems, as well as the superior temporal gyri, thalamus, and brainstem.

While structural neuroimaging involved mostly auditory stimuli, functional neuroimaging, specifically ERP, included both visual and auditory stimuli. Auditory potentials measured by ERP showed an increased amplitude and latency of the P2 response in individuals with mild-to-moderate high-frequency HL. Visual potentials changes included larger amplitudes of the P1, NI, and P2 visual evoked potentials. The visual results are particularly important as they show cross-modal generalization of cognitive changes resulting from HL. Despite the cross-modal impact of HL on cognition, interestingly, most of the neurological structures impacted by HL discussed in this review were related to auditory processing, like the auditory cortex and temporal areas.

A study by Lin and colleagues (2014), showed results related to temporal areas, however these areas are also connected to the hippocampus. This study used region-of-interest analyses to examine brain volume in individuals with hearing loss, and controls. The results showed a reduction in total brain volume, and in regions including the superior, middle, and inferior temporal gyri as well as the parahippocampus. While this study did not discuss the hippocampal region, the parahippocampus is connected both structurally and functionally to the hippocampus (Aminoff et al., 2013; Anand & Dhikav, 2012). Therefore, this study results show changes to areas related to the hippocampus, but not the hippocampus itself.

Another study examined the hypothesis that outer hair cell loss in presbycusis is associated with both cognitive decline and structural brain changes in 95 adults over 65 (Belkhiria et al., 2019). This study included various measures of cognition (e.g. MMSE, Trail Making Test, Backward Digit Span…), pure-tone audiometry to measure hearing

loss, distortion product otoacoustic emissions to measure cochlear ear function, and MRI to measure cerebral thickness and volume. The results showed presbycusis was associated with decreased volume in precentral gyri, postcentral gyrus, and the parahippocampus. Cochlear ear dysfunction itself was correlated with decreased cognitive performance and volume in the cingulate cortices. Finally, cochlear ear dysfunction and pure-tone-audiometry had a correlation, and were related to decreased volume in the superior temporal, right postcentral, and left precentral gyri. These results show that presbycusis correlates with a wide variety of neural structures, as well as cognitive functions like visuospatial abilities.

In addition to the neuroimaging research, a recent review has synthesized the biological and radiological relationship between HL and dementia from 93 articles (Di Stadio et al., 2021). In regards to brain atrophy, the researchers found that in general brain atrophy in the temporal lobe was associated with hearing loss, and more diffuse brain atrophy was associated with dementia. However, researchers discussed that the brain atrophy from the temporal lobe could spread outwards leading to dementia, and conversely diffuse brain atrophy from dementia could move into the temporal lobe leading to HL.

In addition to the changes in brain atrophy, there are also neurological changes like white matter hyperintensisties (WMHs) and gliosis in both individuals with HL and dementia. The presence of WMHs have a negative correlation with speech understanding. Gliosis, which results in altered synaptic transmission, could be a mechanism responsible for the relationship between HL and dementia. In this review, the role of HAs to restore regular connectivity in the brain was linked to activating anti-inflammatory microglia

which may have a role in repairing areas of gliosis. In addition to these biological events, there may be a genetic link between HL and dementia. The apolipoprotein e4 (APOE) allele is present both in developing AD and severe HL (Di Stadio et al., 2021). In summary, brain atrophy as well as the presence of WMHs, gliosis, and the APOE allele have been found to be present in both HL and dementia.

However, not all studies support the neurological and biological correlates of HL and cognition previously discussed. A study of 368 adults born in 1946 that used MRI, positron-emission tomography (PET), in-vivo β-amyloid deposition, and cognitive measures (i.e. the MMSE) showed a mixed relationship between neuropathological and structural changes associated with cognitive decline and HL (Parker et al., 2020). Pure-tone audiometry had a negative relationship with auditory cortex thickness and MMSE scores. However, the relationship between MMSE and pure-tone audiometry scores was not present when an item that asked participants to repeat a phrase was excluded. Furthermore, there was no relationship between pure-tone audiometry, β-amyloid levels, hippocampal volume, and WMHs found in this study. Therefore, while some studies using neuroimaging and neuropathology to investigate the relationship between HL and dementia have shown significant structural, biological, and neuropathological factors, this study did not support those findings.

An interesting perspective that complicates this relationship further is that the specific type of cognitive decline may cause different auditory deficits, as well as implicate different neurological structures. For example, AD usually is accompanied with deficits with auditory scene processing, auditory working memory and phonological processing (Johnson et al., 2021). The neurological structures that are implicated in the

auditory difficulties associated with dementia include the posterior cingulate, precuneus, and lateral temporo-parietal cortex. In contrast, Lewy Body dementia has auditory symptoms like auditory hallucinations, tone and rhythm processing difficulties. In Lewy Body dementia, cortico-subcortical circuits are primarily associated with these auditory symptoms. This research underscores the importance of considering how audition is measured, auditory scene tasks may be more reflective of auditory changes than pure-tone audiometry in AD patients. Furthermore, audition itself is cognitive and separating audition from cognition is a false dichotomy.

While the Johnson and colleagues (2021) review provides insight into the neuropathology associated with HL and dementia, it does not clearly connect to the animal research regarding the role of the hippocampus. The potential role of oxidative stress is discussed, but not hippocampal neurogenesis. The following studies have results specifically related to the hippocampus.

3.2.3 Hippocampal Changes Related to HL and Cognition

While the Johnson and colleagues (2021) review provides insight into the neuropathology associated with HL and dementia, it does not clearly connect to the animal research regarding the role of the hippocampus. The potential role of oxidative stress is discussed, but not hippocampal neurogenesis. The following studies have results specifically related to the hippocampus.

A large study of 2 082 people (ages 40 – 89) investigated the relationship between hearing thresholds (as measured by pure-tone audiometry) and brain volume (Uchida et al., 2018). The hippocampus, entorhinal cortex, Heschl's gyrus, and total gray matter volume were measured. A sub-analysis of the MMSE and the Short Mini-Mental State

Exam (SMMSE) scores was also conducted. The results showed that hearing impaired participants had a smaller hippocampal volume compared to the control group. This relationship was described as dose-response, meaning the more severe a participant's hearing loss, the smaller their hippocampal volume. The volume of the entorhinal cortex and total gray matter did not correlate with HL. The Heschl's gyrus volume had a significant relationship with HL at certain frequencies and levels, but not across the frequency range. Therefore, in this study the hippocampal volume had the clearest relationship with hearing loss.

The relationship between the cognitive measures (MMSE and SMMSE) was moderately related with HL and hippocampal volume. Specifically, the SMMSE and MMSE scores had a significant negative correlation with HL. However, only the SMMSE had a modest significant correlation with hippocampal volume. Therefore, the behavioural impacts of HL-induced hippocampal changes may not be fully captured by the scores on the MMSE and SMMSE. Another task more directly related to hippocampal activity may be more appropriate to measure this relationship.

Another study investigated the levels of tau and β-amyloid in the cerebral spinal fluid, cerebral volume and thickness and participants 479 in various stages of cognitive decline and age related HL (Xu et al., 2019). The results of study showed no association between β-amyloid levels and age-related HL. There was an association between increased tau levels and age-related HL. Neurological changes included reduced volume and thickness in the entorhinal cortex. Interestingly, the baseline volume and thickness of the hippocampus was higher in participants with age-related HL but there was significant

atrophy, particularly in the preclinical stages of cognitive decline. Therefore, changes in the hippocampus may be related to early changes related to HL and cognitive decline.

A study of 32 patients with presbycusis, and controls examined functional connectivity using MRI and the Granger causality analysis (Chen et al., 2020). While these patients did not have cognitive decline, the results of this study reveal connections between the auditory system and the hippocampus. The results showed presbycusis was associated with decreased directed functional connectivity between inferior parietal lobule, insula, right supplementary motor area, middle temporal gyrus and the hippocampus. Various cognitive tests were performed, with significant relationships between the Trail Making Test B, and decline in functional connectivity from parietal lobule to hippocampus. This test was also worse in participants with presbycusis. This study shows a relationship between hippocampal connectivity, cognitive task performance, and presbycusis.

3.2.4 Summary: Human Mechanisms

In summary, neuroimaging and neuropathology research has found many factors that are associated with HL and cognitive decline in humans. Structural and connectivity changes have been shown in diverse areas of the brain, such as the cingulate cortex, superior temporal gyrus, inferior colliculus, auditory cortex, and brainstem. Furthermore, gliosis and WMHs have been associated with both HL and cognitive decline in several studies. Electrophysiology research has demonstrated changes in both auditory and visual evoked potentials. Neuropathological research has shown effects of HL on various biological markers like tau levels, and the presence of the APOE gene. β-amyloid levels have not been shown to be related to HL and cognition.

While each of these observed changes sheds light on potential factors relating HL and cognition, they do not explain the role of the hippocampus in HL and cognition. The hippocampus is a particular structure of interest, as HL has been shown to result in decreased hippocampal neurogenesis and cognitive changes in animal models. Although it is not a large focus of study in the literature investigating HL and cognition in humans, some research has shown HL to be related to decreased hippocampal volume, thickness, and connectivity changes in both participants with and without cognitive decline. These findings provide some support for the potential role of the hippocampus in HL related cognitive decline.

3.3 Relating Human and Animal Mechanisms

The next steps in relating HL and cognitive decline in humans to the animal models is connecting the human research with hippocampal changes. While no known studies have related HL to hippocampal neurogenesis in humans, there is evidence that the hippocampus changes in response to HL (Chen et al., 2020; Uchida et al., 2018; Xu et al., 2019). Furthermore, there is evidence that hippocampal neurogenesis is a neuropathological mechanism in cognitive decline.

Studies have shown hippocampal neurogenesis is a lifelong process in humans as well, even in the 8^{th} and 10^{th} decades of life (Moreno-Jiménez et al., 2019; Tobin et al., 2019). Hippocampal neurogenesis is lifelong, and is persistent even in patients with AD (Moreno-Jiménez et al., 2019; Tobin et al., 2019). However, the hippocampus is one of the most significantly and earliest affected structures in AD (den Heijer et al., 2010). In mild cognitive impairment, a decline in the number of DCX cells has been observed in the early stages of cognitive decline (Tobin et al., 2019). Furthermore, this study found

that the number of DCX cells was associated with higher scores on cognitive measures, and a less severe clinical diagnosis (Tobin et al., 2019). These early changes in hippocampal neurogenesis may be due to abnormal tau hyperphosphorylation which impacts the connectivity and maturation of new neurons (Rodríguez & Verkhratsky, 2011).

While a change in early hippocampal neurogenesis is potentially an early event in neurological changes due to dementia, reduced hippocampal neurogenesis is likely persistent throughout the dementia disease course. The number and maturation of neurons produced by hippocampal neurogenesis was reduced in advanced AD (Moreno-Jiménez et al., 2019). Some researchers believe the reduction in hippocampal neurogenesis may be mechanism underlying memory deficits in AD (Moreno-Jiménez et al., 2019). Furthermore, hippocampal neurogenesis may be sensitive to therapeutic interventions.

Previous research has shown hippocampal neurogenesis is influenced by various environmental factors, and activities. Exercise, and pharmacological interventions like antidepressents have shown to increase levels of hippocampal neurogenesis (Rodríguez & Verkhratsky, 2011). Therefore, hippocampal neurogenesis is a modifiable mechanism.

In summary, some neuroimaging research has revealed changes to the hippocampus due to HL (Chen et al., 2020; Uchida et al., 2018; Xu et al., 2019). These changes have been related to cognition (Chen et al., 2020; Uchida et al., 2018), as well as cognitive decline in humans (Xu et al., 2019). In animals, a reduction in hippocampal neurogenesis has been shown to be directly related to hearing loss, and associated cognitive changes (Liu et al., 2016, 2018). Furthermore, human hippocampal

neurogenesis decreases in cognitive decline (Moreno-Jiménez et al., 2019; Rodríguez & Verkhratsky, 2011; Tobin et al., 2019).

Further research investigating HL and cognitive decline should consider the role of the hippocampus in this relationship. The hippocampus may be the causal link between HL and dementia. Investigating changes in the hippocampus, or hippocampal-related activities in response to HL is crucial for future research into HL and cognitive changes.

CHAPTER 4 A PROPOSED INVESTIGATION OF HL, HA USE, AND THE LPC

Thus far this thesis has focused on the literature that has examined hearing loss, HA use, and cognition. This chapter details a proposed study investigating these factors using ERPs.

4.1 Study Rationale

A vast body of research has shown that HL and cognition are related. Recent animal research has revealed that HL causes decreased spatial learning and memory, as well as reduced levels of hippocampal neurogenesis (Liu et al., 2016, 2018; Zhuang et al., 2020). While the hippocampus has a clear role in the cognitive changes seen in animals with hearing loss, it has only been investigated in a few of human studies of HL and cognition (Chen et al., 2020; Uchida et al., 2018; Xu et al., 2019).

This study aims to investigate the relationship between hearing loss, HA use, and cognition using ERPs. The specific component of interest is the LPC. The LPC is an ERP component related to word-recognition memory, and has been associated with hippocampal activity using simultaneous ERP-MRI research (Hoppstädter et al., 2015). Earlier research examining LPC generation and neurological structures has also associated the LPC with the hippocampus.

One study investigating memory formation using intracranial electrode recordings of ERPs revealed the role of the hippocampus in generating the LPC (Fernández et al., 1999). Researchers found that in a word-recognition task a positivity 500-700ms after presentation of a word was observed in the hippocampus, but not in the surrounding structures (Fernández et al., 1999). The results of this study demonstrate that the

hippocampus itself is a key generator of the positivity that occurs when participants recognize a word.

While this study used intracranial electrodes to measure typical word-recognition memory formation, results from studies of participants with hippocampal damage also demonstrate the key role of the hippocampus in generation of the LPC. One study comparing the word recognition memory of a patient with localized hippocampal damage to controls showed the LPC was functionally absent in the patient with hippocampal damage (Düzel et al., 2001). While the patient with hippocampal damage had unaffected encoding (as measured through an animacy judgement) and the typical earlier N400 response observed in word recognition tasks, his LPC response was significantly impacted (Düzel et al., 2001). Specifically, while controls had more positivity for hits compared to correct rejections on the word recognition task, there was no difference in positivity for the patient with hippocampal damage (Düzel et al., 2001).

The rationale for examining this specific component is that it has been demonstrated to be associated with the hippocampal structure. While this specific ERP experiment cannot be directly used to link LPC changes to hippocampal changes, especially to changes in hippocampal neurogenesis as is seen in animal research on HL and cognition, there is sufficient evidence to assume the LPC is associated with the hippocampus. Therefore, this methodology will investigate functional changes in recognition memory, while using an ERP component that has been associated with the hippocampus.

The key research questions that would be investigated in this proposed experiment are:

i. Does HL change the latency, and amplitude of the LPC response in a word recognition memory task?

ii. Does HA use mediate these changes to the LPC response?

It is hypothesized that participants with HL would have an LPC response reduced in amplitude. It is also hypothesized that these changes in LPC amplitude and latency would be reflected in group differences in recognition memory. Specifically, participants with HL would be less accurate in their hits (recognition of words as *old*) and correct rejections (recognition of words as *new)* which would be reflected in changes to the amplitude of their LPC response. It is hypothesized that HAs would mediate these changes to the LPC response, making the LPC responses of HA-users between that of controls and participants with HL who do not use HAs.

While these participants would all have no diagnoses of dementia and be able to pass cognitive screening to participate, ERPs can be used to detect subtle changes in cognition that can be pre-clinical markers of cognitive decline (Olichney et al., 2011). We hypothesize that hippocampal neurogenesis will be reduced in humans with HL (as it is in mice) and that this will be reflected in lower LPC amplitude than in participants with normal hearing. We also hypothesize poorer word recognition performance in participants with HL than those with normal hearing, given the important role played by the hippocampus in word recognition memory. amplitude and latency

A reduction of LPC amplitude would be seen in participants with HL, as it is hypothesized that this would reflect poorer hippocampal function that may be associated with reduced cognitive performance (specifically word recognition) in participants with HL. While participants with HL would not likely have the same magnitude of

hippocampal damage as the patient studied in Duzel and colleagues (2001), this patient did have a reduced LPC amplitude that was related to reduced word recognition. Therefore, it is likely that a reduction in amplitude of the LPC would accompany changes in word recognition memory in participants with HL.

Furthermore, a different experimental procedure using word repetition and comparing patients with cognitive decline and controls has shown changes in amplitude of the LPC in participants with cognitive decline (Olichney et al., 2011). These electrophysiological changes have also been related to later diagnosis of cognitive decline in participants with mild cognitive impairment (Olichney et al., 2011). While these studies use a different experimental procedure, and examine the effects of repetition on the LPC (which itself changes the amplitude of the LPC response), the results of these studies indicate that changes to the amplitude of the LPC have been seen in participants with cognitive decline.

It is also hypothesized that LPC responses may differ in latency between groups with HL and the control group. This hypothesis is less certain, as the effects of neurological changes on latency of this component are not often discussed and the main characteristic of this component is an increase in positivity. Given that changes in ERP components can be described using amplitude and latency, it is still useful to make a prediction about latency even though the specific timing of this component is less precise. If there are changes to the latency of the LPC component, it is more likely that the changes will result in a later as opposed to earlier response. In general, cognitive decline results in a delay in ERP components, for example the N200 (Olichney et al., 2011). Therefore, it is less likely that changes to latency will be observed, but should there be

changes, it is predicted that an increase in LPC latency, as opposed to a decrease, would be more likely.

4.2 Proposed Methodology

The following section details a proposed methodology to investigate the effects of hearing loss, and HA use on the LPC.

4.2.1 Participants

This study would use three groups of participants: a group with uncorrected HL over 40 dB HL (n=20), a group with corrected HL over 40 dB HL (n=20), and a control group with hearing thresholds ≤ 25 dB HL (n=20). For the purposes of this study, corrected HL refers to the use of HAs or other assistive listening devices. The control group would be matched to the HL groups on factors including age, gender, and education.

4.2.2 Procedures and Measures

Before the participants come to the lab, they would be screened for eligibility using a questionnaire (refer to Appendix A for questionnaire). Exclusionary criteria include any factors that could confound the participant's LPC response. Head injuries like concussions or neurological conditions like epilepsy could affect the brain's electrophysiology, so these participants would be excluded. Non-native speakers of English and/or bilinguals would be excluded as their linguistic experience could affect their English word recognition, and thus their LPC responses. Participants with a hearing level between 26 – 40 dB would be excluded as they would belong in neither the control group nor the experimental groups. Participants in the hearing loss group would need to have self-reported hearing difficulties (in noisy or quiet environments) or diagnosed

hearing loss for a minimum of 1 year. All participants would need normal or corrected-normal vision to read the questionnaires, and to see the study stimuli when presented on the computer monitor. In order to match the 3 groups on factors like age, education and gender, otherwise eligible participants might be excluded to ensure parity between the groups on these factors.

Once they had completed the eligibility questionnaire, participants would be invited to the electrophysiology laboratory to participate in the experiment. In the lab, participants would complete the study consent form, as per ethics guidelines (refer to Appendix B for consent form). All participants would complete a demographic questionnaire (refer to Appendix C for demographic questionnaire). Participants would be screened for their hearing using pure-tone audiometry and otoacoustic emissions. Participants in the control group would need to have thresholds in the normal range (25dB HL or less) and normal otoacoustic emissions. Participants in the hearing loss group would need to have thresholds equivalent to moderate or greater levels of hearing loss (40 dB HL or greater) and absent otoacoustic emissions.

Participants with a HA would complete various measures to assess their HA fit, and satisfaction. Participants would have their HA fit measured using the Audioscan Verifit VF -2 real ear system (Dorchester, ON, Canada). This device measures HA fit by using the participant's individual hearing level. The frequency responses of the HA are measured to ensure the participant's HA is amplifying frequencies to an audible level.

HA satisfaction and daily use would be measured with the Satisfaction with Amplification in Daily Life (SADL) (Cox & Alexander, 1999). This questionnaire was validated with a group of 196 adults with HL from 13 different private clinics (Cox &

Alexander, 2001). The SADL is a questionnaire that assesses HA satisfaction using 15 questions. The questions ask participants about their perspective on their current HAs. Participants select from a scale of A, representing "not at all", to G, representing "tremendously" how much they agree with various statements. The SADL generates a global HA satisfaction measure, as well as measures of the following subcategories: positive effect, service & cost, negative features, and personal image. In addition to these qualitative measures of HA satisfaction, the SADL also asks participants to quantify their HA use. This includes the number of months or years they have worn their HAs, as well as their daily use.

While the SADL provides a self-reported measure of daily hearing-aid use, many modern hearing aids also log the number of hours of daily HA use. If participants consent to sharing this data with the research team, these data logging features could also be used to determine hours of daily HA use.

In addition, participants would also complete the MoCA to screen for cognitive impairment. While the LPC response is a measure of recognition memory, it is important to ensure all groups of participants have similar global cognitive abilities and no cognitive impairment. If global cognitive abilities are not measured, it is possible that study results could be confounded by general cognitive differences between the groups. Therefore, in addition to excluding participants with diagnoses of dementia, the MoCA will also be used as a quick screening measure (Nasreddine et al., 2005).

The MoCA is a screening tool with 30 items that assesses various domains of cognition in approximately 10 minutes. The areas of cognition that are assessed with the MoCA include visuospatial abilities, executive functions, phonemic fluency, verbal

abstraction, attention, concentration, working memory, language, and orientation to time. A version of the MoCA was adapted for hearing-impaired patients by Lin and colleagues (V. Y. W. Lin et al., 2017). This version essentially removes the auditory demands of the MoCA by presenting the instructions in written format. Both the hearing-impaired MoCA and the traditional MoCA have strong psychometric properties including high sensitivity and specificity in detection of mild cognitive decline (V. Y. W. Lin et al., 2017; Nasreddine et al., 2005). Therefore, the hearing-impaired MoCA will be used for all participants. This ensures the performance of the participants with HL is not impacted the auditory demands of the traditional MoCA. Furthermore, all groups using the same version of the MoCA (the hearing-impaired MoCA) minimizes a potential confound of using different versions of the MoCA for different groups.

Once the participant has completed all relevant questionnaires, hearing measurements, and HA fit measures they would proceed to the word recognition task. This ERP task consists of two phases: a learning phase, followed by a testing phase. There would also be a short distractor task in the middle where participants will complete mental math to prevent word rehearsal. This procedure is adapted from research conducted by Hoppstädter and colleagues (2015).

In the learning phase, participants would be instructed to remember the words presented, as they will be tested on the words later. In addition, they would be asked to complete a secondary task that involves making a judgment about whether the word is animate (i.e. a living thing) or inanimate (i.e. a nonliving, or abiotic thing). This is to ensure the participants are attending to the task, and to allow for deeper coding of the words.

Stimuli for the experiment were taken from a list of concrete nouns previously used in a picture-object naming study with participants with aphasia (Wilson et al., 2012). The stimuli are matched on variables including word frequency and length. 100 words were selected from this list, 50 which will be presented in the learning phase and all 100 will be presented in the testing phase. Any words that did not clearly fit into the categories of animate and inanimate (e.g. is *chicken* the inanimate meat or the animate farm animal), or that were otherwise ambiguous (e.g. is *ball* a high society dance or a basketball) were excluded.

The learning phase would proceed in the following sequence. A fixation cross will be presented for 1000 ms. This would be followed by a blank screen with a jitter for between 500 to 1500 ms. Then the target noun would be presented for 2000 ms, followed by another blank screen for 500 ms before the trial repeats again. Refer to Figure 1 for an illustration of this task. In total this section of the procedure would take approximate 3.3 minutes.

The testing phase would proceed in a similar fashion to the testing phase. First, a fixation cross would be presented for 1000 ms followed by a blank screen with a jitter for 500 ms to 1500 ms. Then the lure noun would be presented for 500 ms, and participants will be required to make the old/new judgment. A blank screen would be presented for 500 ms, and then the next trial will continue. See Figure 2 for more details regarding the task. The testing phase will take approximately 8.4 minutes.

The window that would be examined is from 500 ms to 800 ms, timelocked to the old/new stimulus presentation. This window is in line with previous research on the LPC component (E. Düzel et al., 2001; Hoppstädter et al., 2015). Behavioural results of the

old/new task, such as accuracy of word recognition, as well as the LPC responses of participants with and without HL will be compared.

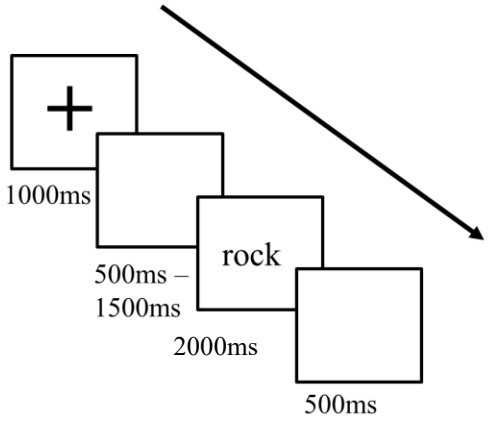

Figure 1. *Learning Phase*

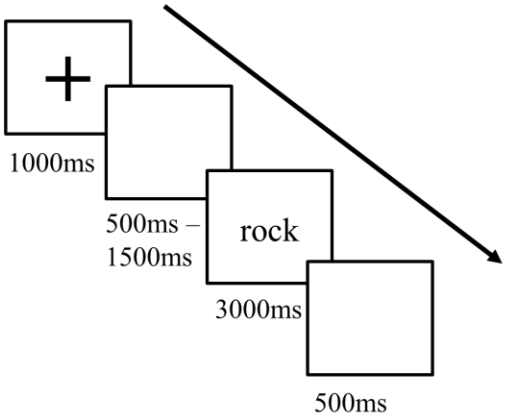

Figure 2. *Testing Phase*

4.2.3 Apparatus and Instrumentation

The ERP system that would be used is a Biosemi Active Two, which has 140 channels. Facial electrodes would be used to control for blinks and other eye movements. The data will be sampled at a rate of 2 kHz.

The experiment would be programmed using PsychoPy. The data would be analyzed using BESA statistics software, version 2.0.

4.3.1 Potential Analysis

Prior to data analysis, several steps would be taken to ensure the data is prepared for analysis. The raw signals would be referenced post-data collection to the mastoid. As well, a bandpass filter of 0.5 to 30 Hz will be applied. Blinks, as well as other artifacts would also be identified and removed from the data as appropriate (Luck, 2014).

Once these steps are completed the data would be analyzed as follows. The data would be separated into *hits* (words correctly identified as *old*) and correct rejections (words correctly identified by participants as *new).* The average ERPs for each group's hits and correct rejections would be compared within and between groups. For example, all of the electrophysiological data would be averaged for every person in the uncorrected HL group for all of the hits responses in the test phase, to give an indication of their LPC response when they recognize words in the task. The responses of this group would be compared to the corrected HL group, and the control group to examine differences in the LPC response. The same procedure would be done with the correct rejection responses.

An analysis of variance (ANOVA) would be computed to compare the average waves of each group. This ANOVA would compare the waveforms on characteristics of latency (the time course of the waveform) and amplitude (the height of the waveform from 0, in a negative or positive direction) between the three groups. Once the ANOVA identifies any statistically significant differences, a post-hoc test would be conducted to determine the direction of the effects.

The behavioral data from the *old/new* task can also be compared with the electrophysiological data to examine any patterns. For example, a correlation between the behavioural accuracy of the groups (i.e. selecting *old* when the stimulus was previously

presented) can be compared to the latency and amplitude of the waveforms to examine if the characteristics of the LPC are related to the behavioural measures. Perhaps reduced behavioral recognition memory performance in one group can be related to functional neurological changes in their LPC responses.

Other factors related to HL and HA use could be analyzed as well. For example, estimated length of diagnosed HL could be analyzed, as well as severity of HL to determine if changes to the LPC response are greater with more severe, long-term HL. In addition, a certain number of hours of HA use, and increased satisfaction with HAs may influence the potential protective factor of HAs with respect to cognitive decline.

In addition to the statistical methods described above, conditional inference random forest modeling (CForest) could be used to analyze the data (McWhinney, 2018). This method could provide useful as it groups electrodes in an *a priori* manner, determining regions of interest in the electrodes (McWhinney, 2018). The CForest method would therefore allow for the examination of the topographic patterns of electrode activation (McWhinney, 2018).

4.3 Potential Findings

4.3.1 Potential Results

The expected outcomes of this study are that the recognition memory and associated neural electrical responses of participants with and without HL will differ. Given the previous findings relating HL and dementia, it is expected that subtle behavioural differences in recognition memory occur between groups with and without hearing loss. In ERP research, significant differences are generally described in terms of

latency (i.e. the timing of components) and amplitude (i.e. the size of the peak of the component).

It is predicted that the participants with HL will have differences in their LPC components from the control group which are illustrated in Figure 3. This diagram shows a delayed LPC component in participants with HL compared to the control group. It is predicted that the participants with HL who wear HAs will have an LPC response in between the control group, and unaided HL group.

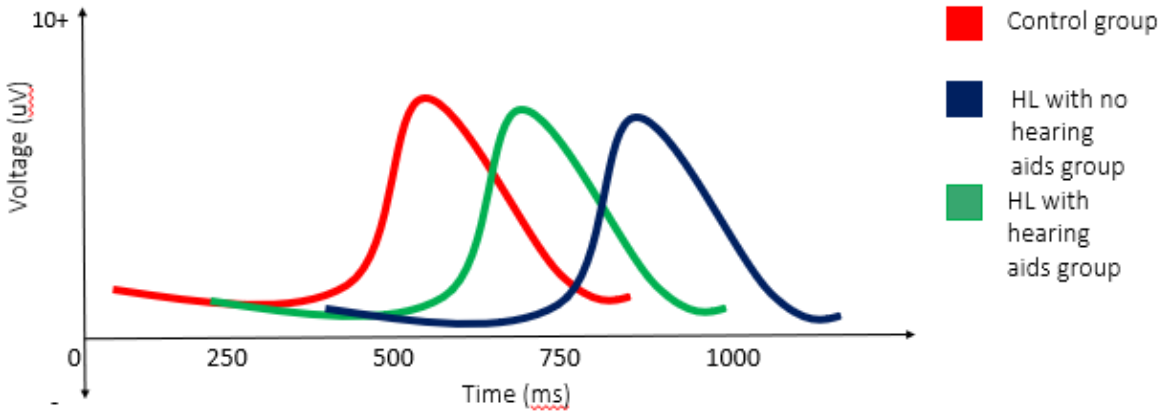

Figure 3. *Difference in latency of LPC responses (hits) for participants with HL and no HAs, HL with HAs, and the control group*

Another possible outcome is a difference in amplitude of the LPC components of participants with and without HL . These predicted results are shown in Figure 4. In this waveform, the participants with HL and no HAs have a much lower amplitude in their LPC responses than the participants in the control group. Again, it is predicted that the participants with HL and HAs will have a response in between the response of the control group, and the group with HL and no HAs.

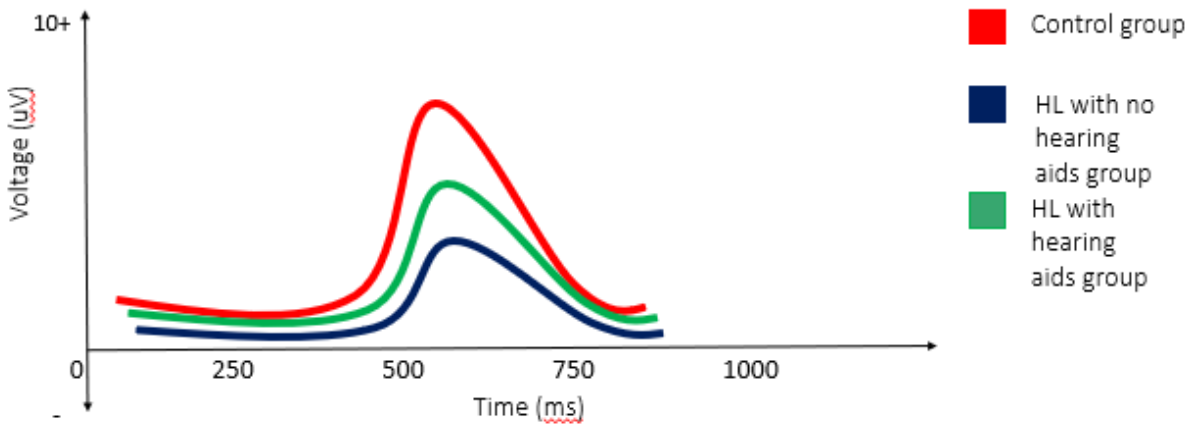

Figure 4. *Potential differences in amplitude of LPC responses (hits) for participants with HL and no HAs, HL with HAs, and the control group*

4.3.3 Potential Contributions to the Research

Researchers have demonstrated an independent association between the HL and dementia (F. R. Lin, 2011). However, the nature of this relationship remains unclear. Behavioural differences in word recognition could indicate differences in cognition related to HL and HA use. Changes in the LPC response in participants with HL and without HL could reveal functional neurological differences that underlie the relationship between HL and dementia. These differences are especially significant given the association between the LPC and the hippocampus.

Although recent research has identified HL as the highest possibly modifiable risk factor for dementia (Livingston et al., 2020).HL is often not treated due to various social or cultural reasons (Davis et al., 2016). The impact of HAs in mitigating the risk of dementia and cognitive decline associated with HL is currently unknown (Desjardins,

2016). By including a group with hearing correction, and a group without hearing correction, this study aims to examine the effects of hearing correction on recall memory.

In addition, many studies linking neurological changes with HL and cognitive function use early ERP components such as the N1, P1, and P2 (Mudar & Husain, 2016). This study will use the later component, the LPC, which will reveal how HL affects later neural electrical responses. These findings could illustrate that HL affects not only basic auditory-perceptual processes, but also higher order cognitive functions, such as memory.

Furthermore, this research would extend the findings from animal research examining HL cognition in mice which was associated with poor spatial and memory functioning on the Morris water maze task (Liu et al., 2016; Liu et al., 2018). HL in mice has led to a reduction in hippocampal neurogenesis, and neuronal changes in the hippocampus such as changes to dendritic structures (Liu et al., 2016, 2018; Zhuang et al., 2020).

Hoppstädter and colleagues found that when observing an LPC response, the hippocampus had significant activation when examined using MRI (Hoppstädter et al., 2015). This study will use the LPC, an ERP component previously shown to be related to hippocampal activity, to examine if hippocampal activity is also a key component of the relationship between cognitive decline and HL in humans. It is predicted that HL will have an effect on this ERP component, because the hippocampus is an early affected structure in cognitive decline in humans (den Heijer et al., 2010). These results would add to the body of literature that shows hippocampal changes are related to hearing loss, and cognitive decline.

CHAPTER 5 Conclusion

While the introduction framed an aging population as a challenge, it is also an opportunity and a call to action. The time to embrace hearing health as an important part of cognitive health is now. There are actionable steps to take in treating hearing health like the crucial part of well-being that it is.

Despite the relationship between hearing health and cognitive health, Canadian public health policy has not reflected the importance of hearing health for cognitive health. For example, Nova Scotia's action plan for aging has no mention of hearing health in their strategy for healthy seniors (Nova Scotia Department of Seniors, 2017). Canada also has no dedicated funding for hearing or communication research, and no national strategy for hearing health.

Policy to fund more research and clinical services for adults with HL and cognitive decline is key to improving the understanding of and services for HL and cognitive decline. However, how this research is conducted and by whom is also a key consideration. Previous reviews have stated that a lack of collaboration across disciplines, between audiologists who study hearing loss and psychologists who study cognition, has lead to stagnation in research and clinical outcomes (F. R. Lin & Albert, 2014). While interdisciplinary collaboration is a key component when considering HL and cognitive decline, another group of practitioners is often missing from this discussion, speech-language pathologists (S-LPs).

S-LPs have a unique role to serve in clinical and research activities on hearing health and cognitive health. The Canadian competencies for S-LPs cite both cognitive

communication, and hearing health as a part of the professions scope of practice (CAASPR, 2018). Aural rehabilitation for pediatric clients with HL is a well-accepted and recognized role for S-LPs to take on a clinical team.

There are certainly some S-LPs who have undertaken research and clinical activities relating to HL and cognition. For example, Hopper, an S-LP, and Hinton, an audiologist, co-authored a review of the literature on HL and cognition, as well as implications for assessment and treatment of hearing and communication (2012). Suggestions in the article are practical, for example the *Blue Box Project* involves putting HAs and other items often misplaced like glasses in a plastic box when not worn by patients in a hospital setting (Hopper & Hinton, 2012). A list of items for each patient is in the box, and staff know to check the box to ensure patients have all of their required visual or auditory aids (Hopper & Hinton, 2012). Loosing or damaging HAs is a common barrier to treatment, and this solution ensures the items are accounted for and secure.

Another treatment option discussed by Hopper and Hinton (2012) is communication partner training. Many of the strategies helpful for individuals with dementia and individuals with HL are the same. For example, reducing background noise, and speaking face-to-face is recommended to communication partners of individuals with HL and dementia (Hopper & Hinton, 2012). Interventions like communication books may also help individuals with cognitive decline and HL as they supplement auditory input, and provide a common reference point for communication partners and patients.

In addition, research has shown hearing screenings can help predict cognitive decline (Castiglione et al., 2019). Adding hearing screenings to cognitive screenings may help identify patients at risk for cognitive decline, especially in patients with mild to moderate HL from 65 to 75 years old (Castiglione et al., 2019). This may be another area where S-LPs can have a valuable role. It is within the scope of practice of S-LPs to conduct cognitive screeners like the MMSE/MoCA, as are hearing screenings. A hearing screening, and full audiological evaluations when indicated, gives clinicians a more complete picture of auditory and cognitive health.

There are many avenues to ensuring good hearing health throughout the lifespan, HAs are one of many options (Davis et al., 2016). Prevention and education on the importance of hearing health is a valuable intervention (Davis et al., 2016). Prevention can include reducing industrial noise exposure, and even appropriate nutrition as nutritional deficits can damage the auditory system (Davis et al., 2016). Furthermore, many individuals have temporary hearing impairments that could be easily treated and managed due to cerumen impaction, or ear infections (Davis et al., 2016). Ensuring access to hearing healthcare throughout the lifespan is crucial for long-term health.

In conclusion, audition is a cognitive process (Johnson et al., 2021). Hearing does not end in the ears, and the brain is an integral part of the auditory system. Furthering our understanding of the impacts of HL on cognitive changes will help prevent, identify, and treat patients with dementia. The causality of the relationship between HL and cognition requires further investigation. However, the impact of hearing health on overall health is clear. Hearing loss is the largest potentially modifiable risk factor for dementia

(Livingston et al., 2020). Policy, research, and clinical practice must reflect this reality, and make hearing health a priority.

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APPENDIX A Screening Questionnaire

DALHOUSIE UNIVERSITY

Screening Questionnaire

1. Are you 50 years of age or older? Y / N

2. Is English your first language? Y / N

3. Do you speak any other languages? Y/N

   i) If you answered yes to question 3, please rate the highest amount of exposure you have ever received in this language. Please include all language exposure including in educational settings, and everyday settings, and in all forms of language (spoken, written, etc.) :

   - ☐ Less than 10% communication
   - ☐ 10 – 19% of communication
   - ☐ 20 % or greater of communication

4. Do you have uncorrected or untreated vision loss? Y/N

5. Are you right- or left-handed? R / L

6. Sex: Male/ Female

7. Gender: Male/ Female/ Other

8. Do you have hearing loss that was diagnosed by an audiologist? Y/N

9. If you have a hearing loss, how long have you had suspected or diagnosed hearing problems?

   - ☐ 6 months to 1 year
   - ☐ 1 year or greater

10. If you have a hearing loss, please indicate the level of your hearing loss if you know it:

    - Mild 25-40dB
    - Moderate 40dB-55dB
    - Moderately Severe 55dB-70dB
    - Severe 70dB-90dB
    - Profound >90dB

11. Do you wear a hearing aid? Y / N

12. Are you on any kind of prescription or illicit medication that might affect your brain function (e.g. **stimulants** a.k.a. 'uppers' like amphetamine, cocaine; **depressants** a.k.a. 'downers', sedatives, hypnotics, or narcotics like opioids, barbiturates, benzodiazepines; **hallucinogens** psychedelics, dissociatives and deliriants like psilocybin, LSD, nitrous oxide; **euphoriants** like MDMA (ecstasy) or MDA; or **anxiolytics** like benzodiazepines; **mood stabilizers** to treat bipolar disorders or schizoaffective disorder; **antipsychotics** to treat schizophrenia or mania; **steroids**) ? Y / N

13. Do you have any psychiatric condition(s), neurological condition(s), or brain injuries that would affect your brain function (e.g. epilepsy, tbi, stroke, aphasia, depression, schizophrenia, ADHD, autism, and obsessive-compulsive disorder) ? Y / N

APPENDIX B Consent Form

DALHOUSIE UNIVERSITY

CONSENT FORM

Project title: Using Functional Neuroimaging to Investigate the Relationship Between Memory and Hearing Loss

Lead researcher: Juliana McLaren, Graduate Student School of Communication Sciences and Disorders, Dalhousie University, Juliana.Mclaren@dal.ca

Other researchers
Dr. Steven Aiken, Associate Professor School of Communication Sciences and Disorders, Dalhousie University, Steve.Aiken@dal.ca

Funding: Faculty of Health Professions Internal Grant – HP Research Establishment Grant

Introduction
We invite you to take part in a research study being conducted by Juliana McLaren, a graduate student at Dalhousie University as part of her master's degree program. Choosing whether or not to take part in this research is entirely your choice. There will be no impact if you decide not to participate in the research, your participation is completely voluntary. The information below tells you about what is involved in the research, what you will be asked to do and about any benefit, risk, inconvenience or discomfort that you might experience.
You should discuss any questions you have about this study with Juliana. Please ask as many questions as you like. If you have questions later, please contact Juliana.

Purpose and Outline of the Research Study
The goal of this study is to examine the brain activity of people with hearing loss who wear hearing aids, and people with hearing loss who don't wear hearing aids. Brain responses to words will be compared between the groups, as well as with a people who do not have hearing loss. We want to examine how hearing loss and hearing aids can affect memory for words.

Who Can Take Part in the Research Study
You may participate in this study if you are 50 years of age or older. You may participate if you have hearing loss, or if you do not have hearing loss. For the purposes of this

study we consider hearing loss as being greater than 40 dB. If you have hearing loss, you may participate if you have a hearing loss, or if you do not.
You may not participate in the study if you have uncorrected hearing loss, as the memory task requires good vision. You may not participate from this study if you were born with a hearing loss. You may not participate in this study if you are left handed. You may not participate in this study if you have had severe brain injuries, concussions, or strokes. You may not participate in this study if your first language is not English. All of these factors would affect the organization, development, or electrical activity of your brain in a way that would make the interpretation of our study results difficult.
Although you may pass the pre-screening requirements, you can still be excluded from the study after testing upon arrival at the lab. We will verify your hearing loss using an audiometric test, and you may be excluded depending on these results. If you have a hearing aid, we will check to make sure that your hearing aid is providing enough sound for you to participate in this study. You may also be excluded if your hearing aid settings do not fit the specifications for this study.
Your cognitive function will also be assessed using the Montreal Cognitive Assessment. You will still be compensated for your time ($10) if you are excluded for these reasons or any others when you arrive at the lab.

What You Will Be Asked to Do
You will be asked to make one visit to the Electrophysiology lab at Dalhousie University's School of Communication Sciences and Disorders. The lab is located on the second floor of the Charles Tupper Medical Building. A research assistant will be there to meet you at the reception desk of the School of Communication Sciences and Disorders prior to your appointment. You will be asked to complete a short questionnaire with some personal information for the purposes of ensuring you are eligible to complete the study, and to get basic information for statistical analysis, such as age, gender, education. Then you will be fitted with an electrode cap.
After you are fitted with the cap, you will be shown 50 words. You will be asked to remember the words and indicate if they are a living thing (ex. animal, plant, person) or a not living thing (ex. rock, car, house). You will then be shown 100 words and you will be asked to indicate if the word was one that you saw in the previous set, or if they are new words.
You will be given the chance to wash your hair after the experiment. You will be shown all products that will be used to apply the electrodes, and given a chance to ask questions about them.
After the study you will be given the opportunity to ask any questions that you may have regarding the study. Should you think of any other questions after you leave the lab, please contact the lead researcher, Juliana McLaren (Juliana.mclaren@dal.ca).

Possible Benefits, Risks and Discomforts
Participating in this study will contribute to the scientific community's knowledge about hearing loss and memory. You will not receive treatment for either of these conditions

for participating.
Some risks of this study include eye irritation from staring at the computer screen. However, you will be given a break between the 1st and 2nd part of the study to minimize this risk. There is also risk of boredom. However, the task takes less than half an hour so we have also minimized this risk. Electrodes are applied first by exfoliating the skin. You may feel some light scraping sensations, however significant irritation is not likely to occur. Alcohol pads are also applied to the skin, but significant irritation is not likely to occur. A salt based gel will be applied to the scalp so that your electrophysiological activity can be recorded. The gel may dry during the course of the experiment, however no discomfort is associated with this. There is no risk of electric shock from the use of this equipment, which is battery-powered.

Compensation / Reimbursement
To thank you for your time, you will be given a $20 reimbursement for your session. You are only eligible to participate in this study one time. If you are deemed ineligible for the study upon arrival in the lab and undergoing further screening procedures, you will be given a consolation of $10 to thank you for your time.

How your information will be protected:
Privacy:
Your privacy will be protected through the following measures. Our lab is located in a private space and you will be away from others who could see or hear the experimental results. Any emails to you will not disclose your participation in the study.

Confidentiality:
Paper copies of confidentiality forms, questionnaires, and screening assessments will be kept in separate locked file cabinets in our lab. We will code any questionnaires, and screening documents with a random series of letters and numbers. This is so that we can look at the relationship between these assessments, and your brain wave patterns. This code will not be linked to you in any identifiable way, and will not be put on this consent form.
All computer files will be kept on a School of Communication Sciences and Disorders computer and password protected. In the event that data files need to be taken offsite, they will be on a password protected laptop or USB stick, and will not indicate your name or identity.
We will not disclose any information about your participation, unless compelled to do so by law. That is, in the unlikely event we witness or suspect abuse or neglect, we are required to contact the authorities.

Data retention:
Information that you provide to us will be kept private. Only the research team at Dalhousie University will have access to this information. We will describe and share our findings in Juliana's thesis, presentations, public media, journal articles. We will be very

careful to only talk about group results so that no one will be identified. This means that ***you will not be identified in any way in our reports***. The people who work with us have an obligation to keep all research information private. All your identifying information will be securely stored. All electronic records will be kept secure in an encrypted file on the researcher's password-protected computer.

If You Decide to Stop Participating

You are free to leave the study at any time. If you decide to stop participating at any point in the study, you can also decide whether you want any of the information that you have contributed up to that point to be removed or if you will allow us to use that information. However, once you leave the lab your data will be deidentified and you will not be able to withdraw it. Should you decide to stop participating, you will be compensated $20.

How to Obtain Results

We will provide you with a short description of group results when the study is finished, if you are interested. No individual results will be provided. Please indicate if you would like the results by indicating as such on the signature page of this form.

Questions

We are happy to talk with you about any questions or concerns you may have about your participation in this research study. Please contact Juliana McLaren (juliana.mclaren@dal.ca) or Steven Aiken at (902 494-1057 , Steve.Aiken@dal.ca) at any time with questions, comments, or concerns about the research study (if you are calling long distance, please call collect). We will also tell you if any new information comes up that could affect your decision to participate.

If you have any ethical concerns about your participation in this research, you may also contact Research Ethics, Dalhousie University at (902) 494-1462, or email: ethics@dal.ca (and reference REB file #).

Signature Page

Project Title: Using Functional Neuroimaging to Investigate the Relationship Between Memory and Hearing Loss

Lead Researcher: Juliana McLaren, Dalhousie University School of Communication Sciences and Disorders, juliana.mclaren@dal.ca

I, _____, have read the explanation about this study. I have been given the opportunity to discuss it and my questions have been answered to my satisfaction. I understand that I have been asked to take part in a study that will use electrodes to record my brainwaves that will occur at the School of Communication Sciences and Disorders Electrophysiology lab. I understand that group analysis will be conducted, and that my personal results will never be made public. I agree to take part in this study. My participation is voluntary and I understand that I am free to withdraw from the study at any time. Should I choose to withdraw, I have the option to indicate if I would like the results already collected to be added to the data for this study, or if I would like them to be deleted. I understand that upon leaving the lab today, I can no longer withdraw my results from the study.

_____	_____	_____
Participant Name	Signature	Date

Please indicate if you would like the group results sent to you, and provide the information where you would like the results sent:

- ☐ I want the group results of the research sent to me
- ☐ I do not want the group results sent to me

I would like the results sent to this email address:

OR I would like the results sent to this mailing address:

_____
_____
_____
_____

APPENDIX C Demographic Questionnaire

Participant Questionnaire

RESEARCHER USE ONLY **Project code:** JM100A **Participant #:** _____ **Date:** _____

Birth month, year: _____
Gender: _____
Dominant hand: _____
Have you had any significant brain injuries (concussions, etc): _____
Do you have any <u>uncorrected</u> visual impairments: _____
Please select the highest level of education you have completed:

- ☐ No formal education
- ☐ Elementary or middle school or incomplete high school
- ☐ High school diploma
- ☐ College/trades school
- ☐ University undergraduate/bachelor's degree
- ☐ Graduate school (masters, doctorate)

Please specify the number of years of formal education you have completed:
_____ years
If you have hearing loss, how long have you had difficulty hearing:_____
What was the first language you learned at birth: _____
Do you speak any other languages? If so list them, and complete question #:
_____
Please complete the following table. Immersion refers to significant exposure to a language, at home, at school or in the community. Significant exposure is anything over 20%.

Language	Year of first exposure (ex. 0)	Were you ever immersed in the language (Y/N)	Year of immersion (ex. 2)

Is there any more information about you that you think is relevant for this study?
_____
_____