Hearing Loss is Associated with Widespread Alterations in Functional Connectivity in Adults with Mild Cognitive Impairment

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ABSRACT

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Hearing-loss (HL) is prevalent in adults with mild cognitive impairment (MCI), a risk state for Alzheimer's disease. Both MCI and HL are associated with alterations in brain connectivity. These connectivity alterations have been associated with cognitive impairment in both groups and progression to Alzheimer's disease in individuals with MCI. This suggests that altered brain connectivity may be related to the cognitive decline and increased dementia risk in these two populations. Despite this, HL and cognitive impairment are rarely investigated together in the context of brain connectivity. Based on this, we characterized the relationship between two measures of hearing and brain connectivity in adults with MCI. All data are from the Comprehensive Assessment of Neurodegeneration and Dementia study of the Canadian Consortium on Neurodegeneration in Aging. Based on a pure-tone screening protocol participants were classified as having either normal hearing (NH, n=60, %female= 40%, age=74.5, education=15.19) or HL (n=35, %female=48%, age=70.07, education=16.5). Groups were matched on gender and did not differ in age/education/Montreal Cognitive Assessment

scores. Speech reception-thresholds were used as a measure of supra-threshold hearing ability. Analyses tested whether default-mode network and Heschl's gyrus connectivity differed as a function each hearing measure. In all analyses, age, education, reading acuity, and contrast sensitivity were included as covariates. In all analyses using speech-reception threshold as a variable, pure-tone HL was controlled for. Hearing loss was associated with widespread alterations in functional connectivity. Compared to participants with NH, those with pure-tone HL had decreased connectivity between the default-mode network and the bilateral caudate and right thalamus. Compared to individuals with NH, those with pure-tone HL had increased connectivity between right Heschl's gyrus and the right insula, the right operculum, and within right Heschl's gyrus itself. They also had decreased connectivity between right Heschl's gyrus and three regions in the left frontal lobe. Poorer speech-reception threshold was also associated with decreased connectivity between right Heschl's gyrus and three regions in the left frontal lobe. Finally, there was no relationship between either measure of hearing and the connectivity of left Heschl's gyrus. These results show that in individuals with MCI HL is associated with altered functional connectivity in regions responsible for sensory and higher order cognitive processing. This suggests that the increased risk for cognitive decline and dementia seen in individuals with HL may be due to alterations in functional connectivity reducing the brains' ability to compensate for aging and Alzheimer's disease related brain pathology.

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1.0 Introduction

This thesis is about the relationships between mild cognitive impairment (MCI), hearing loss, and brain connectivity. The goal of the present study was to examine the relationships between two measures of hearing loss and resting-state brain connectivity in older adults with MCI. Therefore, the present study requires the review of two separate literatures: (1) MCI and the associated changes in resting-state brain connectivity and (2) hearing loss and the associated changes in resting-state brain connectivity.

First, I will introduce Alzheimer's disease (AD) and spectrum of cognitive impairment that manifests in the process of aging. I will then introduce MCI as a clinical entity and address the prevalence, presentation, and the suspected neuropathology of the disorder. Evidence for the importance of alterations in brain connectivity in the development, expression, and progression of MCI will be presented. Next, I will review the clinical implications, prevalence, and presentation of hearing loss in older adults. The alterations in brain connectivity associated with hearing loss and the relationships between these connectivity alterations and cognitive impairment and cognitive decline will be presented. The potential pathways underlying the relationships between hearing loss, brain connectivity, and cognitive impairment/decline will be discussed. Finally, I will review existing evidence regarding the relationships between hearing loss, brain connectivity, and MCI.

1.1 Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder that is the most common cause of dementia. It leads to the progressive damage and loss of neurons in the brain and is characterized by extensive brain atrophy and a loss of cognitive function. The disorder initially affects regions of the brain that are responsible for memory and language, but the widespread

neuronal damage that occurs with disease progression eventually impacts nearly all aspects of cognitive functioning.

Alzheimer's disease is characterized by the abnormal deposition of two abnormal proteins: amyloid-beta and tau (Braak & Braak, 1991, 1997). These two pathologies are known to spread throughout the brain with characteristic patterns (Cho et al., 2016). Extracellular amyloid deposits accumulate and form amyloid-beta plaques and tau contributes to the formation neurofibrillary tangles (Braak & Braak, 1991, 1997). In individuals with AD, amyloid deposition initially occurs diffusely in the association cortices and neocortex and then spreads to the medial temporal lobe, including the hippocampus, and then to the brain stem and cerebellum (Braak & Braak, 1997; Thal et al., 2002). The distribution of amyloid deposits seems to have limited significance to the progression of AD symptomology (Cho et al., 2016). Conversely, tau spreads throughout the brain in a stepwise fashion that is correlated with patterns of neurodegeneration and the manifestation of clinical symptoms in AD (Cho et al., 2016; Ossenkoppele et al., 2016; Schöll et al., 2016). Neurofibrillary tangles, neuropil threads, and neuritic plaques are forms of neurofibrillary changes that are due to the abnormal accumulation of hyperphosphorylated tau (Braak & Braak, 1997). Neurofibrillary tangles and neuropil threads first develop in the transentorinal region of the medial temporal lobe and their distribution pattern and density corresponds with the clinical expression of AD (Braak & Braak, 1997).

To date, there are no disease modifying treatments available for AD. Due to the lack of effective treatments, focus has shifted to the early diagnosis of AD and other dementias. In response, the fields of aging and dementia research have focused on identifying reliable markers that can be used for the early diagnosis of AD and other dementias (Petersen et al., 2014). If cognitive impairment is identified early, interventions can be applied before significant

pathological damage has occurred, which may be a promising strategy for delaying AD progression (Petersen et al., 2018). Several markers that may be used for the early diagnosis of AD have been identified. There is substantial evidence that the brain changes associated with AD are thought to begin 20 years or more prior to the onset of AD symptoms (Braak et al., 2011; 2022 Alzheimer's Association Report, 2022). These findings have influenced the extension of the spectrum of AD to include amnestic MCI, which is now recognized as an important phase in the progression of AD.

1.2 Mild Cognitive Impairment

There is a substantial amount of evidence indicating that there is a phase of AD when individuals gradually experience a progressive cognitive decline (Braak et al., 2011; Petersen et al., 2016; Schneider et al., 2009). This progressive cognitive decline is thought to be due to the accumulation of AD related pathology in the brain (see Markesbery et al., 2010 and Stephan et al., 2012 for reviews). When the cognitive impairment is sufficient to cause interference with daily functioning, the individual may be diagnosed with AD (Petersen et al., 2014). This early phase on the continuum of cognitive impairment is considered a stage of prodromal AD has been termed amnestic MCI (Petersen et al., 2014). Amnestic MCI is characterized by a subjective memory complaint from the individual, objective evidence of memory impairment for their age and education level, generally intact cognitive function, and a lack of dementia (Petersen et al., 2004). It is considered a risk-state for AD based on the presence of early AD pathology and the increased development of AD in these individuals (Petersen, 2004; Jessen et al., 2020).

1.2.1 Evolving Conceptualizations of MCI

Several sets of terminology for MCI and related conditions have evolved over the years. The initial use of the term MCI came from investigators at New York University who conceptualized it as Stage 3 on the Global Deterioration Scale, which is a seven-stage scale that

assesses severity of cognitive decline and dementia (Reisberg et al., 1988). Since then, the conceptualization and criteria for MCI has evolved to represent a growing understanding of the disorder. One important distinction between the various conceptualizations and criteria for MCI has been the role of memory. While some criteria have conceptualized MCI as an isolated memory impairment, others have taken a broader approach and include individuals with mild impairment in domains such as language and visuospatial skills (see Petersen et al., 2014 for a review). Another important distinction between the various criteria is the incorporation of AD related biomarkers, which are measurable physical substances that can indicate the presence of a disease, risk for developing a disease, and disease progression (Petersen et al., 2014).

Early criteria for the detection of early stages of AD focused on the presence of a memory disturbance (Petersen et al. 1999). However, due to accumulating evidence that not all individuals with MCI had an early memory impairment and that not all individuals with MCI had an early form of AD, the Key Symposium was held in 2003 (Petersen et al., 2014). The two goals of the Key Symposium included (1) broadening the MCI classification scheme beyond memory impairment and (2) to recognize that MCI could result from a variety of aetiologies other than AD (Petersen et al., 2004; Winblad et al., 2004). These criteria demonstrated that MCI has syndromic subtypes and led to a distinction between amnestic MCI and non-amnestic MCI, recognizing that MCI subtypes have variable aetiologies and outcomes (Petersen et al., 2016).

Typically, amnestic MCI is considered a form of prodromal dementia due to AD. It is, however, important to note that not all amnestic MCI is early AD and not all individuals with amnestic MCI will progress to developing AD (Petersen et al., 2016). To address this, the National Institute on Aging and Alzheimer's Association developed criteria for the whole AD spectrum to help make the diagnostic criteria more explicit (Petersen et al., 2016). These criteria

incorporated the presence of AD related biomarkers to further understanding of the underlying pathology and predict disease outcomes (Jack et al., 2011; Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011).

To summarize, the concept of MCI and preclinical/prodromal AD has evolved over recent decades (Dubois et al., 2007; Dubois et al., 2010; Dubois et al., 2014; Petersen et al., 2016). While early conceptualizations of MCI focused on the presence of an isolated memory impairment, the concept was broadened to define a clinical syndrome with multiple clinical profiles thought to be due to a variety of aetiologies (Winblad et al., 2004; Petersen et al., 2004). The current conceptualization is that MCI is an intermediate stage of cognitive impairment between normal age-related cognitive decline and dementia. It is often, but not always, a transitional phase between normal aging and dementia (Petersen et al., 2014). In this new definition, the initial purpose of diagnosing early AD was restricted to a subtype of MCI, termed amnestic MCI or MCI due to AD (Petersen et al., 2014).

1. 22 MCI Subtypes

While this thesis focuses on the subtype of MCI that is thought to be a form of prodromal AD, it is important to note that there are several subtypes of MCI that are thought to be associated with various aetiologies and outcomes (Petersen et al., 2004; Petersen et al., 2014). One way to classify individuals with MCI is: amnestic MCI (MCI) in the case where the impairment is in memory, and non-amnestic MCI in the case where the impairment is in a domain or domains other than memory, such as executive functioning, language, or visuospatial abilities (Petersen et al., 2016). In addition, the impairment could also be restricted to one cognitive domain or to multiple cognitive domains (single domain vs multi-domain MCI). As previously noted, cases of MCI considered to be a form of preclinical AD refers only to the cases of amnestic MCI, in which the impairment is in the domain of memory (Petersen et al., 2014).

Criteria for MCI subtypes may also include the presence of certain AD related pathologies, such as biomarkers for abnormal amyloid and tau (Dubois et al., 2014).

1.23 MCI Prevalence

Estimates of MCI prevalence have been variable; however, it is thought that a great deal of the variability in these prevalence figures can be explained by methodological heterogeneity and the use of different MCI criteria across studies (Petersen et al., 2016). For example, estimates of MCI prevalence that have been restricted to individuals with amnestic MCI typically underestimate MCI prevalence (Petersen et al., 2016). Studies using the more recent, expanded criteria for MCI have produced considerably higher estimates (Petersen et al., 2014). Other factors that have influenced variability in MCI prevalence estimates include factors such as the retrospective vs prospective application of criteria to data and the method of data collection (Petersen et al., 2016). Despite this, numerous international studies involving several thousands of subjects have been completed and have estimated the overall prevalence of MCI in the 12%-18% range in persons over the age of 60 years (Busse et al., 2006; Di Carlo et al., 2007; Ganguli et al., 2010; Larrieu et al., 2002; Manly et al., 2008).

1.24 MCI Risk Factors

The major risk factors associated with cognitive decline and dementia are also associated with MCI. There is increasing evidence that multiple factors, including diabetes, obesity, physical inactivity, depression, smoking, race, and a lower level of education play a role in the development and expression of MCI and AD (Lopez et al., 2003; Petersen et al, 2014; Ritchie, 2004; Tervo et al., 2004). While there is no strong agreement on the extent of the associations between the above risk factors and MCI, this may be due to corrections for age and education levels on the neuropsychological tests that are used to classify MCI (Petersen et al., 2014). In addition, the different subtypes of MCI may have variable relationships with different risk

factors. Risk factors for MCI include non-modifiable risk factors, such as age and genetic factors, and modifiable risk factors such as vascular factors and education level (Ravaglia et al., 2006; Roberts & Knopman 2013). In addition, the e4 allele of the APOE4 gene, which is a well-known risk factor for AD, has also been identified as a risk factor for MCI (Lin et al., 2018a,b; Lopez et al., 2003).

1.25 MCI Progression

The progression of individuals with MCI has been a focus of recent aging and dementia research (Petersen et al., 2016). The annual rate of progression from MCI to AD is estimated to be between 8% and 15% per year (Petersen et al., 2016). In addition, several longitudinal studies have followed cognitively normal subjects to characterize their progression rate to MCI. The Mayo Clinic Study of aging followed individuals aged 70 years and older for a median duration of 5 years and found a progression rate of 5-6% a year (Roberts et al., 2012). Progression rates are lower in younger subjects and increase with age (Petersen et al., 2016). Finally, estimates of cognitively normal people progressing to MCI and individual with MCI progressing to AD have both been somewhat variable, and certain methodological issues likely explain some of the observed variation (Petersen et al., 2016).

There is evidence that clinical variables, such as neuroimaging and biomarker characteristics, can predict disease progression in individuals with MCI (Petersen et al., 2016). In general, medial temporal lobe atrophy measured with magnetic resonance imaging (MRI) and a hypometabolic pattern consistent with that seen in AD on positron emission tomography (PET) imaging tend to predict progression from MCI to AD (Weiner et al., 2015; Dickerson et al., 2005; Landau et al., 2010; Landau et al., 2012). It is also suggested that the spread of tau outside of the medial temporal lobe and into the lateral temporal structures is associated with poorer prognosis and a more likely and more rapid progression from MCI to AD or dementia.

Additionally, it is well known that the APOE4 genotype is associated with AD susceptibility and carriers of the APOE4 genotype are more likely to progress rapidly along the continuum of cognitive decline (Koutsodendris et al., 2022). Finally, it is speculated that lower brain connectivity predicts more rapid cognitive decline, and that amyloid burden accelerates this process (Lin et al., 2018a).

Knowledge of the mechanisms that contribute to conversion from cognitively normal to MCI and MCI to AD could help modify available therapies and contribute to the development of new treatments that may slow or halt disease progression. Neuroimaging studies have provided some evidence for how MCI progresses to AD (Lin et al., 2018a,b). While there is no current consensus on the mechanisms responsible for MCI to AD conversion, resting-state MRI may be useful in predicting AD-related cognitive decline (Lin et al., 2018a,b). The method of resting-state MRI will be discussed in a later section.

1.26 MCI Neuropathology

As a progressive disorder, AD related brain pathology is thought to begin decades before symptom onset. The abnormal accumulation of amyloid beta plaques, tau, and neurofibrillary tangles in the brain is thought to begin 10-20 years prior to symptom onset (Bateman et al., 2012; Bennett et al., 2005; Galvin et al., 2005; Markesbery et al., 2006; Perl, 2010; Petersen et al., 2006; Saito & Murayama et al., 2007). AD related brain pathology is present in individuals with MCI and seems to lie on a continuum between cognitively normal individuals and individuals with AD (Beason-Held et al., 2013; Petersen et al., 2014; Schneider et al., 2009).

The accumulation of amyloid and tau in the brain disrupts biological processes and results in neuropathology, neuroinflammation, neurodegeneration, network deficits, and clinically observable cognitive decline. Individuals with AD experience widespread neurodegeneration and a loss of functional connectivity as the disease progresses, indicating that

neural network dysfunction may be an important marker for the early detection of AD (Buckner et al., 2005; Seeley et al., 2009). Findings regarding functional connectivity in individuals with preclinical AD and MCI have been less consistent. In individuals with MCI and preclinical AD, many studies have reported decreased functional connectivity with increased amyloid burden while other studies have reported both regions of increased and decreased functional connectivity with increasing amyloid burden (Schultz et al., 2017). Based on this, it is thought that AD shows a pattern of increased brain connectivity in some regions in the early stages of the disease that is followed by a increasing and widespread loss of connectivity as the disease progresses. According to this view early amyloid accumulation is associated with an initial increase in functional connectivity (Schultz et al., 2017). Following this, increasing tau pathology is associated with a progressive loss of functional connectivity (Schultz et al., 2017). Finally, tau pathology is thought to disrupt functional connectivity to a greater extent than amyloid levels (Schultz et al., 2017).

1.27 MCI Biomarkers

The early identification of AD at the MCI and/or preclinical disease stages depends on the identification of biomarkers that can aid in early AD diagnosis (Badhwar et al., 2017). Some biomarkers directly reflect AD pathology by providing evidence for the presence of key proteins that are known to be deposited in the brain throughout the course of AD, such as levels of amyloid and tau (Albert et al., 2011). Other biomarkers provide indirect evidence of AD through indices of neuronal injury, which can be measured with various imaging methods (Albert et al., 2011).

The amyloid plaques that are a hallmark feature of AD can be directly measured in plasma and cerebrospinal fluid. Markers for amyloid-beta deposition include lower cerebrospinal fluid levels of amyloid beta and positron emission tomography evidence for amyloid deposition

in the brain (Blennow & Hampell, 2003; Shaw et al., 2005; Selkoe, 2006). Tau accumulation is measured by increased total tau or phosphorylated tau in the cerebrospinal fluid (Blennow & Hampell, 2003; Shaw et al., 2005; Selkoe, 2006). These biomarkers directly reflect amyloid and tau deposition in the brain (Fagan et al., 2006).

There are also markers for neuronal injury present in individuals with MCI and AD that are considered indirect markers of AD pathology. Several lines of research using various imaging modalities have provided evidence of certain brain changes across the trajectory of normal aging, MCI, Alzheimer's disease, and other dementias (Petersen et al., 2014). Elevated tau levels are associated with the pathophysiological processes of AD and have damaging effects on neurons and synapses (Albert et al., 2011). There are structural and functional brain changes in individuals with MCI that appear to reflect damage to neurons and synapses (Jack et al., 2008). Many of these alterations are the same location and type as the neurodegeneration that is seen in AD and may be associated with tau pathology (Albert et al., 2011). For example, a loss of hippocampal volume can be detected in individuals with MCI using MRI, this is notable as the hippocampus is known to be preferentially affected by AD (Albert et al., 2011).

Changes in brain connectivity are thought to begin years before an AD diagnosis and may be an important marker for early AD (Sperling et al., 2011; Matthews and Hampshire 2016; Vemuri et al., 2012). Brain connectivity can be measured with resting-state functional magnetic resonance imaging (fMRI), which indirectly measures brain connectivity using blood oxygenation. Alterations in resting-state fMRI can be detected prior to extensive neurodegeneration and neuronal loss associated with AD pathology, suggesting that it is a biomarker for neuronal injury that holds promise for early diagnosis (Jack et al., 2018). The

findings regarding changes in brain connectivity in individuals with MCI are presented after a review hearing loss and its relevance to MCI.

1.3 Hearing Loss

1.31 Hearing Loss Prevalence and Cost

Hearing loss is the third most common chronic health condition in older adults and the third largest cause of years lived with disability globally (Chadha et al., 2021). Hearing loss currently impacts an estimated 20% of the global population, with over 1.5 billion people currently experiencing some degree of hearing loss (Chadha et al., 2021). It is estimated that by 2050, nearly 2.5 billion individuals, will be living with some degree of hearing loss (Chadha et al., 2021).

Hearing loss has high costs for societies and families, increasing the social, economic, and healthcare needs of older adults (Powell et al., 2022). The annual global cost of unaddressed hearing loss is an estimated US$1 trillion (Chadha et al., 2021). In addition to the financial burden, hearing loss is also associated with declines in self-reported activities of daily living and overall quality of life. Indeed, the loss of communication and social interaction that accompanies hearing loss can cause great distress (Chadha et al., 2021).

1.32 The Presentation of Hearing Loss

Age-related hearing loss, also called presbycusis, accounts of the largest percentage of hearing loss cases around the world and presents as a gradual decrease in hearing ability (Powell et al., 2022). The outer hair cells and sensory cells in the cochlea are progressively damaged, which results in the impaired coding of sound, decreased hearing precision, and a distorted auditory signal being sent to the brain (Powell et al., 2022). Age-related hearing loss is thought to first impair the ability to understand speech and subsequently the ability to detect, identify, and localize sounds (Gates & Mills, 2005).

Age-related hearing loss affects the ability to detect the higher frequency of speech sounds before it does low frequency sounds (Powell et al., 2022). This results in the reduced ability to hear high frequency consonants, which are the parts of speech that provide clarity (Powell et al., 2022). Indeed, many older adults with hearing loss report that speech sounds are "muddled" or "garbled", especially in the presence of background noise. This can lead to difficulties hearing others in noisy settings and can result in difficulty communicating or interacting with others (Powell et al., 2022).

1.33 Measuring Hearing Ability

An individual's hearing ability depends on two processes and components of the auditory system: 1) the peripheral auditory system and 2) the central auditory system and additional non-auditory influences, such as cognitive processing, education, situational influences, and self-perception (Musiek and Baran 2018). The auditory systems and their components are inter-related and work together to allow an individual to detect and understand sound (Powell et al., 2022).

1.34 Peripheral Auditory Function

Measures of peripheral hearing are the most used measure of hearing loss. The peripheral auditory system includes the outer ear, ear drum, middle ear bones, and cochlea (Musiek and Baran 2018). These components transform the auditory sound waves captured by the outer ear and ear drum into mechanical energy in the middle ear and encode information as an electrical signal in the cochlea to be sent to the central auditory system in the brain (Musiek and Baran 2018). An individual's ability to detect the presence of auditory stimuli initiates in and is dependent on the peripheral system (Musiek and Baran 2018).

A test of pure-tone audiometry with the results graphically recorded on an audiogram is the most common clinical tool for measuring peripheral hearing acuity (Katz, 2015). An auditory

stimulus (pure tone) is presented at several frequencies [measured in Hertz (Hz)], commonly within the range of 250-8000 Hz. The presentation level of each pure tone begins at an audible level and is decreased to determine the lowest threshold level [i.e., the volume in decibels hearing level (dB HL)] at which the individual can detect the tone (Powell et al., 2022).

1.35 Central Auditory Function

After passage through the peripheral auditory system, the electrical signal created by the cochlea is sent to the auditory nerve where is it decoded by the brain (Musiek and Baran 2018). Central hearing ability depends on the integrity of the auditory signal passed from the peripheral auditory system and higher-level cognitive processing, as the brain must understand and make sense of environmental sounds (Gates, 2012; Humes et al., 2012; Powell et al., 2022).

Central auditory function is often measured with the presentation of speech within the presence of selected types of background noise with increasing volume (i.e., speech-in-noise testing) or tasks of central auditory processing ability, such as listening to degraded speech (Gates, 2012). Current clinical audiologic testing of central auditory function primarily considers basic speech-in-noise ability, not necessarily higher-level auditory cognitive tasks. It is, however, important to note that central hearing ability encompasses more than speech-in-noise ability. In addition, the interdependence between the central auditory function and cognitive processing blurs the distinction between the two processing abilities and their measurement (Powell et al., 2022).

1.4 Hearing Loss and Cognition

Hearing loss has been associated with several adverse health outcomes, including cognitive impairment, decline, and dementia. Hearing loss has been associated with declines in global cognitive function, executive function, processing speed, and memory (Loughrey et al., 2018). Even mild levels of hearing loss (i.e., the pure-tone average of hearing thresholds at 0.5,

1, 2, and 4 kHz within 25-40 dB) can increase risk for cognitive decline in those who are cognitively normal at baseline but hearing impaired (Lin et al., 2011; Gallacher et al., 2012). Moreover, the relationship between hearing loss and accelerated cognitive decline and dementia is well-established (Deal et al., 2019). Indeed, recent work has linked hearing loss with roughly a two-fold increase for cognitive decline and dementia (Lin et al., 2011; Livingston et al., 2017, 2020; Loughrey et al., 2018).

There is increasing evidence for a strong link between hearing loss and the development of dementia in older age. The Lancet Commissions (Livingston et al., 2017, 2020) reported a pooled relative risk of 1.9 times greater risk of incident dementia in individuals with hearing loss aged 55 years and older compared to those with normal hearing. Moreover, hearing loss is the leading potentially modifiable risk factor for dementia, with up to 8% of global dementia cases estimated as being attributable to hearing loss (Livingston et al., 2017; Livingston et al., 2020). This is notable, as delaying the onset of dementia by 5 years could lead to a 57% reduction in the number of dementia cases (Sperling et al., 2011).

1.41 Hearing Loss and Cognitive Impairment

Hearing loss is prevalent in and associated with mild cognitive impairment (MCI). A recent systematic review and meta-analysis observed a significant association between hearing loss and MCI (Lau et al., 2021). The pooled risk ratio of MCI prevalence in people with hearing loss was 1.44 and significantly more people with peripheral hearing loss had MCI compared to those without hearing loss (risk ratio = 2.06). This indicates that adults with hearing loss have a 1.44 greater risk of receiving an incident MCI diagnosis than those without peripheral hearing loss (Lau et al., 2021).

Although the association between peripheral auditory function and cognitive decline is well-established (Livingston et al., 2020), the relationship between cognitive decline/dementia

and central auditory function is less understood (Powell et al., 2022). However, several studies have reported a relationship between central hearing loss and cognitive impairment and decline (Gates et al., 1996; Gates et al., 2008; Gates et al., 2011). Indeed, there is some evidence that central auditory dysfunction may be a precursor to AD (Gates et al., 2011). For instance, central auditory dysfunction is more prevalent in adults with MCI compared to cognitively normal older adults (Gates et al., 2008). In addition, central auditory dysfunction has been shown to precede an incident dementia diagnosis by 3 to 12 years with a risk ratio of 9 to 12, indicating that adults with central auditory dysfunction have a 9 to 12 times greater risk of receiving an incident dementia diagnosis than those without central auditory dysfunction (Gates et al., 1996). Measures of central auditory dysfunction have also been shown to predict the risk of a subsequent AD diagnosis three years after baseline measurements (Gates et al., 2011). Tests of central auditory function also correlate with the thickness of several cortical structures and with the connectivity of several brain regions that are commonly affected by AD (Tuwaig et al., 2016). Based on this, the central auditory dysfunction may reflect the presence of neurodegeneration and other AD related pathology and predicts risk for later dementia (Gates et al., 2011; Littlejohn et al., 2017).

1.42 Hearing Loss and Brain Plasticity

The human cortex has the capacity for neuroplasticity across the lifespan and can adapt to alterations in sensory input (Sharma & Glick, 2017). Indeed, neuroplastic reorganization of several brain regions and networks accompanies hearing loss. One form of neuroplasticity seen in individuals with hearing loss is intra-modal plasticity, where changes in brain structure and function are induced within a cortical region, such as the primary auditory cortex, because of decreased auditory input (Sharma & Glick, 2017). Hearing loss may also result in cross-modal

plasticity, whereby the auditory cortex is recruited for visual or somatosensory processing (Sharma & Glick, 2017). This plasticity is not restricted to individuals with severe and profound hearing loss or deafness; cross-modal plasticity appears to occur in mild-moderate hearing loss that is related to aging (Sharma & Glick, 2017). In individuals with hearing loss, there is often increased connectivity seen between auditory and visual regions or auditory and frontal regions (Sharma & Glick, 2017). This is thought to represent a compensatory recruitment of additional cortical regions in response to decreased input to the auditory cortex taxing the brain (Sharma & Glick, 2017). Importantly, alterations in brain connectivity have been implicated in the predominant hypotheses that attempt to explain the relationship between hearing loss and cognitive decline.

1.5 Potential Pathways Linking Hearing and Cognition

Five hypotheses have been proposed to explain the relationship between sensory loss and cognitive decline (Lindenberger & Baltes, 1994). These hypotheses include the information degradation hypothesis, sensory deprivation hypothesis, the cognitive load on perception hypothesis, the common cause hypothesis, and the social mediation hypothesis (Powell et al., 2021; Pronk et al., 2019; Wayne & Johnsrude, 2015; Whitson et al., 2018). For the present study, their relevance only to hearing loss will be considered.

Current hypotheses of the mechanistic pathways between hearing loss and cognition predominantly consider peripheral hearing loss as a potential contributor to developing dementia (Powell et al., 2022). However, there is also evidence that measures of central hearing are associated with cognition and that central auditory dysfunction is a marker of cognitive decline (Powell et al., 2022). While the mechanisms involved in the relationship between hearing loss and cognitive impairment/decline have been extensively researched, it remains unknown which

of these hypotheses are correct (Whitson et al., 2018). I will now describe these hypotheses and the evidence for each.

1.51 Information Degradation Hypothesis. The information degradation hypothesis posits that the association between hearing loss and cognitive impairment/decline is due degraded auditory input being received by the brain. Importantly, the information degradation hypothesis posits that impaired cognitive performance occurs as soon as the degraded auditory input reaches the brain (Pronk et al., 2019). According to this view, resources that are typically used for higher-level cognition are reallocated to processing the degraded auditory input (Pronk et al., 2019). This increased need for cognitive resources also requires greater listening effort, particularly in terms of memory, attention, and executive function (Wingfield et al., 2005; Tun et al., 2009; Pichora-Fuller et al., 2016; Peelle, 2018). The greater cognitive and listening effort associated with hearing loss is thought to increase cognitive load, reducing the resources an individual has available for cognitive processing and resulting in impaired cognitive performance (Pronk et al., 2019).

There is substantial evidence for this mechanism (see Pronk et al., 2019 for a review). It is known that high processing load during perception interferes with the encoding of speech (Wingfield et al., 2005). There is evidence that long and short-term memory for degraded words and sentences is poorer than clearly presented speech stimuli (Murphy et al., 2000; Pichora-Fuller et al., 2006). In addition, even mild levels of background noise have been shown to negatively impact older adults' performance on the Montreal Cognitive Assessment (Dupuis et al., 2016). Importantly, the information degradation hypothesis essentially posits an acute cognitive impairment (Powell et al., 2022). Therefore, if auditory input was restored through

hearing loss treatment such as hearing aids there may be some restoration of cognitive performance on higher-level tasks (Powell et al., 2022).

1.52 Sensory Deprivation Hypothesis. The sensory deprivation hypothesis posits that the hearing loss-cognitive decline association is due to slower and more permanent changes in brain structure and function that result from long-term sensory deprivation (Pronk et al., 2019; Whitson et al., 2018). It is thought that a loss of sensory input causes under stimulation and subsequent tissue loss in certain brain areas, and that this results in impaired performance on tasks that rely on these brain areas (Pronk et al., 2019). Cortical reorganization due to prolonged sensory deprivation is thought to increase neuronal deafferentation and neuronal loss, weakening the potential for further neuroplastic changes and interfering with the brains ability to compensate for aging and AD related brain pathology (Griffiths et al., 2020; Whitson et al., 2018). This reduced ability to compensate is thought to result in the earlier presentation of cognitive impairment and dementia in individuals with hearing loss (Whitson et al., 2018). Moreover, compensation for hearing loss may trigger neurovascular and neurophysiological changes similar to those associated with dementia that may lead to declines in cognition (Wong et al., 2009).

This sensory deprivation hypothesis is supported by evidence for cortical changes as a results of hearing loss (Campbell & Sharma; Glick & Sharma, 2017; Lin et al., 2014). There is also evidence that the brain regions most affected by hearing loss are pertinent for cognition, memory, and language (Husain et al., 2011). In addition, several studies have reported that baseline hearing loss is significantly associated with subsequent changes on various measures of cognitive function (Pronk et al., 2019). What remains unknown is the extent of cortical reorganization that is necessary to evoke brain atrophy and changes in cognitive performance

(Powell et al, 2022). It is, however, important to note that the association between long-term sensory impairment and cognitive impairment does not seem to persist in younger adults (see Vernon, 2005 for a review). This suggests that impaired sensory input is not the sole factor contributing to the relationship between sensory and impairment.

1.53 Common Cause of Both Conditions. The common cause hypothesis posits that hearing loss and cognitive impairment may arise from the same underlying mechanism or mechanisms (Baltes & Lindenberger, 1997; Wayne & Johnsrude, 2015). Potential common pathological mechanisms include vascular pathologies, inflammation, and the neurodegeneration that is common in aging resulting in decreased auditory and cognitive ability (Wayne & Johnsrude, 2015; Whitson et al., 2018). Various studies have provided support for the common cause hypothesis (Wayne & Johnsrude, 2015). The common-cause hypothesis accounts for the concurrent decline of several sensory modalities associated with aging, however, the association persists in large epidemiological studies that have controlled for common aging factors (Powell et al., 2022). In addition, AD related pathology is not well established as occurring in structures of the peripheral auditory system, such as the cochlea (Griffiths et al., 2020). Finally, while dementia pathology may lead to early central auditory dysfunction prior to the onset of cognitive decline it does not explain the associations between pure-tone hearing loss and cognitive decline (Johnson et al., 2021). Therefore, a common underlying pathology is not believed to solely account for the relationship between hearing loss and cognitive impairment (Pronk et al., 2019).

1.54 Cognitive Load on Perception Hypothesis. According to the cognitive load on perception hypothesis, cognitive impairment precedes sensory impairment (Pronk et al., 2019). This hypothesis posits that cognitive impairment leads to sensory impairment because there are fewer cognitive resources available to process auditory input (Pronk et al., 2019). In this view, the cognitive resources required depends on the difficulty of the listening situation, with more difficult listening situations requiring greater cognitive resources for auditory processing (Pronk et al., 2019).

There is observational and experimental evidence supporting the cognitive load on perception hypothesis (Pronk et al., 2019). Low baseline scores on the Mini-Mental State examination have been independently associated with a faster decline in pure tone average thresholds (Kiely et al., 2012). Cognitive abilities such as reasoning, memory, and processing speed have also been independently associated with a decreased ability to detect spoken digits in noise (Moore et al., 2014; Pronk et al., 2013). In addition, there is evidence that declining processing speed partly explained declines in speech-in-noise recognition over time (Moore et al., 2014; Pronk et al., 2013). There is also evidence that increasing cognitive load results in poorer performance on speech perception tasks (Mitterer & Mattys, 2017). Moreover, when compared to groups of younger and older adults with high working memory capacity, same age peers with lower working memory capacities exhibited greater difficulty recognizing speech in noise (Gordon-Salant & Cole, 2016).

1.55 Socially Mediated Hypothesis. The socially mediated hypothesis posits that hearing loss is indirectly associated with cognitive impairment and decline through social factors. This hypothesis posits that hearing loss causes cognitive impairment/decline because it is associated with difficulties in social communication and leads to social withdrawal (Pronk et al., 2019; Whitson et al., 2018). This is hypothesis is supported by evidence that hearing loss may lead to social isolation, depression, and physical inactivity and that these factors can exacerbate cognitive decline (Pronk et al., 2013; Whitson et al., 2018).

1. 56 Challenges of Multiple Pathways. While none of these hypotheses can account for all the findings, they are not mutually exclusive. This suggests that multiple pathways are likely involved in the association between hearing loss, and cognitive impairment, and dementia (Pronk et al., 2019; Whitson et al., 2018). Interestingly, some of these hypotheses incorporate alterations in brain structure and function as a potential mechanism for the increased cognitive impairment and cognitive decline in individuals with hearing loss. Much of the evidence for the potential pathways between hearing loss and cognitive impairment comes from studies using MRI. The present study has restricted its review to changes in brain function, specifically alterations in functional brain connectivity, which can be measured with functional MRI (fMRI). The concepts of brain connectivity and fMRI, as well as key findings regarding the relationships between MCI, hearing loss, and brain connectivity are presented below.

1.6 Brain Connectivity

In the context of neuroimaging, functional connectivity refers to the relationship between the neuronal activation patterns of separate brain regions (van den Heuvel & Hulshoff, 2009). Functional connectivity is measured with the regional synchrony of low frequency fluctuations in the blood oxygenation level dependent signal that are measured with fMRI (Joel at al., 2011). Therefore, functional connectivity can be defined as a temporal correlation between the

activation time series in spatially separated brain regions (Biswal et al., 1995; Lowe et al., 1998). This temporal correlation is thought to reflect connectivity between brain regions. Using fMRI, consistent, large-scale patterns of correlated signal are now recognized as functional brain networks (Biswal et al., 1995; Lowe et al., 1998).

1.61 Resting-state Networks

Functional MRI that is recorded in the absence of an explicit task is called resting-state fMRI and it measures the functional connectivity of the brain at rest. During resting state fMRI individuals rest with their eyes closed while in the MRI machine. For patients with a cognitive impairment, this is less taxing than task-based fMRI or neuropsychological tests that require focused and sustained cognitive effort (Biswal et al., 2010). Resting-state fMRI has revealed the presence of intrinsic resting-state brain networks that support core perceptual and cognitive processes (Cole, 2010). Resting-state networks are spatially separate and functionally connected brain regions that are metabolically co-active when a person is at rest (i.e., not engaging in an externally oriented or attention demanding task). There is accumulating evidence that both MCI and hearing loss are associated with brain network alterations.

1.62 MCI and Functional Connectivity

Studies using resting-state fMRI have shown that alterations in brain network connectivity occur early in AD and are associated with AD pathophysiology (Badhwar et al., 2017, Jack et al., 2018). Several systematic reviews and meta-analyses have investigated resting-state network connectivity across the spectrum of AD; despite the methodological differences and clinical heterogeneity that exists across the spectrum of cognitive impairment, certain patterns of altered connectivity have emerged. For instance, in individuals with AD neural networks generally show widespread disruption and a progressive loss of functional connectivity, particularly in the default-mode network, a resting state-network that will be described in a later

section (Badhwar et al., 2017; Sanz-Arigita et al., 2010). This loss of functional connectivity has been associated with AD pathology and the cognitive symptoms of AD (Jack et al., 2018). Alterations in functional connectivity are thought to occur early in disease progression before the onset of the cognitive symptoms of AD (Jack et al., 2018). Indeed, individuals with MCI also have altered resting-state brain connectivity. Recent reviews have shown that MCI is characterized by disrupted functional connectivity within the default-mode network (Zhang et al., 2012, Han et al., 2011, Koch et al., 2015).

The alterations in connectivity present in individuals with MCI and AD are thought to reflect neuronal injury due to underlying AD pathology. This is well-supported by the evidence for a relationship between functional connectivity, amyloid burden, and tau pathology (Koutsodendris et al., 2022). Early amyloid accumulation is associated with increased functional connectivity and increasing tau pathology is associated with a progressive decline in functional connectivity (Dickerson et al., 2005). In addition, a progressive decline in functional connectivity has been associated with decreasing cognitive function (Di et al., 2016). This suggests that neural network connectivity may be a useful marker for the early detection of AD related pathology (Koutsodendris et al., 2022).

1.63 The Default-mode Network

The default-mode network is a set of widely distributed brain regions in the parietal, temporal and frontal cortex (Smallwood et al., 2021). It is a resting-state network that includes several regions, such as the medial prefrontal cortex, the posterior cingulate cortex, and the precuneus (Wang et al., 2020). Regions of the default-mode network show greater activity when a person is at rest and reduced activity when an individual is actively engaged in external, cognitively demanding tasks (Han et al., 2010; Smallwood et al., 2021). It is thought to be

involved in processes related to self-referential processing, such as in autobiographical memory and visuospatial processing (Smallwood et al., 2021).

It is suggested that the posterior components of the default-mode network (i.e., the posterior cingulate cortex and precuneus) are among the first to be affected by age, MCI, and dementia pathology (Cavanna & Trimble, 2006). This is supported by the unique metabolic and connective properties of the posterior cingulate cortex and precuneus that are thought to make these structures vulnerable to the neurodegeneration processes associated with aging and dementia pathology (Matsuda, 2001; Mega et al., 1999). Indeed, the posterior cingulate cortex and precuneus are known to be metabolically expensive and highly connected regions of the brain (Cavanna & Trimble 2006). Neuronal activity stimulates aerobic glycolysis, which may increase amyloid beta production and neurodegeneration (Ruan et al., 2016; Sperling et al., 2011). This is notable as increased amyloid beta in the brain increases the risk of cognitive decline and developing dementia. Moreover, increased deposition of amyloid in the default-mode network has also been associated with impaired performance on measures of memory (Han et al., 2010, Sperling et al., 2011).

In addition to alterations within the default-mode network, there is also evidence for altered functional connectivity within and/or between other brain networks such as the executive control, salience, dorsal attention, and sensory motor networks in individuals with MCI (Agosta et al., 2012; Badhwar et al., 2017; Bai et al., 2012; Brier et al., 2012). However, the present study has focused on the connectivity patterns of the default-mode network.

1.64 The Default-mode Network and Mild Cognitive Impairment

There have been several reviews indicating the presence of altered default-mode network connectivity across the spectrum of cognitive decline and AD (See Badhwar et al., 2017; Eyler et al., 2019; Lin et al., 2018a; Ruan et al., 2016; Tam et al., 2015; Wang et al., 2018 for reviews).

There is extensive evidence of altered default-mode network connectivity in adults with MCI (Bi et al., 2018; Cha et al., 2013; Esposito et al., 2017; Gomez-Ramirez & Wu 2014; Han et al., 2010; Li et al., 2017; Rombouts et al., 2005; Seo et al., 2013; Wang et al., 2013). There has, however, been substantial heterogeneity in the literature regarding the nature of alterations in default-mode network connectivity and MCI.

The pattern of default-mode network connectivity observed in individuals with MCI has been complex and varied. Several recent meta-analyses have reported substantial inconsistency across studies comparing default-mode network connectivity between cognitively unimpaired individuals and individuals with MCI (Eyler et al., 2019, Wang et al., 2018). Compared to healthy controls, individuals with MCI have shown no differences in functional connectivity, increased connectivity, decreased connectivity, and regionally mixed directions of effect (Eyler et al., 2019). Despite this, altered default-mode network connectivity has been consistently reported in individuals with MCI (Eyler et al., 2019).

There is evidence that default-mode network connectivity is important for cognition. For instance, the presence of altered default-mode network connectivity has been associated with severity of cognitive impairment in individuals with MCI and AD (Binnewijzend et al., 2011; Dicks et al., 2018). In addition, altered default-mode network connectivity has shown utility in predicting further cognitive decline and conversion to AD in individuals with MCI (Petrella et al., 2011). Moreover, there is evidence that the connectivity patterns of certain hub regions in the default-mode network have diagnostic power to distinguish older adults with MCI from those with AD (see Ibrahim et al., 2021 for a review).

While it is reported that methodological differences do not appear to fully explain the inconsistencies in the literature investigating default-mode network connectivity in individuals

with MCI, these studies did not include hearing loss as a variable. As there is also evidence that hearing loss is associated with altered default-mode network connectivity, this omission could have a substantial influence on the heterogeneity in the literature on the relationship between MCI and brain connectivity. The alterations in brain function associated with hearing loss are described in a section below.

1.65 Clinical Implications of Functional Alterations in MCI

Resting-state fMRI has greatly increased our understanding the mechanisms underlying AD and potential biomarkers for cognitive decline and early AD pathology (Lin et al., 2018a). There is evidence that the observed alterations in brain connectivity in individuals with MCI are due to the pathological process of AD (Lin et al., 2018a). For instance, Brier et al. examined two groups of cognitively healthy individuals with or without AD-related cerebral spinal fluid biomarkers and it is suggested that AD pathology accounted for a large portion of the observed alterations in functional connectivity in their results (Brier et al., 2014; Lin et al., 2018a). Despite this, it is not fully understood how and when elevated AD pathology affects functional connectivity, indicating that the relationship between functional connectivity and AD pathology requires further study (Lin et al., 2018a).

The default-mode network is a multimodal network that interconnects with cortical regions responsible for various cognitive functions, suggesting that highly connected regions in the brain may be an early target of AD pathology (Badhwar et al., 2017). Multimodal networks are also metabolically expensive and display higher rates of cerebral blood flow, aerobic glycolysis, and oxidative glucose metabolism (Crossley et al., 2014). These characteristics of multimodal networks make them vulnerable to early AD pathology, such as the accumulation of amyloid and neurodegeneration (Crossley et al., 2014). This is supported by observations that the spatial deposition of tau and amyloid overlaps with brain tissue loss in the hub regions of

multimodal networks (Mišić et al., 2015; Sepulcre et al., 2016). Based on this, highly connected regions of multi-modal networks such as the default-mode network may be potential markers for AD pathology and risk for AD.

1.66 Hearing Loss and Brain Connectivity

There is substantial evidence that hearing loss is associated with altered brain function in cognitively healthy and cognitively impaired older adults (Jafari et al., 2021). These alterations in brain function have been associated with increased cognitive impairment and cognitive decline in individuals with hearing loss (Jafari et al., 2021). It is thought that the cognitive impairment that is often present in adults with hearing loss is due to the disruption of the brain network connectivity. It is also thought that cortical reorganization due to hearing loss utilizes areas typically involved in higher-level cognition, subsequently hindering the brains' ability to adapt to aging and AD pathology (Griffiths et al., 2020; Pronk et al., 2019). This suggests that the alterations in functional connectivity due to hearing loss may be a potential pathway or mechanism by which hearing loss is related to cognitive impairment (Griffiths et al., 2021; Jafari et al, 2021).

Research investigating the relationship between hearing loss and functional connectivity has primarily been focused on regions involved in auditory processing, such as the primary auditory cortex, or Heschl's gyrus. However, these is also evidence for widespread alterations in connectivity associated with hearing loss, including altered default-mode network connectivity (Jafari et al., 2021; Xing et al., 2020). Moreover, altered default-mode network connectivity has been associated with cognitive impairment in older adults with hearing loss (Xing et al., 2020). Findings of altered connectivity in the auditory processing regions as well as in the default-mode network in individuals with hearing loss are presented below.

1.67 Heschl's Gyrus Connectivity and Hearing Loss

Due to its role in auditory processing, the connectivity of Heschl's gyrus has been studied in cognitively healthy older adults with hearing loss. However, there have been relatively few studies that have examined the relationship between age-related hearing loss and resting-state network connectivity. In these studies, the reported changes in resting-state network connectivity as a function of hearing loss have been heterogenous, with some findings being more consistent than others. For instance, the increased coupling between the sensory cortices in individuals with hearing loss is relatively well established. There is evidence for increased connectivity between the auditory, visual, and somatosensory cortices in adults with age-related hearing loss (Fitzhugh et al., 2019; Jafari et al., 2021; Puschman & Thiel, 2017). These findings are consistent with evidence for cross-modal plasticity as a compensatory mechanism for the reduced auditory input the brain receives in individuals with hearing loss (Jafari et al., 2021).

How hearing loss is related the overall connectivity patterns of Heschl's gyrus has been less studied. In addition, how increased listening effort is associated with long-term changes in resting-state brain connectivity remains unknown (Rosemann & Thiel et al., 2019). A recent study found that listening effort, but not pure-tone hearing loss, was associated with decreased functional connectivity between Heschl's gyrus and the inferior frontal cortex (Rosemann & Thiel et al., 2019). Interestingly, in this study listening effort was also associated with decreased connectivity between the precuneus and a hub region of the default-mode network (Rosemann & Thiel et al., 2019). These results were interpreted as evidence that even mild to moderate age-related hearing loss has long term effects resting-state brain connectivity. This evidence supports the information or sensory degradation hypotheses and indicates that age-related hearing loss is associated with changes in the function of brain regions responsible for auditory, language, and cognitive processing (Jafari et al., 2021).

There is some evidence that AD pathology impacts auditory structures. For instance, a pattern of neurodegeneration has been identified in the auditory system of AD patients (Sinha et al., 1993). In the same study, senile plaques and neurofibrillary tangles were also present in the primary and secondary auditory association areas (Sinha et al., 1993). However, this research is limited and suggests a relatively minor involvement of the primary auditory cortex in AD pathology (Esiri et al., 1986; Sinha et al, 1993). Despite some evidence for the presence of AD pathology and in brain structures involved in auditory processing and the high comorbidity between hearing loss and cognitive impairment, the relationship between hearing loss and Heschl's gyrus connectivity has not been studied in adults with MCI.

1.68 The Default-mode Network and Hearing Loss

There is evidence that hearing loss is associated with altered default-mode network connectivity. Many of the studies that have explored the relationship between hearing loss and brain connectivity have focused on sensory-neural hearing loss, which occurs due to inner ear damage or due to problems with the nerve pathways that extend from the inner ear to the brain (Musiek & Barran, 2018). While sensory-neural hearing loss is thought to contribute to the development of age-related hearing loss, there are other factors involved, such as damage to the hair cells of the outer-ear (Musiek & Barran, 2018). Therefore, age-related hearing loss cannot be solely attributed to sensory-neural hearing loss and these two types of hearing loss may have different causes and aetiologies. As a result, these two types of hearing loss may have differential effects on brain connectivity. Despite this, evidence for the relationship between sensory-neural hearing loss and altered default-mode network connectivity is presented below due to the comparably lack of data on default-mode network connectivity in individuals with age-related hearing loss.

Studies using fMRI have found altered default-mode network connectivity in individuals with sensorineural hearing loss (Husain et al., 2014; Wang et al., 2013). A study that compared default-mode network connectivity between normal hearing individuals and adults with long-term unilateral sensory-neural hearing loss found that hearing loss was associated with alterations in default-mode network connectivity (Zhang et al., 2015). One recent study that compared default-mode network connectivity between normal hearing adults and adults with sensory-neural hearing loss found between and within network connectivity alterations in default-mode network as a function of hearing loss (Li et al., 2017). Another recent study of brain connectivity in adults with unilateral sensory-neural hearing loss reported decreased default-mode network connectivity in hearing impaired participants compared to normal hearing participants (Zhang et al., 2018). Similar results have been found using graph theory approaches to fMRI analysis, where between and within network connectivity was compared between a normal hearing group and a group with bilateral sensorineural hearing loss (Luan et al., 2020). Results indicated that sensorineural hearing loss was associated with widespread disruptions in functional connectivity, including regions of the default-mode network (Luan et al., 2020). In this study, alterations in functional connectivity were associated with scores on tests of processing speed (Luan et al., 2020).

There is also some evidence for altered default-mode network connectivity as a function of pure-tone hearing loss. A recent study that compared a group of normally hearing and a group of hearing-impaired older adults reported an association between pure-tone hearing loss and altered default-mode network connectivity (Xing et al., 2020). In this study, alterations in default-mode network connectivity were also associated with poorer performance on neuropsychological tests (Xing et al., 2020). In addition, age-related hearing loss has been

associated with decreased connectivity between key nodes of the default-mode network; in individuals with age-related hearing loss, these alterations were associated with cognitive impairment (Ren et al., 2021). There is also a known association between age-related hearing loss and widespread disruptions of functional connectivity outside of the default-mode network (Chen et al., 2018; Yong et al., 2022). Moreover, in individuals with age-related hearing loss, these alterations in brain connectivity have been associated with cognitive performance and speech/language processing abilities (Chen et al., 2018; Yong et al., 2022).

Studies investigating changes in functional connectivity related to MCI rarely accounted for participant hearing abilities. This is notable, as the biggest risk factors for both MCI and hearing loss are age. Hearing loss is also the third most common chronic health disorder in older adults, indicating that hearing loss and MCI are highly comorbid (Lau et al., 2021). In addition, even mild hearing loss has been shown to have widespread effects on brain structure and function (Campbell & Sharma, 2014; Glick & Sharma, 2017). The high prevalence of hearing loss in individuals with MCI in combination with evidence that hearing loss affects brain connectivity suggests that hearing loss may have contributed to the observed patterns of altered default-mode in individuals with MCI. This indicates that hearing loss should at the very least be documented in research investigating the relationships between brain connectivity and cognitive impairment or decline and this shortcoming is part of the rationale for the present study.

1.7 Measures of Functional Connectivity

Resting-state connectivity has been characterized via model driven and data-driven analyses. Two of the methods most used to investigate resting-state functional connectivity are seed-based resting state functional connectivity analysis (eg., Biswal et al., 1995; Castellanos et al., 2008; Greicius et al., 2003; Fox et al., 2005) and independent component analysis (ICA) (e.g., Beckmann et al., 2005; Calhoun et al., 2001, 2004; Stevens et al., 2009).

1.71 Seed-Based Connectivity Analysis. In seed-based resting state functional connectivity analyses, Pearson's correlation coefficients are calculated between the time course of a preselected region or regions of interest (also called a seed) and the time courses of all other voxels in the brain. Next, correlation coefficients are typically converted into normally distributed scores using a Fisher transformation to allow for second level General Linear Model Analysis. This method requires the a priori selection of a voxel, cluster, or atlas region from which to extract time-series data (Cole et al., 2010). These time-series data are then used as a regressor in a linear correlation or general linear model analysis to calculate whole-brain voxel-wise functional connectivity maps or covariance with the seed region (Cole et al., 2010). The primary advantage of seed-based connectivity analysis over other methods is its straightforward interpretability relative to other methods, as they show the network of regions with the strongest functional connection with the seed voxel or region of interest (Cole et al., 2010).

1.72 Independent Component Analysis (ICA). Many researchers have adapted multivariate network methods to analyze resting-sate fMRI data to avoid some methodological problems associated with seed-based methods. Network measures summarize properties of the entire voxel-voxel connectome, or all functional connections between every pair of voxels in the brain. Network measures include data-driven measures such as independent component analysis (ICA).

ICA decomposes a two-dimensional data matrix into the time courses and associated spatial maps of the underlying signal sources (Cole et al., 2010). Although several different approaches to ICA are used in neuroimaging, common concepts and core methods underlie their application (Cole et al., 2010). As with seed-based methods, the ICA approach has been used to identify resting-state networks. However, due to the ability of the method to account for the

existence of structured noise effects within additional (non-resting-state network) ICA components, resting-state networks identified with ICA can be less prone to artefactual effects from noise than those of seed-based methods of resting-sate fMRI data (Cole et al., 2010).

The ICA approach is advantageous to seed-based methods in terms of avoiding prior spatial assumptions, noise attached to the seed, and the ability to simultaneously compare the coherence of activity in multiple distributed voxels (Cole et al., 2010). This is, however, at the expense of losing specificity in relation to a single well-defined region of interest (Cole et al., 2010).

2.0 Research Objectives and Hypotheses

To summarize, there is evidence for links between brain connectivity, hearing loss, and cognitive impairment. There is also evidence that altered brain connectivity is associated with cognitive impairment and cognitive decline in both individuals with MCI and in individuals hearing loss. The high prevalence of hearing loss in individuals with MCI suggests the possibility that the abnormal default-mode network connectivity in individuals with MCI may be driven or potentiated by hearing loss. This suggests that hearing loss may cause or contribute to cognitive decline through altered functional connectivity reducing the brain's capacity to cope with aging and AD related brain pathology.

The relationships between hearing loss, functional connectivity, and MCI remain poorly understood. Based on this, the present study sought to characterize the relationships between hearing loss and the resting-state connectivity of two cortical areas in adults with MCI. First, Heschl's gyrus, which has been studied in individuals with hearing loss but not in individuals with MCI. Second, the default-mode network, which has been extensively studied in individuals with MCI and early AD and has been associated with hearing loss. In addition, most research investigating the relationship between hearing and resting-state connectivity has only included

measures of peripheral hearing loss. However, measures of central hearing ability have also been shown to be related to brain function and cognitive impairment. Based on this, the present study has included measures of peripheral and central hearing loss.

Our first research objective was to characterize the relationships between pure-tone hearing loss (a measure of peripheral hearing loss), speech-reception threshold (a measure of central hearing ability), and the connectivity patterns of Heschl's gyrus in individuals with MCI. Our second research objective was to characterize the relationships between pure-tone hearing loss, speech-reception threshold, and default-mode network connectivity in individuals with MCI. It was expected that both measured of hearing loss would be associated with alterations in the connectivity of Heschl's gyrus and the default-mode network.

Methods

3.1 Data

All data are from the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study of the Canadian Consortium on Neurodegeneration in Aging (CCNA). The CCNA was established by the Canadian Institutes of Health Research (CIHR) to coordinate and strengthen Canadian research on AD and other neurodegenerative diseases (Chertkow et al., 2019). The CCNA includes 19 established teams of senior Canadian researchers in dementia with vast expertise that ranges from basic science to clinical areas of dementia research. Further details of the CCNA are available at www.ccna-ccnv.ca.

COMPASS-ND is the signature study of the CCNA. It is a national initiative that includes cohorts of individuals with various types and degrees of cognitive concerns and/or neurodegenerative diseases (Chertkow et al., 2019). COMPASS-ND participants include cognitively healthy individuals and individuals with subjective cognitive decline, MCI, AD, and other types of dementia (Chertkow et al., 2019). Aims of the COMPASS-ND study include

better understanding neurodegenerative disease, improving quality of life for individuals living with dementia, and working towards dementia prevention (Chertkow et al., 2019).

COMPASS-ND participants were recruited from 31 centres across Canada (i.e., memory, movement disorder, and stroke clinics). At an intake interview a nurse or physician assessed study participants to determine their demographics, medical history, and eligibility based on inclusion and exclusion criteria. Participants then completed comprehensive evaluations that included clinical and neuropsychological assessment, bio sample collection, and MRI neuroimaging. Further details of the COMPASS-ND study are available at http://ccna-ccnv.ca/compass-nd-study/). Data used in the present study are currently stored on the Longitudinal Online Research Imaging System database (see https://ww.ccna.loris.ca).

3.2 Participants

The present study includes a subset of COMPASS-ND participants from the second data release (December 2021) that met the criteria for MCI. Of the 104 COMPASS-ND participants meeting the criteria for MCI, 9 were excluded because they did not have MRI data, or their MRI data failed quality control during the preprocessing phase. This led to a final total of 95 participants in the present study. Participant demographics are in Table 1. The general inclusion and exclusion criteria for the COMPASS-ND study are in Table 2 and Table 3, respectively. Written and informed consent was obtained from all participants. The COMPASS-ND study was approved by all relevant Research Ethics Boards.

Table 1.

Demographic Characteristics for Participants in the Normal Hearing and Hearing Loss Groups.

Normal Hearing	Hearing Loss
Total N = 60	Total N = 35
Female: N = 29, %= 48	Female: N = 14, % = 40
Right-handed: N = 52, % = 87	Right-handed: N = 33, % = 94
White: N = 30, % = 86	White: N = 49, % = 82
Tested in English: N = 31, % = 89	Tested in English: N = 53, % = 88

	M	SD	M	SD
Age	70.07	5.60	74.5	7.05
Education	16.05	3.65	15.19	4.53
Montreal Cognitive Assessment (MoCA)	24.43	2.83	23.31	3.35
Contrast sensitivity (CS) in log CS units	1.71	0.14	1.68	0.16
Reading acuity in logMAR units	0.12	0.15	0.16	0.15

Table 2.

COMPASS-ND General Inclusion Criteria.

Criteria	Description
1. Age range	Age range of 60-90 years for candidates with AD or vascular spectrum disorders such as SCI, MCI, VMCI, AD, Mixed. Age range of 50-90 years of age for candidates with FTD or LBD spectrum disorders (FTD of various subtypes, PD, PD-MCI, PDD, LBD)
2. Clinical Dementia Rating (CDR)	Candidate has a global Clinical Dementia Rating (CDR) ≤ 0.5
3. A reliable study partner that meets specific criteria	Self-reported proficiency for speaking and understanding English and/or French
4. Geographic accessibility	Candidate must be within a two-hour drive to the study site
5. Montreal Cognitive Assessment (MoCA)	MoCA score ≥ 13
6. Pure Tone Audiometry	Candidate must undergo test of pure-tone audiometry at screening visit. If the participant does not pass all frequencies in both ears and does not have their own, working, hearing or communication device available, they were required to use the POCKETTALKER Ultra during all subsequent screening, clinical, and neuropsychological testing)

Table 3.

COMPASS-ND General Exclusion Criteria.

Criteria	Description
1. The presence of other significant, known, chronic brain disease (e.g., moderate to severe)	The presence of other significant known chronic brain disease (e.g., moderate to severe chronic static leukoencephalopathy including previous traumatic injury), multiple sclerosis, a serious developmental handicap, malignant tumors, Huntington's disease, and other rarer brain illnesses
2. Substance use	Ongoing alcohol or drug abuse
3. Study partner	Subject does not have a study partner
4. Language proficiency	Individuals without proficient English or French
5. Montreal Cognitive Assessment (MoCA)	Total score on the Montreal Cognitive Assessment (MoCA) < 13

3.3 Criteria for MCI Participants

Participants were classified as MCI if they met the following criteria: 1) Concern regarding a change in cognitive function from previous levels based on the participants or informants report; 2) impairment in one or more cognitive domains that is greater than expected for the participant's age and education (Albert et al., 2011): evidenced by a WMS-III Logical-Memory II score below the Alzheimer's Disease Neuroimaging Initiative education adjusted cut-offs, a CERAD word list recall score less than 6, a MoCA score between 13-24, and a global CDR score greater than 0; 3) assigned a CDR of ≤ 0.5 to not be given a diagnosis of dementia; and 4) have preservation of independence in functional abilities, evidenced by a score greater than 14/23 on the Lawton-Brody Instrumental Activities of Daily Living scale (Chertkow et al.,

2019). To be classified as MCI, participants also had to have an absence of diffuse subcortical cerebrovascular disease. The COMPASS-ND diagnostic criteria for MCI are in Table 4.

Table 4.

COMPASS-ND MCI Inclusion Criteria.

Criteria	Description
1. Change in cognition	Candidate and/or informant reports a concern regarding a change in cognition
2. Clinical Dementia Rating (CDR)	Candidate has a global Clinical Dementia Rating (CDR) ≤ 0.5
3. One or more of the following	a) Logical Memory II (Delayed Recall) score below ADNI education-adjusted cutoffs i) <0 for 16+ years of education ii) <5 for 8-15 years of education iii) <3 for 0-7 years of education b) CERAD Word List Recall Score <6 c) MoCA Score between 13-24 (inclusive) d) Global CDR Score > 0
4. Lawton-Brody IADL Scale	Candidate scores $\geq$ 15 on the Lawton-Brody IADL Scale

Cognitive function was assessed using a comprehensive neuropsychological battery. The neuropsychological battery was designed to assess a range of cognitive domains and to be sensitive to a range of ability levels, including older adults with relatively intact cognitive abilities to participants diagnosed with dementia (Chertkow et al., 2019). Broad cognitive domains were assessed, including attention, learning and memory, speech production and language, executive function, and visuospatial function. The neuropsychological test battery requires 2-3 hours to administer and is separate from the cognitive tests used to classify participants (Chertkow et al., 2019).

3.4 Measures of Hearing Loss

3.41 Pure-tone Audiometry

Pure-tone audiometry was assessed with an abbreviated screening protocol using a GSI 8 audiometer in a quiet clinical examination room at each site. This screening protocol assessed participants' ability to detect at least one of two pure tones presented at each of three pre-selected selected frequencies at fixed dB HL levels. Each ear was tested separately. First, a 2 kHZ pure tone was presented at 40 dB HL during two trials. If the participant was able to detect at least one of these, then two trials at 25 dB HL were presented at 2 kHz, 1 kHz, and 4 kHz. Participants who failed to hear a 2 kHz pure tone at 40 dB HL were provided with a Pocket Talker assistive listening device throughout the neuropsychological and clinical assessment if they did not have their own hearing aid. Participants were classified into one of six categories ranging from normal hearing to moderate-to-severe hearing loss based on their ability to detect at least one of the 2 kHz tones at 40 dB HL or at 25 dB HL (as described in the left-hand column of table 5; Giroud et al., 2021). The COMPASS-ND hearing loss classification system has been validated against two data sets that measured audiometric thresholds with full audiometric assessments in older adults (see Giroud et al., 2021).

Table 5.

Validation of the 6-level COMPASS-ND Hearing Classification System Used in the Current Study.

Hearing loss categorization			PTA for 1, 2, 3, 4 kHz (dB HL)		ASHA grade (dB HL)	
	Better ear	Worse ear	Left	Right	Left	Right
Category 1: 'Normal Hearing' both ears detected tone at 25 dB HL	<=25 dB	<=25 dB	16.4	15.0	Slight (16-25)	Normal (<=15)
Category 2: 'Mild 1' better ear detected tone at 25 dB HL, worse ear at 40 dB HL	<=25 dB	26-40 dB	29.9	31.5	Mild (26-40)	Mild
Category 3: 'Mild 2' both ears detected tone at 40 dB HL	26-40 dB	26-40 dB	39.1	36.7	Mild	Mild
Category 4: 'Moderate 1' better ear detected tone at 25 dB HL, worse ear failed at 40 dB HL	<=25 dB	>40 dB	41.0	45.4	Moderate (41-55)	Moderate
Category 5: 'Moderate 2' better ear detected tone at 40 dB HL, worse ear failed at 40 dB HL	26-40 dB	>40 dB	50.9	50.7	Moderate	Moderate
Category 6: 'Moderate 3' both ears failed to detect tone at 40 dB HL	>40 dB	>40 dB	59.9	57.7	Moderate-severe (56-70)	Moderate-severe

Note. Table 5 demonstrates the pure-tone averages (1, 2, 3, and 4 kHz) of participants in the Canadian Longitudinal Study on Aging when the classification system used in the current study was applied to them (Giroud et al., 2021). PTA = pure-tone average, ASHA = American Speech-Language-Hearing Association. Table from Giroud et al., 2021.

After being assigned to one of six hearing loss categories based on the classification system described above, the hearing loss group was collapsed across the categories with some degree of hearing loss due to small group sizes in the different hearing loss categories. Therefore,

participants were ultimately assigned to one of two hearing categories, normal hearing, or hearing loss, based on their ability to detect at least one of the two 2-kHz tones.

3.42 Canadian Digit Triplet Test

The Canadian Digit Triplet Test (CDTT) was used to assess participants speech-reception threshold (speech-reception threshold), which is a measure of speech perception ability in an adverse listening condition. Scores on the CDTT were used to compute speech-reception thresholds for each participant, which correspond to the signal-to-noise ratio at which triplets of digits were recognized 50% of the time. Participants were instructed to listen to and repeat three digits presented in speech-shaped background noise. The CDTT uses an adaptive 1-up-1-down procedure (speech level decreases after a correct response and increases after an incorrect response) and responses were considered correct if all three digits were repeated correctly at the triplet level (i.e., in the correct order) (Ellaham et al., 2016; Giguère et al., 2020). The CDTT application was run on a Dell XPS laptop using a USB audio card (Creative Sound Blaster X-Fi Go! Pro). The standard deviation of the responses by each participant and the number of their reversals were used to identify erratic runs. Based on this procedure, one participant's data whose speech-reception threshold was greater than 3 standard deviations were coded as missing in analysis using speech-reception threshold as an independent variable.

3.5 Measures of Visual Function

3.51 Reading Acuity

The MNRCharts were used to obtain measures of reading acuity (the ability to read sentences at a given distance) by assessing participants reading performance using various font sizes (Mansfield et al., 1993). Participants were instructed to read aloud sentences on a hand-held chart viewed perpendicularly and at 40cm away. They were instructed to use both eyes and to start reading at the top of the chart and to continue until they could not read any words in a sentence. If available, participants were permitted to wear their habitual corrective lenses.

Reading acuity was operationalized as the smallest print size that the participant could read the entire sentence without making significant errors. Reading acuity was measured as the logarithm to the base 10 of the minimum angle of resolution (logMAR10) of the last sentence the participant was able to read. The calculation considered number of sentences correctly read, words missed, and errors made: [acuity=1.4-(amount of all sentences read x 0.1) + (total amount of errors x 0.01)].

3.52 Contrast Sensitivity

The MARS contrast sensitivity test was used to assess contrast sensitivity (the ability to distinguish an object from its background) by measuring the sensitivity of the eyes in processing letters across different levels of contrast (Dougherty, 2005). For this task participants read letters on a chart held perpendicularly by the participant, with the participants eyes at 50 cm from the chart. Participants were instructed to read the letters with both eyes from the left to right of each line, from the top to the bottom of the chart. When the participants made two consecutive errors, this task was discontinued. Participants were encouraged to wear their habitual corrective lenses if available. Contrast sensitivity was operationalized as the last letter correctly read by the participant. The log contrast sensitivity was calculated by identifying the value at the lowest

contrast letter prior to two incorrectly identified letters and subtracting it by the number of errors prior to the final correct letter (Mars Perceptrix, 2020).

3.6 MRI Data Acquisition and Preprocessing

3.61 Data Acquisition

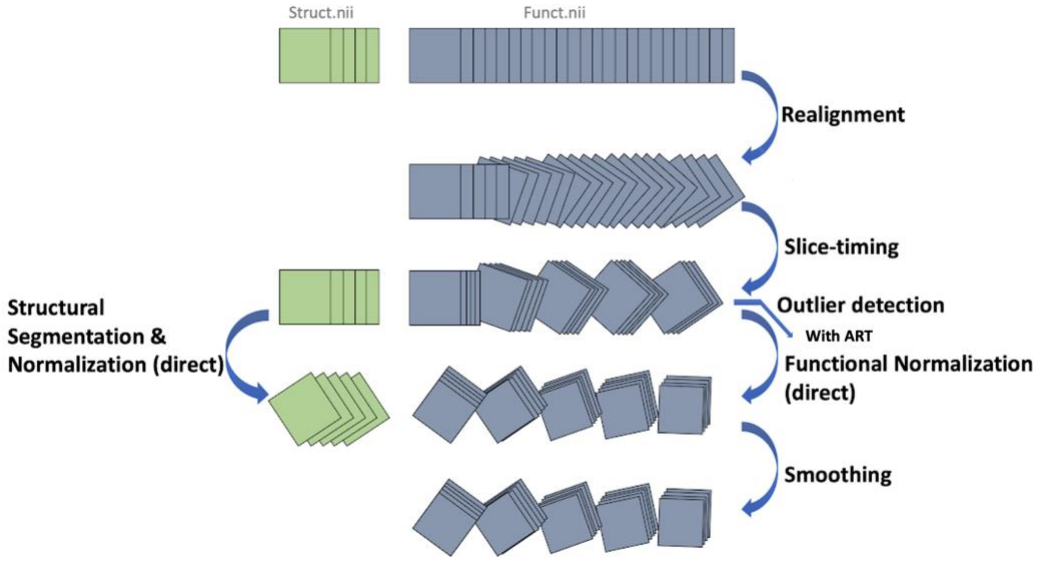
T1-weighted images and resting-state scans were obtained using 3T scanners from different COMPASS-ND sites across Canada following the Canadian Dementia Imaging Protocol (CDIP) (Duchesne et al., 2019). The CDIP is a validated, harmonized protocol for MRI data acquisition in individuals with neurodegeneration and is available for GE, Phillips, and Siemens scanners. The sequences used are standardized across MRI machines throughout the country and were used to obtained 3D T1, PD/T2, FLAIR, gradient echo, resting state fMRI and Diffusion Tensor Imaging (DTI) scans for all participants. The parameters for the acquisition of the 3D T1-weighted images and resting-state scans can be found here https://www.cdip-pcid.ca/. Acquisition of resting-state scans used a T 2-weighted BOLD-sensitive sequence, with a resolution of 3.5 x 3.5 x 3.5 mm^3, TR 5 2110 msec (GE: 2500 msec), and 300 volumes over time 10 minutes (Duschene et al., 2018). Parameters varied depending on the scanner type and version allowing for the images to be as comparable as possible.

3.62 MRI Data Preprocessing

All image preprocessing and data analysis was completed using the CONN functional connectivity toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) based on SPM12 (Penny et al., 2007) in the 2021version of MATLAB. Image preprocessing was done with CONN's default preprocessing pipeline. This preprocessing pipeline performs the following steps: functional realignment and unwarp, slice-timing correction, outlier identification, direct segmentation and normalization, and functional smoothing. See Figure 1 for a schematic illustration of the default minimal preprocessing pipeline in CONN.

Figure 1.

CONN Toolbox's Default Preprocessing Pipeline



Note. The CONN Toolbox's default preprocessing pipeline performs the following steps: functional realignment and unwarp; slice-time correction; outlier identification; direction segmentation and normalization; and functional smoothing. Figure 1 was adapted from www.conn-toolbox.org.

3.64 Functional Realignment and Unwarp

Functional data was realigned using the SPM12 realign & unwarp procedure (Andersson et al., 2001). All scans were co-registered and resampled to a reference image (the first scan of the first image). CONNs default preprocessing pipeline addresses potential susceptibility distortion-by-motion interactions by estimating derivatives of the deformation field with respect to head movement and re-sampling the functional data to match the deformation field of the reference image.

3.65 Functional/anatomical Co-registration and Slice Timing Correction

Functional data were co-registered to anatomical data using the SPM12 inter-modality co-registration procedure (Collignon et al., 1995, Studholme et al., 1998). CONN's preprocessing pipeline uses SPM12's slice-timing correction procedure (Henson et al., 1999).

3.66 Outlier identification

In CONNs default preprocessing pipeline, the observed global BOLD signal, and the amount of subject-motion in the scanner are used to identify potential outlier scans. Acquisitions with a framewise displacement above 0.9 or global BOLD signal changes above 0.5 SD are flagged as potential outliers.

3.67 Direct Segmentation and Normalization

Using the SPM12 unified segmentation and normalization procedure (Ashburner & Friston, 2005) functional and anatomical data were normalized into standard MNI space and segmented into grey matter, white matter, and CSF tissues. The unified segmentation and normalization procedures are applied separately to the functional data (using mean BOLD signal as the reference image) and to the structural data (using the raw T1-weighted volume as reference image).

3.68 Functional Smoothing

Functional data was smoothed using spatial convolution with a Gaussian kernel of 8mm full width half maximum. This was done to increase the BOLD signal-to-noise ratio and reduce the influence of residual variability in the function and anatomy of the gyri across subjects.

3.69 Denoising and Quality Control

When analyzing functional MRI data, it is critical to address noise to avoid possible confounding effects, such as spurious correlations based on non-neural noise (Whitfield-Gabrieli & Nieto-Castanon, 2012). The anatomical component-based noise correction method (aCompCor) used in CONNs denoising pipeline increases the validity, sensitivity, and specificity of functional connectivity analyses (Whitfield-Gabrieli & Nieto-Castanon, 2012). Compared to methods that subtract global signals from noise regions of interest, the aCompCor method is more flexible in its ability to characterize noise (Whitfield-Gabrieli & Nieto-Castanon, 2012).

CONN's default de-noising pipeline was used to address noise in the data. The aCompCor procedure implemented by potential confounding effects includes noise components from cerebral white matter and cerebrospinal areas (Behzadi et al., 2007), estimated subject-motion parameters (Friston et al., 1995), identified outlier scans or scrubbing (Power et al., 2014), constant and first-order linear session effects (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Temporal frequencies below 0.008 Hz or above 0.09 Hz were removed from the BOLD signal to focus on slow-frequency fluctuations while minimizing the influence of physiological, head-motion, and other noise sources (Hallquist et al., 2013).

ART was used to ensure the quality and validity of the data. CONN is interoperable with Artefact Detection Tool (ART;www.nitrc.org/projects/artifact_detect/). ART is a quality assurance and artefact rejection software that saves a matrix of outlier, artifactual time points from your data that can be entered as first-level covariates in CONN.

3.7 First level analyses: MRI data

3.71 Seed-based Connectivity Analysis

Metrics obtained with seed-based connectivity analyses characterize the brains connectivity patterns with a pre-defined seed or region of interest. Seed-based connectivity maps represent the level of functional connectivity between a seed/region of interest and every voxel in the brain. Seed-based connectivity maps were computed as fisher transformed bivariate correlation coefficients between the regions of interests' BOLD time series and the BOLD timeseries of each individual cerebral voxel. The spatial maps representing connectivity with the regions of interest generated in this step were used to make group-comparisons in the subsequent analyses presented in the current study.

3.72 Independent Component Analysis

CONN's ICA implementation follows Calhoun's group-ICA methodology (Calhoun et al., 2001). It includes optional subject-level dimensionality reduction, concatenation across subjects, group-level Singular Value Decomposition for dimensionality reduction, a fastICA algorithm for group-level independent component definition and the options of GICA1 or GICA3 for subject-level back projection (Calhoun et al., 2001 for a detailed description of this method).

Group-level ICA was used to derive measures of resting-state network connectivity (i.e., networks of functionally connected brain regions). The fast ICA algorithm implemented by the CONN toolbox concatenated volumes across participants and resting-state conditions to estimate independent components. Back-projection of these components onto individual subjects resulted in maps of regression coefficients that represent connectivity between the network and every voxel in the brain (see Calhoun et al., 2001 for details).

Based on research indicating that ICA results are affected by the number of independent components (IC's) when the number is smaller than the number of source signals (Cole et al., 2010; Zuo et al., 2010), 30 ICs were estimated. In these 30 IC's, dice coefficients and spatial correlations (the spatial overlap of suprathreshold areas) with CONNs network atlases were used to identify which of the components had the greatest correspondence with the default-mode network. The average spatial map for an identified component within each group represents the network associated with that component and the connectivity pattern within that network and the rest of the brain. Comparing a spatial map across two groups compares the whole-brain connectivity with this network across the two groups. The spatial map of the default-mode network generated in this step was used to make group-comparisons in the subsequent analyses presented in the current study.

3.8 Second Level Analyses: Statistical Analyses and Covariates

Following the computation of seed-to-voxel connectivity maps and voxel-to-voxel measures of functional connectivity for each participant, these measures were entered into a second level general linear model to obtain population-level estimates and inferences. Hypotheses of the present study were tested using between-subjects contrasts to compare functional connectivity patterns between the hearing loss and normal hearing groups. In the present study, two families of second level statistical analyses were conducted, including three one-way ANCOVAS and three linear regressions.

3.81 Linear Regression

A total of three linear regressions were performed to investigate the effect of speech-reception threshold on functional connectivity in individuals with MCI. Two linear regressions were used to separately investigate the effect of speech-reception threshold on the intra and inter

region connectivity of left and right Heschl's gyri. In these two regressions, the independent variable was speech-reception threshold, and the dependent variable was inter- and intra-region connectivity with left and right Heschl's gyrus (represented by the correlation between the regions of interest timeseries and every other cerebral voxels timeseries).

A third linear regression was used to investigate the effect of speech-reception threshold on the inter and intra network connectivity of the default-mode network. In this regression the independent variable was speech-reception threshold, and the dependent variable was default-mode network connectivity (represented with the correlation between the default-mode network timeseries and every other voxel in the brain).

3.82 Analysis of Variance with Covariates

Analysis of variance with covariate control (ANCOVA) was used to compare both inter and intra region and inter and intra network connectivity between the normal hearing and hearing loss groups. Three one-way ANCOVAS were conducted with hearing ability as a between-subjects variable and functional connectivity as the dependent variable. Each ANCOVA investigated the functional connectivity of a different network or region of interest. In the first and second ANCOVA's, the dependent variables were the inter and intra region connectivity of right and left Heschl's gyri, respectively. In the third ANCOVA the dependent variable was the inter and intra network connectivity of the default-mode network.

In all analyses, age, education, contrast sensitivity and reading acuity scores were included as covariates. In all analyses, Type 1 false positive error control was implemented though a combination of a voxel-level height threshold, defined by FDR-corrected voxel level p-values ([$p < 0.05$, voxel thresholded at $p < 0.001$] (Worsley et al., 1996), and a cluster-level extent threshold, defined by FDR-corrected cluster level *p*-values. Bonferroni corrections were

applied to account for multiple comparisons and the threshold for FDR-corrected p values ($pFDR < 0.05$) across all comparisons. All reported coordinates refer to MNI anatomical space.

Results

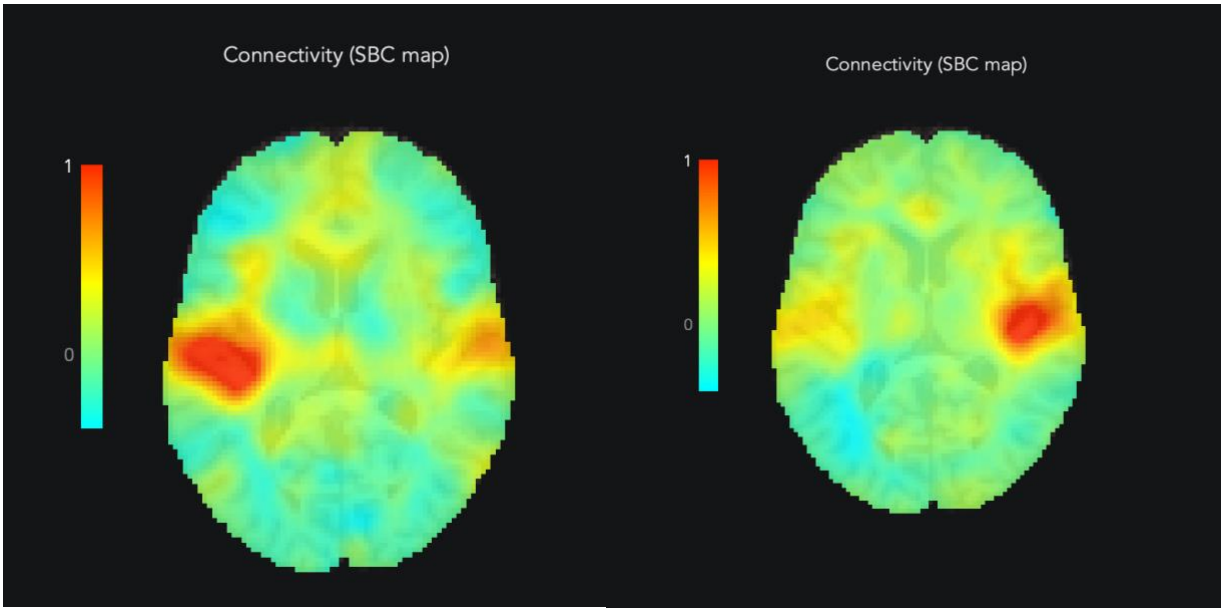
4.1 First Level Results

4.11 Seed-based Connectivity

Two separate seed-based correlation maps were created using two different regions of interest: one using right Heschl's gyrus and one using left Heschl's gyrus. The seed-based connectivity maps for left and right Heschl's gyri estimated for one participant in the present study are depicted in Figure 2. The individual seed-based connectivity maps for each participant were subsequently used in second-level group analyses.

Figure 2.

Seed-Based Connectivity Map from a Single Participant Using Left Heschl's Gyrus as the Seed Region.



Note. For all participants, seed-based connectivity maps were created in first-level analyses. Left: connectivity map representing the connectivity pattern of left Heschl's gyrus for a single participant. Right: connectivity map representing the connectivity pattern of right Heschl's gyrus for a single participant. The color bar represents Fisher transformed correlation coefficient units. These connectivity maps were subsequently used in linear regressions and ANCOVA's to

investigate the relationship between pure-tone hearing, speech-reception threshold, and Heschl's gyrus connectivity.

4.12 Independent Component Analysis

The spatial correlation coefficients and the dice coefficients between the independent components estimated in the present study and CONN's resting-state network templates are in Table 6 and Table , respectively. Kurtosis, skewness, variability, and frequency values for the independent components estimated in the present study with the greatest correspondence to CONNs resting-state network templates are in Table 8. The fifth component had the highest spatial correlation (r=0.48) and dice coefficient (r=0.54) with the default-mode network template. The independent component estimated in the present study that corresponds to the default-mode network is depicted in Figure 3.

Table 6.

Independent Components with the Greatest Correspondence to CONNs' Resting-State Network Templates Based on Spatial Correlation Coefficient.

Network	Component	Spatial Correlation Coefficient
Default-Mode	5	r=0.48
Sensori-Motor	22	r=0.45
Visual	19	r=0.54
Salience	26	r=0.2
Dorsal-Attention	24	r=0.19
Fronto-Parietal	6	r=0.3
Language	6	r=0.34
Cerebellar	25	r=0.36

Note. In the presents study, the correspondence of an independent component to CONNs' resting-state network template was based on the spatial correlation coefficients between independent components and the resting-state network templates.

Table 7.

Independent Components with the Greatest Correspondence to CONNs' Resting-State Network Templates Based on Dice Coefficient.

Network	Component	Dice Coefficient

Default-Mode	5	r=0.54
Sensori-Motor	28	r=0.49
	22	r=0.48
Visual	19	r=0.58
Salience	26	r=0.17
Dorsal-Attention	24	r=0.27
Fronto-Parietal	8	r=0.27
Language	6	r=0.41
Cerebellar	25	r=0.42

Note. In the presents study, the correspondence of an independent component to CONNs' resting-state network template was based on the dice correlation coefficients between independent components and the resting-state network templates.

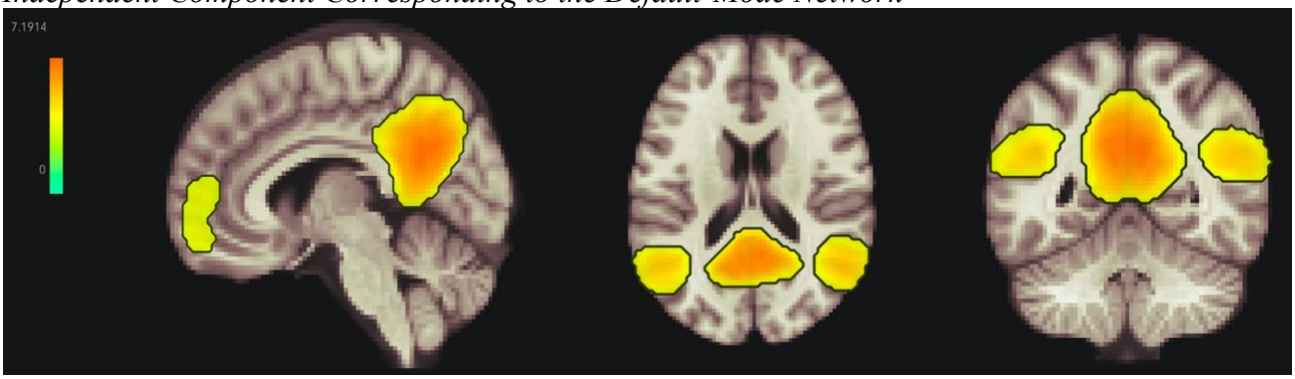
Table 8.

Kurtosis, Skewness, Variability, and Frequency Values for Resting-state Networks Estimated in the present study.

Network	Kurtosis	Skewness	Variability	Frequency
Default-mode network	8.53	1.81	0.10	0.05
Sensori-motor	12.03	2.08	0.11	0.05
Visual	18.10	3.55	0.11	0.05
Salience	7.86	1.73	0.12	0.05
Dorsal attention	9.85	1.86	0.12	0.05
Frontoparietal	6.65	1.4	0.11	0.05
Language	5.31	0.59	0.11	0.05
Cerebellar	6.91	1.22	0.13	0.05

Figure 3.

Independent Component Corresponding to the Default-Mode Network



Note. Figure 3 depicts the independent component estimated in the first level analysis corresponding to the default-mode network. The color bar represents the activation of each voxel

transformed to a z-statistic. This network was subsequently used in linear regressions and ANCOVA's to investigate the relationship between pure-tone hearing, speech-reception threshold, and default-mode network connectivity.

4.2 Second Level Results

Second level analyses allow researchers to make inferences about properties of groups or populations by generalizing from observations of a subset of subjects in a study (Nieto-Castanon, 2020). CONN uses the General Linear Model for all second level analysis of functional connectivity data (Nieto-Castanon, 2020). The General Linear Model defines a multivariate linear association between a set of independent measures and a set of dependent measures. Using the general linear model framework, it is possible to specify classical analyses on the seed-based connectivity maps and independent components estimated in the first-level analyses, including regression models and ANOVAS.

In all second level analyses, family-wise error corrected, and false-discovery rate corrected p-values were used to control for Type 1 error. The voxel thresholds, cluster thresholds, cluster size settings, and directionalities used across all second level analyses in the present study are in Table 9. Pure-tone hearing loss was controlled for in analyses using speech-reception threshold.

Table 9.

Voxel Threshold, Cluster Threshold, Cluster Size, and Directionality Parameters Used in all Second Level Analyses.

Voxel Threshold	Cluster Threshold	Cluster Size	Directionality
$p < 0.001$	$p < 0.05$	p-FWE corrected p-FDR corrected	two-sided

4.21 Seed-based Connectivity

A linear regression using speech-reception threshold as the independent variable and inter- and intra- region connectivity with right Heschl's gyrus as the dependent variable was conducted to determine if speech-reception threshold was associated with the functional

connectivity of right Heschl's gyrus. Speech-reception threshold was significantly associated with one pattern of altered connectivity with right Heschl's gyrus (p-FWE = 0.00072, p-FDR=0.001865), namely decreased connectivity between right Heschl's gyrus and a portion of the left frontal pole (MNI coordinates= -18 +54 +14). The cluster coordinates, cluster size, and associated p-values are in Table 10. The regions showing significantly decreased connectivity as a function of speech-reception threshold, the number of voxels in each significant region, and their percentage contribution to the total number of significant voxels in the overall cluster are in Table 11. Figure 4 depicts the brain regions with decreased connectivity with right Heschl's gyrus as a function of speech-reception threshold. Results of a second linear regression indicated that speech-reception threshold was not significantly associated with the inter or intra region connectivity with left Heschl's gyrus ($p > 0.05$).

Table 10.

Cluster Location, Size, and Corrected and Uncorrected P-Values for Cortical Region with Decreased Connectivity with Right Heschl's Gyrus as a Function of Speech-Reception Threshold.

Location MNI Coordinates (x, y, z)	Size	Size p-FWE	Size p-FDR	Size p-unc	Peak p-FWE	Peak p-unc
-18 +54 +14	664	0.000722	0.001865	0.000078	0.016617	0.000000

Note. Table 10 displays the results for the linear regression investigating the relationship between speech-reception threshold and the connectivity of right Heschl's gyrus. MNI = Montreal Neurological Institute, FWE = family-wise error rate, FDR = false discovery rate, unc = uncorrected. Results indicated that speech-reception threshold was associated with one pattern of altered connectivity, represented by the cluster of voxels with decreased functional connectivity.

Table 11.

Regions of the Brain Showing Significantly Decreased Connectivity with Right Heschl's Gyrus as a Function of Speech-reception Threshold.

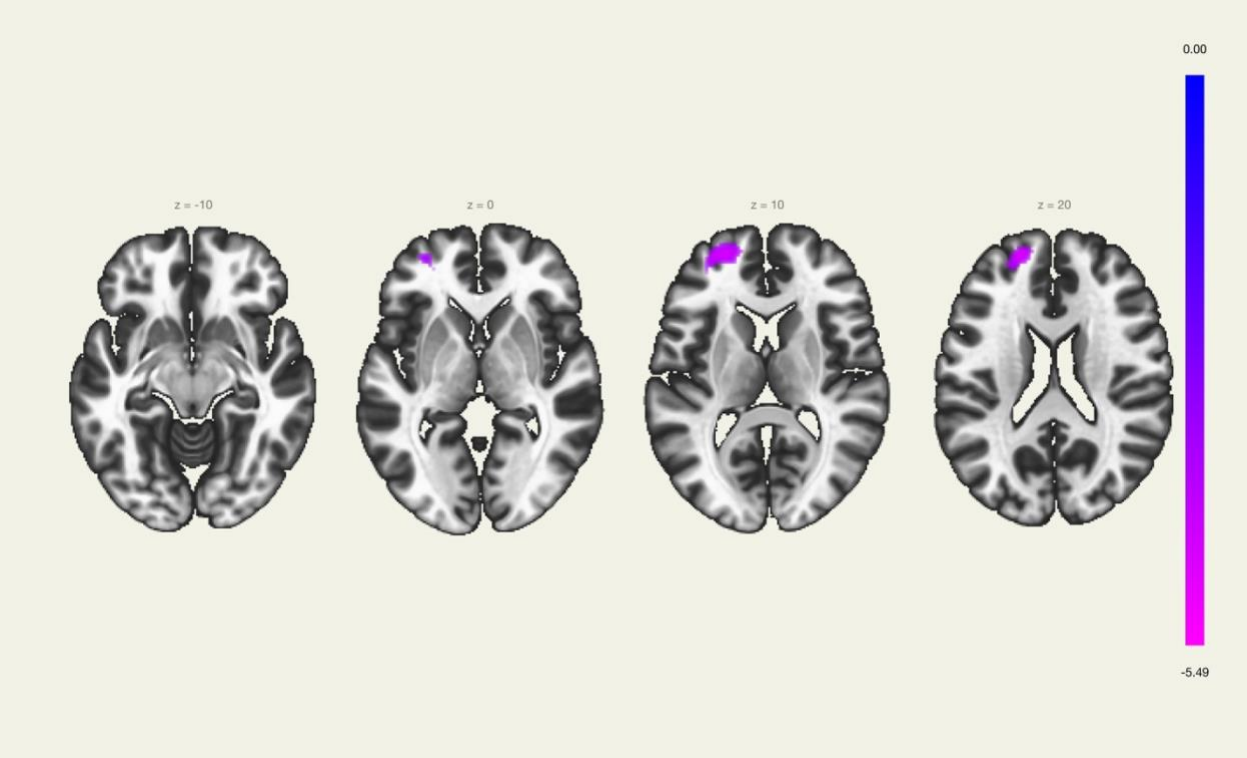
Region	Size	Proportion of atlas

Frontal Pole Left	556 voxels (84%)	covering 8% of atlas Frontal Pole Left
Superior Frontal Gyrus Left	2 voxels (0%)	covering 0% of atlas Superior Frontal Gyrus Left
Atlas not labelled	106 voxels (16%)	covering 0% of atlas not labeled

Note. Regions of the brain showing decreased connectivity as a function of speech-reception threshold. Size of the significant region in voxels, each significant regions contribution to the total amount of significant voxels, and the proportion of the relevant atlas that is included in the regions of significance.

Figure 4**.**

Cortical Regions Showing Altered Connectvity with Right Heschl's Gyrus as a Function of Speech-reception Threshold.



Note. Results of the linear regression investigating the relationship between speech-reception threshold and right Heschl's gyrus connectivity. The color bar represents the one-sample test statistic from the linear regression. Results indicated that speech-reception threshold was associated with decreased connectivity between the right Heschl's gyrus and a portion of the left frontal pole.

A one-way ANCOVA using pure-tone hearing loss as the independent variable and inter- and intra-region connectivity with right Heschl's gyrus as the dependent variable was conducted to investigate the relationship between pure-tone hearing loss and the functional connectivity with right Heschl's gyrus. Pure-tone hearing loss was associated with two patterns of altered connectivity with right Heschl's gyrus: 1) decreased inter-region connectivity between right Heschl's gyus and the left frontal pole, inferior frontal gyrus, and the left middle frontal gyrus and 2) increased intra-region connectivity between portions of the right central opercular cortex, the right insular cortex and with right Heschl's gyrus itself. The cluster coordinates, cluster sizes,

and associated p-values are in Table 12. The regions showing significantly altered connectivity as a function of pure-tone hearing loss and the related statistics are in Table 13. Figure 5 depicts the brain regions with altered connectivity with right Heschl's gyrus as a function of pure-tone hearing loss. Results of a second one-way ANCOVA indicated that pure-tone hearing loss was not associated with the inter or intra region connectivity of left Heschl's gyrus ($p > 0.05$).

Table 12.

Cluster Location, Size, and Corrected and Uncorrected P-Values for Regions with Altered Connectivity with Right Heschl's Gyrus as a Function of Pure-Tone Hearing.

Cluster location (x, y, z)	Size	Size p-FWE	Size p-FDR	Size p-unc	Peak p-FWE	Peak p-unc
-18 +56 +16	1292	0.000004	0.000012	0.000000	0.018398	0.000001
+44 -12 +08	326	0.025929	0.039821	0.002844	0.010095	0.000000

Note. Results of the ANCOVA investigating the relationship between pure-tone hearing and the connectivity of right Heschl's gyrus. MNI = Montreal Neurological Institute, FWE = family-wise error rate, FDR = false discovery rate, unc = uncorrected. Results indicated that pure-tone hearing loss was associated with two patterns of altered connectivity, represented by the two clusters of voxels.

Table 13.

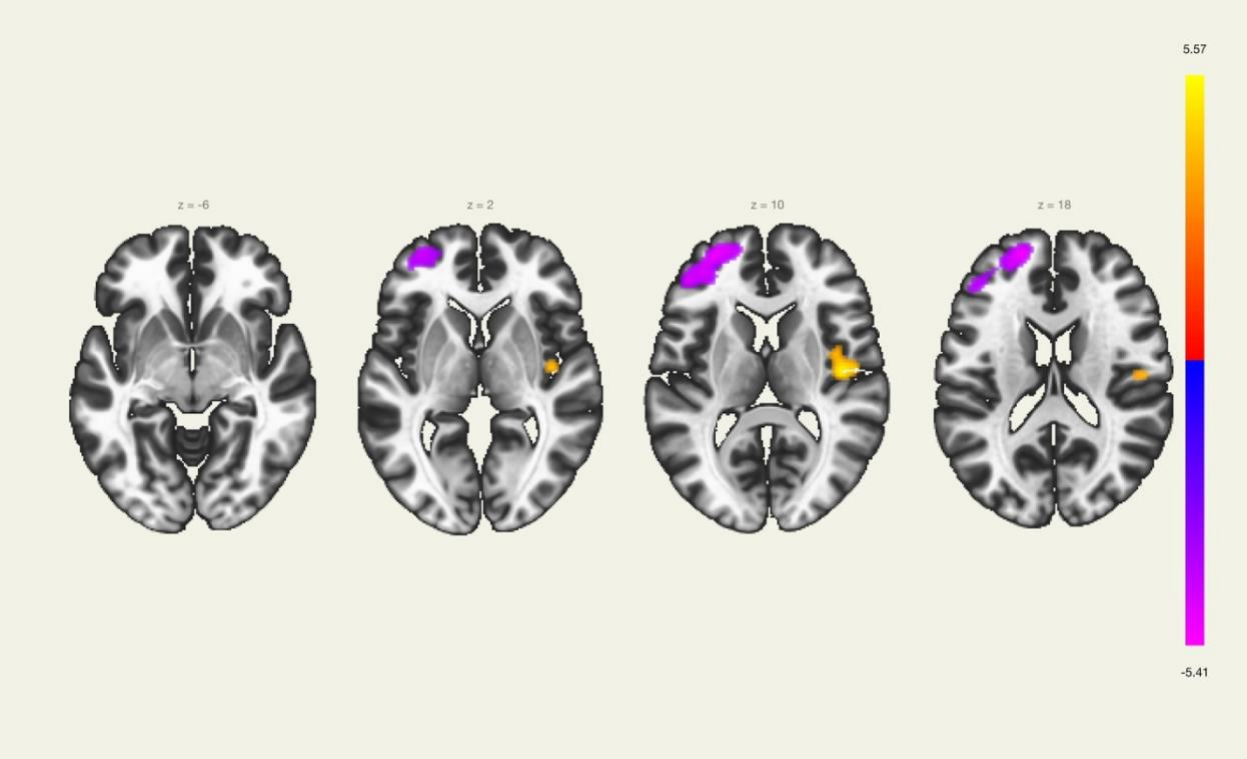
Regions of the Brain Showing Altered Connectivity with Right Heschl's Gyrus as a Function of Pure-Tone Hearing.

Region	Size	Proportion of atlas
Frontal Pole Left	1120 voxels (69%)	covering 16% of atlas Frontal Pole Left
Central Opercular Cortex Right	150 voxels (9%)	covering 17% of atlas Central Opercular Cortex Right
Insular Cortex Right	139 voxels (9%)	covering 10% of atlas Insular Cortex Right
Heschl's Gyrus Right	35 voxels (2%)	covering 12% of atlas Heschl's Gyrus Right
Inferior Frontal Gyrus Left	30 voxels (2%)	covering 5% of atlas Inferior Frontal Gyrus Left
Middle Frontal Gyrus Left	13 voxels (1%)	covering 0% of atlas Middle Frontal Gyrus Left
Atlas not labelled	131 voxels (8%)	covering 0% of atlas not labelled

Note. Regions of the brain showing altered connectivity as a function of pure-tone hearing loss. Size of the significant region in voxels, each significant regions contribution to the total amount of significant voxels, and the proportion of the relevant atlas that is included in the regions of significance.

Figure 5.

Cortical Regions Showing Altered Connectivity with Right Heschl's Gyrus as a Function of Pure-tone Hearing Loss.



Note. Results of the ANCOVA investigating the relationship between pure-tone hearing loss and right Heschl's gyrus. The color bar represents the two-sample t-test statistic. Results indicated that pure-tone hearing loss was associated with two patterns of altered connectivity with right Heschl's gyrus. One pattern of altered connectivity was decreased connectivity between a portion of the left frontal lobe and right Heschl's gyrus. The second pattern of altered connectivity was increased connectivity between right Heschl's gyrus and several regions involved in auditory processing, including the right temporal operculum, the right insula, and right Heschl's gyrus itself.

4.22 Independent Components Analysis

A linear regression using speech-reception threshold as the independent variable and voxel-to-voxel connectivity with the default-mode network as the dependent variable was conducted to determine if speech-reception threshold was associated with default-mode network connectivity. Results indicated that there was no significant association between speech-reception threshold and default-mode network connectivity ($p > 0.05$).

A one-way ANCOVA using pure-tone hearing loss as the independent variable and default-mode network connectivity as the dependent variable revealed differences in default-mode network connectivity as a function of pure-tone hearing loss. Compared to individuals with normal hearing, individuals with pure-tone hearing loss had decreased connectivity between the default-mode network and the left caudate, the right caudate, and small portion of the right thalamus (MNI coordinates= -10 +04 +12, p-FWE = 0.010, p-FDR=0.009). The cluster coordinates, cluster size, and associated p-values are in Table 14. The regions with altered connectivity, the number of voxels in region, and their percentage contribution to the total number of significant voxels in the cluster are in Table 15. Figure 6 depicts the brain regions with altered connectivity with the default-mode network as a function of pure-tone hearing loss.

Table 14.

Cluster Location, Size, and Corrected and Uncorrected p-Values for Regions with Altered Connectivity with the Default-Mode Network as a Function of Pure-Tone Hearing.

Cluster (x, y, z)	Size	Size p-FWE	Size p-FDR	Size p-unc	Peak p-FWE	Peak p-unc
-10 +04 +12	434	0.010353	0.008525	0.001218	0.029058	0.000001

Note. Results of the ANCOVA used to investigate the relationship between pure-tone hearing and default-mode network connectivity. MNI = Montreal Neurological Institute, FWE = family-wise error rate, FDR = false discovery rate, unc = uncorrected. Results indicated that pure-tone hearing loss was associated with one pattern of decreased connectivity with the default-mode network.

Table 15.

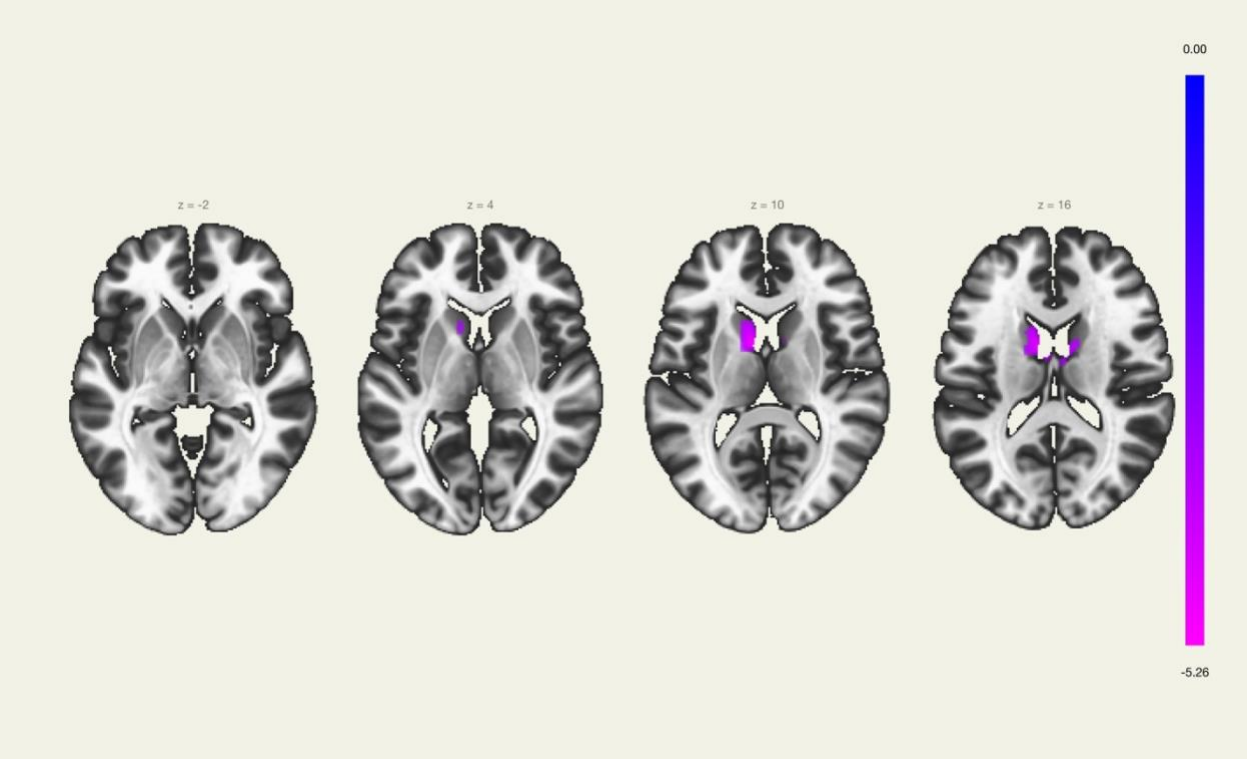
Regions of the Brain Showing Altered Connectivity with the Default-Mode Network as a Function of Pure-Tone Hearing.

Region	Size	Proportion of atlas
Caudate (left)	202 voxels (47%)	38%
Caudate (right)	41 voxels (9%)	8%
Thalamus (right)	7 voxels (2%)	1%
Atlas not labelled	184 voxels (42%)	0%

Note. Regions of the brain showing decreased connectivity as a function of pure-tone hearing loss. Size of the significant region in voxels, each significant regions contribution to the total amount of significant voxels, and the proportion of the relevant atlas that is included in the regions of significance.

Figure 6.

Cortical Regions Showing Altered Connectivity with the Default-Mode Network as a Function of Pure-tone Hearing Loss.



Note. Results for ANCOVA using investigating the relationship between pure-tone hearing loss and default-mode network connectivity. The color bar represents the two-sample t-test statistic. Results indicated that pure-tone hearing loss was associated with decreased connectivity between the default mode network and portions of the bilateral caudate and the right thalamus.

Discussion

The aim of the present study was to characterize the relationships between two measures of hearing loss and the connectivity of Heschl's gyrus and the default-mode network in adults with MCI. The relationships between speech-reception threshold, pure-tone hearing loss, and the functional connectivity of left and right Heschl's gyri and default-mode network connectivity were examined separately. All participants were older adults with MCI. In analyses with pure-tone hearing, there was a normal hearing and a hearing loss group that was based on pure-tone

hearing loss. Normal hearing and hearing loss groups were matched on age, gender, education, and Montreal Cognitive Assessment scores. As a continuous variable, the association between speech-reception threshold and brain connectivity was investigated across all participants, including normal hearing and hearing loss participants with MCI.

5.1 Functional Connectivity of Heschl's Gyri

There were no differences in the connectivity of left Heschl's gyrus as a function of either measure of hearing loss. However, both speech-reception threshold and pure-tone hearing loss were associated with altered right Heschl's gyrus connectivity. Pure-tone hearing loss was associated with two patterns of altered connectivity and speech-reception threshold was associated with one pattern of altered connectivity.

5.2 Right Heschl's Gyrus Connectivity

5.21 Intracortical Connectivity (within auditory cortex)

Pure-tone hearing loss was associated with a pattern of increased connectivity between right Heschl's gyrus and three regions that are involved in auditory and multimodal sensory processing. Specifically, pure-tone hearing loss was associated with increased connectivity between right Heschl's gyrus and the right temporal opercular cortex, the right insular cortex, and right Heschl's gyrus itself. The functions of each of these regions and their relevance to hearing are briefly described below.

Pure-tone hearing loss was associated with increased connectivity between right Heschl's gyrus and the right temporal operculum. The operculum covers the insula and consists of the three portions: the frontal, parietal, and temporal/central opercula (Mallia et al., 2018). While its functions are complex and not fully understood, the temporal operculum is known to be involved in auditory processing. This view is supported by evidence indicating that the temporal operculum is the termination point of the afferent auditory pathway and contains Heschl's gyrus (Mallia et al., 2018). This shows that in the present study pure-tone hearing loss was associated

with increased intra-cortical connectivity in right lateralized auditory processing regions, including increased connectivity within the temporal operculum and within Heschl's gyrus itself.

It is well established that hearing loss is associated with altered brain structure and function. For instance, in a longitudinal study comparing normally hearing older adults and older adults with a hearing impairment (i.e., with a pure-tone hearing average greater than 25 decibels in better ear), hearing loss was associated with accelerated whole-brain volume loss, especially in the right temporal lobe (Lin et al., 2014). It is suggested that these alterations are due to the impoverished auditory signal associated with hearing loss altering neuronal activation and causing subsequent changes in cortical reorganization and brain morphometry (Lin et al., 2014). Based on this, it is possible that the increased temporal opercular connectivity seen as a function of pure-tone hearing loss in the present study is due to the negative effects of comorbid MCI and hearing loss on the brain. The increased connectivity may be due to the brain volume loss that is seen in both individuals with hearing loss and MCI. This brain volume loss could necessitate greater intrinsic functional connectivity to process auditory information. There is also evidence that the right hemisphere shows greater volume loss as a function of hearing loss than the left hemisphere (Lin et al., 2014). This suggests that our finding of increased intracortical connectivity within right auditory processing regions may represent a compensatory mechanism related to the accelerated brain volume loss in the right hemisphere (and not the left) as a function of hearing loss. This will be tested in subsequent analyses incorporating measures of structural MRI.

Pure-tone hearing loss was associated with increased connectivity between right Heschl's gyrus and the right insular cortex. The insula subserves a wide range of processes, including auditory and multimodal sensory processing (Bamiou et a., 2003). Functional MRI studies have

demonstrated the insulas involvement in allocating auditory attention, tuning into novel auditory stimuli, temporal and phonological processing, and auditory-visual integration (Xu et al., 2019a). Notably, in older adults with sensorineural hearing loss, altered insula connectivity has been associated with performance on neuropsychological measures of cognition (Xu et al., 2019a). In addition, the insula is a hub for several brain networks and is known to be affected by early AD (Xie et al., 2012). Indeed, when compared to cognitively healthy older adults, adults with amnestic MCI showed disrupted intrinsic connectivity of the insula (Xie et al., 2012). This disrupted connectivity was associated with impaired episodic memory in adults with amnestic MCI but not cognitively healthy controls (Xie et al., 2012). Based on this, altered insular connectivity may be implicated in the increased cognitive impairment, cognitive decline, and dementia risk associated with hearing loss. Moreover, our finding of increased connectivity between right Heschl's gyrus and the insula may be related to the association between hearing loss and accelerated brain volume loss necessitating intra-cortical reorganization to process the impoverished auditory signal.

We observed that pure-tone hearing loss was associated with increased intrinsic connectivity within right Heschl's gyrus. The primary auditory cortex, which is responsible for the first level of cortical auditory processing, is located within Heschl's gyrus (Cardin et al., 2016). A recent review has shown that age-related hearing loss is associated with alterations in the structure and function of Heschl's gyrus (Cardin et al., 2016). Previous evidence has also indicated that hearing loss is associated that increased functional connectivity within auditory regions such as Heschl's gyrus (Cardin et al., 2016). It thought that this increased connectivity may represent processing deficiencies or compensatory mechanisms to cope with the increased

volume loss associated with hearing loss and the negative effects of hearing loss on the brain (Cardin et al., 2016).

5.22 Intercortical Connectivity (between auditory and frontal cortex)

Both speech-reception threshold and pure-tone hearing loss were associated with decreased connectivity between right Heschl's gyrus and a portion of the left frontal lobe that encompassed portions of three frontal regions. Specifically, pure-tone hearing loss was associated with decreased connectivity between right Heschl's gyrus and a portion of the left frontal pole, a portion of the left inferior frontal gyrus, and a portion of the left middle frontal gyrus. Speech-reception threshold was associated with decreased connectivity between right Heschl's gyrus and a portion of the left frontal pole and the left superior frontal gyrus. The functions of each of these regions and their relevance to hearing are briefly described below. The pattern of decreased connectivity associated with speech-reception threshold was largely overlapping with but encompassed a smaller region of the cortex than the pattern of decreased connectivity associated with pure-tone hearing loss.

Our results are consistent with previous findings. The left inferior frontal gyrus has been identified as a language processing region in early models conceptualizing the neurobiology of language (Poeppel et al., 2012; Rudner et al., 2019). The middle frontal gyrus, a region thought to be associated with cognitive control, has been shown to have lower gray matter volumes in individuals with hearing loss (Rudner et al., 2019). Hearing loss has also been associated with altered functional connectivity in the left superior frontal gyrus (Rudner et al., 2019). Therefore, our findings are consistent with previous evidence that hearing loss is associated with smaller brain volume and altered connectivity in auditory and cognitive processing regions (Rudner et al., 2019).

One explanation for the loss of connectivity between right Heschl's gyrus and regions in the left frontal lobe is that the functional recruitment of brain regions to cope with the impoverished auditory input associated with hearing loss causes the functional reorganization of and subsequent neuronal loss in these regions (Rudner et al., 2019). Our findings may suggest that both measures of hearing are associated with the functional disconnection of right Heschl's gyrus and regions in the left frontal lobe. Based on this, decreased connectivity between these auditory and cognitive processing regions may underly the cognitive impairment associated with hearing loss.

5.3 Default-mode Network Connectivity with the Caudate and Thalamus

In the present study, pure-tone hearing loss was associated with decreased connectivity between the default-mode network and portions of the left and right caudate and a portion of the right thalamus. There was no relationship between speech-reception threshold and default-mode network connectivity. The functions of these regions and their relevance to hearing loss are briefly discussed below.

5.4 Caudate Structure and Function

The caudate is part of the striatum in the basal ganglia, a region of the brain responsible for sensorimotor coordination (Grahn et al., 2008). The caudate has dense connections with the cortex and is involved in several neural networks subserving complex cognitive and behavioral functions (Middleton & Strick, 2000). For example, the caudate is thought to be critical in supporting the planning and execution of behavior needed to achieve complex goals (Grahn et al., 2008). The thalamus is also a part of the striatum.

5.5 Caudate Dysfunction and Cognitive Impairment

It is well known that the structures of the striatum (i.e., the caudate and thalamus) are affected by AD pathology (Braak & Braak, 1990, 1991). Caudate dysfunction has been related to cognitive impairment in normally aging individuals and individuals with other neurodegenerative

diseases (Fjell at al., 2016; Pasquini et al., 2019). Both amyloid and tau have been shown to accumulate in the caudate.

Reduced caudate volume on the right (but not left) has been associated with cerebrospinal fluid tau levels and future conversion to AD in individuals with MCI (Madsen et al., 2010). Volume of the left caudate has been shown to be reduced in individuals with AD, vascular dementia, and Lewy Body dementia compared to healthy controls (Barber et al., 2002). Caudate volumes are also lower in individuals with MCI compared to cognitively unimpaired older adults (Madsen et al., 2010). Baseline Mini-Mental Status Examination scores have been associated with caudate atrophy in a group containing cognitively normal, MCI, and AD participants (Madsen et al., 2010). Right caudate atrophy has also been associated with one-year declines in scores on the Mini-Mental Status Examination in adults with MCI (Madsen et al., 2010). In addition, in individuals with MCI and AD, the sensitivity, specificity, and positive and negative predictive power of the volume reduction of the caudate has been shown to have better predictive value for clinical decline than the measures of the entorhinal cortex (Elshafey et al., 2014).

Subcortical structures such as the caudate may be implicated early in the AD process in individuals with the Apoe4 genotype. In individuals with MCI, the ApoE genotype has been associated with changes in the caudate (Novellino et al., 2019). In addition, there is evidence that decreased functional connectivity of the caudate is associated with ApoE status in individuals with Parkinson's disease and a concurrent cognitive impairment (Shang et al., 2020). Moreover, reduced caudate volume has been identified as a potential biomarker in the pre-symptomatic and early stages of familial AD (Ryan et al., 2013). Taken together, these results seem to indicate that the structural and functional characteristics of the caudate may be an important marker for cognitive impairment and risk for cognitive decline. Based on this, our finding of decreased

caudate connectivity as a function of pure-tone hearing loss indicates that hearing loss may contribute to a greater loss of functional connectivity in individuals with MCI.

5.6 Thalamus Structure and Function

While the thalamus is classically known for its role as a sensory relay station, it also has significant roles in motor activity, emotion, memory, arousal, and sensorimotor association functions (Rikhye et al., 2012). In the present study, pure-tone hearing loss was associated with decreased connectivity between the default-mode network and a small portion of the right thalamus.

5.7 Thalamus Connectivity and Hearing Loss

Our finding of altered thalamic connectivity as a function of pure-tone hearing loss is consistent with previous studies that found altered thalamic connectivity as a function of hearing loss (Rikhye et al., 2012; Alderson et al., 2017; Xu et al., 2019b). There is evidence for altered thalamic connectivity in individuals with sensorineural hearing loss classified based on pure-tone audiometry (Xu et al., 2019b). There is also evidence that hearing loss is associated with altered connectivity between the thalamus and several hearing related brain regions, including Heschl's gyrus (Xu et al., 2019b). Moreover, alterations in thalamic connectivity have been associated with cognitive impairment in adults with hearing loss (Xu et al., 2019b).

5.8 Thalamus Connectivity and MCI

Mild cognitive impairment has previously been associated with altered thalamic connectivity. There is evidence that individuals with MCI have decreased connectivity between the thalamus and thalamus-related cortical networks, such as the default-mode network (Wang et al., 2012). In addition, altered thalamic connectivity has been associated with cognitive impairment in individuals with MCI and it has been suggested that altered thalamic connectivity drives the altered default-mode network connectivity that is seen in individuals with MCI and AD. Considering the previous findings regarding alerted thalamic connectivity in adults with

hearing loss and in adults with MCI, our results suggest that hearing loss is associated with a loss of thalamic connectivity despite the presence of MCI pathology.

5.9 Default-mode Network Connectivity and Hearing Loss

Our finding of altered default-mode network connectivity as a function of pure-tone hearing loss is supported by the findings of other recent studies. For example, a recent study that compared normal hearing individuals to individuals with pure-tone hearing loss found that hearing loss was associated with decreased connectivity within the default-mode network (Xing et al., 2020). Moreover, these network alterations were associated with impaired scores on cognitive assessments (Xing et al., 2020). This suggests that despite MCIs' neurodegenerative pathology, pure-tone hearing loss is associated with a loss of functional connectivity in adults with MCI. This is notable as AD is characterized by a widespread loss of functional connectivity and loss of functional connectivity may be an indicator of disease progression in individuals with MCI and AD. This suggests that hearing loss may increase the pathological burden of AD on the brain. This is supported by evidence that a loss of functional connectivity is associated with AD pathology, such as neurofibrillary tangles.

5.9.1 Laterality of Findings

It is important to consider the known functional and anatomical differences between left and right hemisphere when interpreting the results of the present study. There is a well-documented right ear, or left hemisphere advantage in hearing sensitivity for speech and language processing (Hiscock & Kinsbourne, 2011; Hugdahl & Westerhausen, 2016). This is notable as pure-tone hearing loss and speech-reception threshold were both associated with the connectivity of right, but not left Heschl's gyrus in the present study. Perhaps this finding is due to the left hemisphere advantage for speech-processing precluding the need for the functional reorganization of left Heschl's gyrus due to hearing loss. This is supported by evidence that

aging has a greater impact on the functional connectivity in the right hemisphere compared to the left hemisphere (Fjell at al., 2016). Indeed, there is evidence that the functional connectivity of the left hemisphere is preserved in individuals with hearing loss (Lin et al., 2014). In addition, as previously noted, pure-tone hearing loss has been associated with greater brain volume loss in the right compared to left temporal lobe (Lin et al., 2014). To summarize, our finding of the altered connectivity of the right, but not left Hechl's gyrus is in line with previous research documenting the association between hearing loss induced brain volume loss in the right hemisphere and preservation of functional connectivity in the left hemisphere.

6.0 Implications

The present study is the first to investigate the relationship between hearing loss and resting-state functional connectivity in individuals with MCI. Our finding of decreased connectivity between right Heschl's gyrus and the left frontal lobe as well as increased connectivity within the right auditory cortex itself and regions involved in auditory processing is notable. In cognitively healthy older adults' task-based and fMRI studies have reported increased connectivity between auditory regions and the frontal lobe in individuals with hearing loss. In task-based fMRI studies, this pattern of increased auditory-frontal connectivity has often been interpreted as a mechanism to compensate for hearing loss (Campbell & Sharma, 2014; Sharma & Glick, 2017). The absence of increased connectivity between the frontal and auditory regions in the present study suggests that individuals with MCI and hearing loss may be unable to compensate for hearing loss with increased connectivity between auditory regions and the frontal cortices. This is supported by evidence that compensation may have negative downstream effects on brain function, indicating that the potential for increased compensatory connectivity may be temporary (Wong et al., 2009).

Our results represent novel findings that hearing loss is associated with reduced connectivity of the default-mode network in individuals with MCI. This is a valuable insight as the default-mode network shows a widespread loss of connectivity in individuals with AD. This suggests that individuals with both MCI and hearing loss experience a greater loss of functional connectivity than individuals with MCI and normal hearing. In addition, our results suggest that the heterogenous literature on the relationship between MCI and default-mode network connectivity may be partially attributed to hearing loss not being included in analyses.

There are several notable strengths of the present study. The present study was the first to explore the relationship between hearing loss and resting-state brain connectivity in individuals with MCI. In addition, the present study used both pure-tone audiometry and speech-reception thresholds to measure hearing. Although pure-tone hearing loss and speech-reception thresholds represent distinct types of hearing loss, many studies only use one measure to operationalize hearing loss. This is notable as these measures capture different hearing processes (i.e., peripheral vs central) with potentially different relationships with brain function and cognition. The relationship between pure-tone hearing loss and brain function has received greater research attention than the relationship between speech-reception threshold and brain function. Even less is known about the relationship between these measures and the functional connectivity of the brain at rest. In addition, the sample size of the present study (n=94) is large for a study using functional MRI data and is another strength. Therefore, our findings extend the literature on whether hearing has implications for brain function and add to previous work identifying a relationship between hearing loss and alterations in brain function in the primary auditory cortex, temporal regions, and frontal regions. Based on this, the findings of the present study represent a

novel contribution to the field and the existing literature on hearing ability, brain connectivity, and cognitive impairment.

There are several limitations of the present study that must be noted. Although we initially classified participants into one of six categories based on a pure-tone audiometry screening, the hearing loss group was collapsed across the hearing loss categories due to small group sizes in some of the hearing loss categories. This resulted in the hearing loss group containing adults with mild hearing loss to moderate/severe hearing loss and restricted the detail at which we could explore the relationship between hearing loss and brain connectivity. We were also unable to investigate the effects sex on the relationship between hearing measures and brain connectivity, also due to small cell sizes. This is notable as sex is known to have differential effects of both hearing loss and dementia. In addition, the participants in the present study are a predominately white and highly educated group of volunteers. Therefore, the relative homogeneity of the COMPASS-ND cohort in terms of their demographic characteristics may limit the generalizability of our findings. It is important to note, however, that the sample homogeneity may also regarded as a strength of the present study as it limits the sources of variability in the data.

7.0 Conclusion

Several cortical regions showed altered connectivity with the regions and networks of interest as a function of hearing ability. The cortical regions implicated in the present study include regions involved in auditory and sensory processing and higher-order cognitive processing, and a brain network that has been implicated in early AD. Several of the patterns of altered connectivity were similar to those that have been associated with hearing loss in cognitively unimpaired older adults (i.e., increased connectivity within auditory processing regions). Our results provide evidence that hearing loss is associated with a loss of functional

connectivity in individuals with MCI. This is a notable finding as loss of functional connectivity is a marker of neurodegeneration and the presence of AD pathology. These results indicate that the observed connectivity alterations may suggest functional disconnection due to the negative effects of hearing loss on the brain in individuals with MCI. In addition, these results also suggest that the pathological burden and neurodegeneration may be greater in individuals with both MCI and hearing loss. Based on this, loss of functional connectivity is a potential mechanism by which hearing loss is associated with cognitive impairment, cognitive decline, and increased risk for dementia.

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