NEUROCOGNITIVE FUNCTION IN AGE-RELATED HEARING LOSS: EFFECTS OF

EARLY TREATMENT WITH HEARING AIDS

by

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Neurocognitive Function in Age-Related Hearing Loss: Effects of Early Treatment with

Hearing Aids

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ABSTRACT

Age-related hearing loss is a leading chronic health condition among adults and has been associated with neurocognitive decline, including dementia. While the causal link between hearing loss and cognitive decline is poorly understood, auditory deprivation may tax the brain, inducing compensatory re-allocation of cortical and cognitive resources. In the long-term, structural and functional brain changes associated with hearing loss may deplete cognitive reserve, precipitating neurocognitive degeneration.

Visual cortical cross-modal re-organization is a form of compensatory neuroplasticity observed in hearing loss, but the mechanisms underlying such brain changes remains unclear. Hearing loss is associated with increased neuronal excitability and decreased inhibition in the auditory cortex, possibly unmasking latent non-auditory connections (resulting in cross-modal plasticity) and altering top-down modulation of attention and cognitive processes. However, it remains unclear how alterations in cortical neuroplasticity relate to cognitive outcomes. Further, clinical treatment effects with hearing aids on visual cortical neuroplasticity in age-related hearing loss has not been investigated. In Study 1, we examined the association between visual cortical neuroplasticity and speech perception and cognitive function in untreated, mild-moderate age-related hearing loss, relative to normal

hearing listeners. In Study 2, we evaluated whether hearing aid treatment provided neurocognitive benefit.

Consistent with previous investigations, untreated hearing loss was associated with visual cross-modal re-organization. Greater visual cross-modal re-organization was associated with severity of hearing loss, poorer auditory speech perception abilities, and poorer cognitive function, but not enhanced dependence on visual (lip-reading) cues. Hearing aid treatment reversed cross-modal recruitment of auditory cortex for visual processing over the course of 6 months, coinciding with gains in auditory speech perception abilities and improvements in cognitive performance. Further, pre-treatment visual cross-modal re-organization predicted 6-month post-treatment auditory speech perception outcomes, providing evidence that the functional status of the auditory cortex may limit post-treatment success with hearing aids.

Results of this study provide evidence that hearing aid use may reverse deprivation-induced changes in cortical resource allocation in the auditory cortex and enhance cognitive function in early-stage hearing loss. Further, this study highlights the utility of neurocognitive assessment tools in the audiology clinic for guiding early identification, treatment, and rehabilitation of hearing loss.

DEDICATION

To three generations of women who helped foster my *sisu*: My great grandmother,

grandmother, and mother.

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INTRODUCTION

Age-related hearing loss, or presbycusis, is one of the leading chronic conditions among adults in the United States (Agrawal et al., 2008). The high prevalence of age-related hearing loss and its association with numerous health issues—including risk for neurocognitive decline and dementia—have kindled growing public health concern in recent years (PCAST, 2015; NASEM, 2016). Despite the adverse consequences associated with untreated hearing loss, the hearing healthcare landscape for elders in the United States is complex, presenting many barriers preventing access to and utilization of hearing aids. It is estimated that only 15% of adults who could benefit from hearing aids have them (Chien & Lin, 2012).

Potential causal mechanisms linking age-related hearing loss to neurocognitive decline are not clear. One hypothesis is that hearing loss may tax the brain, resulting in effortful listening. That is, additional resources may be devoted or re-allocated to listening, but may deplete cognitive spare capacity available for other tasks (e.g. memory). While in the short-term these changes may be advantageous, in the long-term these compensatory strategies may affect downstream cognitive processing and induce widespread neuroplastic changes in the brain, precipitating neurocognitive decline and/or decreasing cognitive reserve to withstand neuropathology (Lin & Albert, 2014; Pichora-Fuller et al., 2016; Pichora-Fuller & Daneman, 2010).

Cortical visual cross-modal re-organization is one type of neuroplasticity observed in hearing loss, whereby the auditory cortex becomes 're-purposed' for visual processing (Bavalier & Neville, 2002). The mechanisms underlying visual cross-modal re-organization are unclear. Auditory deprivation has been associated with an upset in normal excitatory-

inhibitory balance in the auditory cortex (Kotak et al., 2007; Kral et al., 2005; Raggio et al., 1999), potentially unmasking latent multimodal inputs (contributing to cross-modal re-organization) and altering typical top-down inhibitory control of sensory processing. Alterations attentional and cognitive processing of sensory stimuli has been reported in hearing loss (Lesicko & Llano, 2017), but it is unclear how these changes relate to long-term cognitive outcomes.

The association between visual cross-modal neuroplasticity and behavioral and cognitive function is not well understood. In this thesis, we evaluated the association between visual cross-modal re-organization and behavioral outcomes, including speech perception and cognitive function, in adults with normal hearing and adults with untreated, age-related hearing loss. Second, we conducted an experimental investigation as to whether clinical intervention with well-fit hearing aids provides neurocognitive benefit over the course of 6 months of hearing aid use.

This study provides preliminary evidence of the positive benefits of early intervention with hearing aids on cognitive function and restoration of typical cortical sensory processing. There are an estimated 47 million people in the world living with dementia, with global cost totaling US$818 billion (Livingston et al., 2017). Thus, effective and timely interventions (e.g. hearing aids) that could prevent or delay the onset of dementia by even a few years has potential to greatly reduce the worldwide burden of dementia. Further, this study supports incorporation of cognitive assessment into hearing aid candidacy evaluation and outcome measurement, where neurocognitive outcomes may be used in a clinical setting to guide early intervention, treatment, and rehabilitation for aging adults with hearing loss.

CHAPTER 1

LITERATURE REVIEW

1.1.   Age-Related Hearing Loss

Age-related hearing loss affects approximately 34%, 53%, and 77% of adults in their 40s, 50s, and 60s (Agrawal et al., 2008), respectively. Age-related hearing loss is nearly ubiquitous among older adults, with nearly 80% of adults over age 80 years demonstrating signs of clinically significant hearing impairment (Lin et al., 2013). The high prevalence of age-related hearing loss makes it a leading chronic health condition in the United States (Agrawal et al., 2008) and among the top leading causes of burden of disease worldwide (Mathers & Loncar, 2006).

Age-related hearing loss negatively impacts communication and quality of life (Dalton et al., 2003; Hawkins et al., 2012); physical frailty, including balance disturbances and falls (Albers et al., 2015; Lin et al., 2012; Lin & Albert, 2014; Lin & Ferrucci, 2012; Genther et al., 2015; Kamil et al., 2016); psychosocial status, including depression and social isolation (Chen, 1994; Gopinath et al., 2012); employment and economic status (Emmet & Francis, 2015; Stucky et al., 2010); and healthcare utilization, including hospitalization (Simpson et al., 2016). As will be described in Section 1.2.4, age-related hearing loss is also associated with cognitive impairments, accelerated neurocognitive decline, and elevated risk for dementia (Ford et al., 2018; Loughrey et al., 2018; Thompson et al., 2017; Wei et al., 2017; Zheng et al., 2017). Though the effects of age-related hearing loss are far reaching, management of adult-onset hearing loss has not been a top healthcare priority among society and policy makers in the United States.

1.1.1. Clinical Diagnosis

Age-related hearing loss typically presents in the form of a bilateral sensorineural hearing loss (Gates & Mills, 2005). A sloping configuration is quite common, where higher frequency sounds (e.g. /s/, /sh/) are most affected. Mild and moderate (early-stage) age-related hearing loss is the most prevalent form of age-related hearing loss, followed by severe and profound hearing loss (Cheng et al., 2009). As adults age, severity increases by approximately 1-9 decibels (dB) per decade (Davis et al., 1990). Age-related hearing loss typically presents as a symmetrical loss, whereby both ears are equally affected (Cruickshanks et al., 1998). Prevalence of age-related hearing loss among males is slightly higher than females (Cruickshanks et al., 2003).

Clinical diagnosis of age-related hearing loss is based on case history, physical examination, and a comprehensive audiological examination, which may include pure tone air and bone conduction threshold testing, threshold and suprathreshold speech perception testing, and immittance measures. Pure tone thresholds assess the lowest level (in decibels hearing level, or dB HL) that a person can detect across the frequencies most important for speech understanding (0.25-8 kHz). Pure tone thresholds may range from mild (26-40 dB HL), moderate (41-55 dB HL), moderately-severe (56-70 dB HL), severe (71-90 dB HL), to profound (>90 dB HL) across the frequency range. Degree of hearing loss is commonly reported in terms of a pure tone average (PTA) (average pure tone air conduction thresholds at 0.5, 1, and 2 kHz) or a high frequency pure tone average (HFPTA) (average pure tone air conduction thresholds at several higher frequency thresholds, e.g. 2, 4, 6 kHz). Many adults with age-related hearing also present with loudness recruitment, whereby loud sounds become intolerable much faster in sensorineural hearing loss, relative to normal hearing listeners (Moore et al., 2007). The elevated pure tone audiometric thresholds coupled with

reduced uncomfortable loudness levels thus results in a reduced dynamic range for listeners with age-related hearing loss. Acoustic immittance results (tympanometry and acoustic reflex thresholds) useful in differentiating outer/middle ear pathology from inner ear pathology are typically normal in this population (Osterhammel & Osterhammel, 1979; Wiley et al., 2005).

Speech recognition thresholds (SRT) in quiet are typically elevated in age-related hearing loss. The SRT is typically commensurate with the degree of pure tone audiometric loss, proportionate with degree of cochlear pathology (Carhart & Porter, 1971). Suprathreshold word recognition scores (WRS) in quiet tend to be minimally impacted, but poorer scores may be observed in severe-profound age-related hearing loss the auditory speech signal is significantly more degraded (Dubno et al., 1995). Suthrathreshold speech perception abilities are least affected under ideal listening situations (e.g. in quiet with a single talker) and more negatively affected in degraded listening situations (e.g. in background noise, in the context of competing talkers, and in reverberant environments) (Souza et al., 2007). Section 1.2.1 describes the impact of hearing loss on speech perception in noise in greater detail.

1.1.2. Pathophysiology

Beyond normal aging, intrinsic and extrinsic factors over the course of a lifetime may contribute to age-related hearing loss. Intrinsic factors may include genetic factors (e.g. genetic heritability, gene mutations, oxidative stress)—all of which may increase risk of hearing loss. Examples of extrinsic factors include occupational or recreational noise exposure and use of ototoxic medications. Various health co-morbidities such as cardiovascular disease, diabetes, inflammation, and smoking are known risk factors for age-

related hearing loss. See Yamasoba et al. (2013) for a comprehensive review of the multi-factorial contributors to the manifestation of age-related hearing loss.

Age-related hearing loss was originally classified into discrete categories by correlating clinical audiometric characteristics with post-mortem temporal bone characteristics: A sensory category (attributed to loss of hair cells in the inner ear); a neural category (related to loss of neurons in the cochlea); a metabolic category (attributed to atrophy of the stria vascularis and spiral ligament providing blood flow to the cochlea); and a mechanical category (related to stiffening of the basilar membrane and organ of corti) (Schukenecht, 1969; Schukenecht & Gacek, 1993). However, this original classification system paints an overly simplistic view, since phenotypic presentation of age-related hearing loss is quite heterogeneous (Allen & Eddins, 2010). Furthermore, new research has uncovered pathology at higher levels in the central auditory system, with impacts beyond the auditory periphery (Ouda, Profant, & Syka, 2015).

Structural changes in the auditory periphery include loss of outer hair cells, loss of inner hair cells (in more severe cases of age-related hearing loss), deterioration of the stria vascularis, alterations in synaptic connections between the inner hair cells and auditory nerve, and deterioration of spiral ganglion neurons (see Jayakody et al., 2018 for a review). Likely as a result of these structural changes in the inner ear, functional changes may occur, including a decline in cochlear endolymphatic potentials (EP) resulting in impairment of the cochlear amplifier (Gates & Mills, 2005). Asynchronous firing of the auditory nerve in age-related hearing loss has also been reported (Gates & Mills, 2005).

The central auditory system is also affected by age-related hearing loss. Primary nuclei in the central auditory pathway include the superior olivary complex, dorsal and ventral cochlear nuclei, lateral lemniscus, inferior colliculus, medial geniculate body, and the primary auditory cortex. White matter declines are evident via diffusion tensor imaging (DTI)

techniques at the level of the superior olivary complex, lateral lemniscus, and inferior colliculus (Chang et al., 2004; Lin et al., 2008). Auditory-driven neural activity is also reduced over regions of the medial geniculate body, inferior colliculus, and cochlear nucleus, as detected through a reduction in blood-oxygen-level dependent (BOLD) hemodynamic response (HDR) activity via functional magnetic resonance imaging (fMRI) techniques (Boyen et al., 2014).

The auditory cortex is similarly affected by age-related hearing loss. For example, decreased gray matter and white matter volumes in regions of the auditory cortex of the temporal lobe (e.g. superior, middle temporal gyrus, and inferior temporal gyri) are evident via structural MRI (Eckert et al., 2012; Hussain et al., 2011; Peelle et al., 2011). Declines in gray matter volumes in the temporal lobe appear to accelerate over time in age-related hearing loss, decreasing 1.2 cm^3/year faster on average over a 6-year follow-up period compared to normal older adults (Lin et al., 2014). The right temporal lobe appears more susceptible to atrophy in age-related hearing loss, where regions of right superior, middle, and inferior temporal gyri and parahippocampus exhibit accelerated regional volume loss compared to left temporal regions (Lin et al., 2014).

It is hypothesized that structural changes in the auditory cortex may be driven, at least in part, by decreased or degraded auditory input from the auditory periphery. For example, Peelle et al. (2011) observed a significant negative correlation between gray matter volumes in the auditory cortex and degree of pure tone audiometric hearing loss, indicating a relationship between degree of hearing loss and structural atrophy in the auditory cortex. Peripheral deafferentation associated with deafness and hearing loss has been shown to result in increased neural excitability in the auditory cortex and decrease inhibition (Kotak et al., 2007; Kral et al., 2005; Raggio et al., 1999). Deprivation to the auditory cortex may also affect top-down modulation from the cortex to subcortical structures. For example, Kral et al.

(2000) recorded auditory cortical field potentials in a group of deaf cats and a group of normal hearing cats. In their study, delayed activation in supragranular layers and reduced activity in infragranular layers were observed in the deaf animals. Since infragranular layers of auditory cortex project to subcortical structures, this suggests a 'functional de-coupling' or upset in typical top-down modulation from auditory cortex to subcortical structures (e.g. auditory thalamus, midbrain, and brainstem). Overall, peripheral deafferentation from cochlear hearing loss may profoundly affect structure and function in the auditory periphery, as well as the central auditory system. The functional effects of age-related hearing loss on compensatory cortical neuroplasticity, including visual cross-modal re-organization, are described in Section 1.2.2.

1.1.3. Treatment Options

The primary goal of hearing rehabilitation is to reduce functional deficits associated with age-related hearing loss (e.g. participation restrictions and activity limitations that arise from communication difficulties), and to improve quality of life (Boothroyd, 2007). Treatment options for age-related hearing loss may include hearing aids, cochlear implants, and/or assistive listening devices. Hearing aids cannot reverse structural damage to the peripheral auditory system in age-related hearing loss, but they can increase audibility and provide better access to speech (Dillon, 2012). Cochlear implants are the recommended treatment option for adults with more severe hearing loss, for whom hearing aids provide limited benefit. Cochlear implants provide direct stimulation of the auditory nerve, bypassing peripheral cochlear damage (Zeng, 2004). Assistive listening devices can be used alone or in conjunction with hearing aids and cochlear implants. Assistive listening devices aim to maximize auditory function in specific situations (e.g. using the telephone; watching television; hearing in places of worship, lecture halls, or public venues). Personal sound

amplification products (PSAPs) have also emerged in recent years as an over-the-counter treatment option for mild-moderate hearing loss in adults. In the United States, PSAPs fall under a different regulatory class by the Federal Drug Administration (FDA) than traditional hearing aids.

Hearing aids consist of 4 primary components: A microphone, a digital signal processor, a receiver, and a battery. The microphone captures acoustic sound from the environment and transfers it to an amplifier, where the sound is enhanced. Sound is then digitally modified and filtered by the digital signal processor and sent to the receiver delivering sound to the ear (Dillon, 2012). Hearing aids come in a variety of styles. Open-fit, receiver-in-the-ear (RIC) style hearing aids are commonly prescribed for age-related hearing loss. With this style of hearing aid, the receiver is coupled to an acoustic dome or earmold that sits in the ear canal. By moving the receiver closer into the ear and leaving the ear canal open with a vented acoustic dome or earmold, RIC-style hearing aids allow selective amplification of higher frequencies and avoid undesirable low-frequency occlusion effects (Dillon, 2012).

Advanced digital signal processing features in modern hearing aids include multi-band wide dynamic range compression, multi-channel noise reduction, directional microphones, acoustic feedback cancellation, and binaural processing capabilities. Wide dynamic range compression ensures audibility of soft sounds and tolerable comfort of loud sounds by providing different amounts of amplification (gain) based on the input level, thus mapping the wide dynamic range of speech that a normal hearing listener can capture onto the reduced dynamic range of age-related hearing loss. The 'amount' of dynamic range compression can be modified by adjustment of the compression ratio. The 'speed' of response to inputs to the hearing aid can be modified through adjustment of the attack and release times. The automatic gain control characteristics in modern hearing aids are typically

applied separately across select frequency bands, referred to as multi-band dynamic range compression. Multi-channel noise reduction is another common strategy employed in modern hearing aids that allows for enhancement of the speech signal by reducing frequency band(s) dominated by noise (e.g. background noise). Noise reduction technology is often coupled with directional microphone technology, which adaptively or manually sets the microphone polar plot to enhance speech coming from the front of the listener and reduces speech coming from behind the listener. Together, directional microphones and noise reduction technology can enhance the signal-to-noise ratio (SNR) of the speech signal relative to the background noise. Acoustic feedback cancellation algorithms prevent amplified sound from leaking out of the ear and picked back up from the microphone. Binaural processing capabilities capitalize on inter-aural level differences (ILDs) and inter-aural timing differences (ITDs) arriving between the two ears to enhance speech perception in background noise. See Dillon (2012) for an overview of the signal processing features in modern digital hearing aids.

Gold-standard clinical fitting of hearing aids for adults consists of an initial fitting (where a hearing aid prescriptive fitting formula is prescribed based on a patient's audiometric characteristics), followed by fine-tuning adjustments. Best practice recommendations support additional verification of the hearing aid fitting via probe microphone measurements. In this procedure, a microphone is inserted into the ear, the hearing aid is placed on the patient's ear, and the to gain provided by the hearing aid is measured and compared to prescriptive target gain for soft, medium, and loud speech inputs across the frequency range. A variety of prescriptive fitting targets exist for modern hearing aids, each with a slightly different goal in maximizing and balancing audibility, speech intelligibility, and comfort for the individual (Dillon et al., 2012).

1.1.4. Barriers to Access and Utilization of Hearing Rehabilitation

There exists a multitude of barriers contributing to low intervention and usage rates of hearing aids among older adults (Barnett et al., 2017). As it currently stands, less than 15% of adults with hearing loss use hearing aids, and prevalence of hearing aid use is even lower (<4%) among adults with early-stage (mild-moderate) age-related hearing loss (Chien & Lin, 2012). For those adults who do seek treatment for hearing loss, treatment is often delayed, about a decade from the initial onset of the hearing loss, typically only after the hearing loss has significantly affected daily function and quality of life (Davis et al., 2007). What's more, it is estimated that only about 29% of adults in the United States have ever had their hearing tested (National Center for Health Statistics, 2010). Currently, there exists no universal hearing screening recommendations for adults or best practice guidelines for the education and management of age-related hearing loss, particularly in its early stages. As a result, adult-onset hearing loss is largely dismissed as a "normal" process of aging by patients, physicians, and healthcare policy-makers.

Lack of referral to audiology by primary care physicians is a known issue that may prevent access to hearing healthcare (Laplante-Levesque et al., 2012). Next to a house and a car, hearing aids can be the third most expensive purchase for an older person in the United States (Blustein & Weinstein, 2016). Socioeconomic status, high cost of hearing aids, and lack of insurance coverage for hearing aids under Medicare and private insurance policies are among other commonly cited access barriers (Bainbridge et al, 2014; Laplante-Lavesque et al., 2010, 2012; Meister et al., 2008). The traditional service delivery model of hearing aids may also limit access to hearing healthcare. Under the traditional 'medical model', hearing healthcare and rehabilitation services are provided by an audiologist, or in some cases, a hearing aid dispenser or technician. Particularly in rural areas or for elders with transportation difficulties, access to a hearing healthcare provider may be limited in these cases (Barnett et al., 2017). Further, insufficient number of audiology education programs,

shortage of hearing healthcare specialists, and shortage of community health workers with expertise in the area of hearing loss may constrain the number of trained professionals who can meet current hearing healthcare demands (Goulios & Patuzzi, 2008).

A variety of patient factors affect uptake and use of hearing aids. Personal motivational factors (Wallhagen, 2010) and the stigma associated with hearing loss (e.g. issues of identity, aging/ageism, and disability) (Southall, Gagne, & Jennings, 2010; Wallhagen, 2010) have been cited as possible contributors. Low levels of self-efficacy and lack of social support may also prevent acquisition and utilization of hearing aids (Meyer, Hickson, & Fletcher, 2014; Kotchkin et al., 2007). These factors, combined with lack of education surrounding the importance of hearing healthcare, likely explains low levels of hearing aid uptake and use among the general population.

1.2.   Neurocognitive Effects of Age-Related Hearing Loss

1.2.1. Cognitive Framework of Speech Perception in Noise

One of the most commonly reported issues among adults with age-related hearing loss is the inability to function in adverse, real-world listening scenarios such as background noise. For instance, patients with age-related hearing loss may complain that they are unable to distinguish talkers in group situations or when background noise is present. While stimulus factors such as the audibility and saliency of the speech signal, the type of speech signal (e.g. words, sentences), the type of background noise (e.g. steady-state, modulated noise, or speech noise), the signal-to-noise ratio (SNR), and the rate of speech may all affect speech perception in noise performance (Pichora-Fuller & Singh, 2006), it has been known for decades that cochlear hearing loss puts listeners at a greater disadvantage in background noise compared to normal hearing listeners (Akeroyd et al., 2008; Carhart & Tillman, 1970;

Dubno et al. 1984; Humes & Dubno, 2010; Killion & Niquette 2000; Larsby et al., 2008; Souza et al. 2007). Reduced frequency resolution, reduced temporal resolution, loudness recruitment, loss of the ability to take advantage in temporal fine structure cues, and presence of cochlear dead regions are important peripheral factors that may negatively impact suprathreshold speech perception in real-world contexts (Moore et al., 2007).

However, peripheral factors alone may not account for the difficulty that age-related hearing loss listeners experience in background noise. Increasingly, it has become apparent that central factors also play a role (Pichora-Fuller et al., 2016). Speech perception in noise is a complex process, where parsing of the speech signal involves a combination of processing both bottom-up and top-down cues to facilitate comprehension (Desjardins & Doherty, 2014; Gatehouse, 2003; Humes et al., 2006). Under a cognitive framework of speech perception, information processing is thought to operate in a limited capacity system (Daneman & Carpenter, 1980; Kahneman, 1973). That is, resources are finite. For example, if one task requires a great deal of processing resources, then this may deplete the available resources that can be dedicated to a different task. Cognitive spare capacity refers to the unused resources available for additional tasks. Cognitive load refers to the extent to which a task consumes cognitive spare capacity (Pichora-Fuller et al., 2016).

Following this cognitive framework of speech perception in noise, when bottom-up cues are degraded (e.g. due to age-related hearing loss), when a person is in an acoustically difficult listening situation (e.g. background noise), or when a person is in an informationally complex situation (e.g. multitasking), speech comprehension may pose a greater challenge. Listening may be perceived as effortful (Eckert et al., 2016), and, as a result, may place an increased cognitive load on the brain. In order to compensate for the degraded auditory input, adults with hearing loss may need to recruit or re-allocate cognitive resources to parse the speech signal (Pichora-Fuller et al., 2016).

However, the greater processing resources required to parse the speech signal, the less cognitive spare capacity is available for other tasks, like memory (e.g. recalling what was just said) (Wingfield et al., 2005). Working memory refers to the ability to store, manage, and retrieve information during while operating a complex task (e.g. speech perception) or simultaneously operating more than one task (Pichora-Fuller et al., 2016). Working memory may be limited by individual factors, as well as the cognitive demands of the task. Research evidence supports the idea that working memory abilities may only be negatively affected and have downstream effects on cognitive function when the demands of a particular task (e.g. speech perception in noise) exceed an individual's cognitive spare capacity (Mishra et al., 2014). Motivational factors, attention, and individual differences may also limit cognitive spare capacity (Eckert et al., 2016; Pichora-Fuller et al., 2016).

In real-world communication, speech perception is even more complex because it is an inherently multi-modal process. In these contexts, both auditory and visual cues are available for speech perception. Visual cues available to a listener may include the lips, tongue, and teeth, helping to convey when to attend to a speaker (Carlyon et al., 2001; Helfer & Freyman, 2005), the temporal amplitude envelope of speech signal (Chandrasekaran et al., 2009), and the syllabic and lexical categories of speech (Peelle & Davis, 2012). Studies indicate that adults perform better on speech perception tasks in auditory-visual conditions compared to conditions where only auditory cues or only visual cues are available (Grant et al., 1998; Ross et al., 2007; Sommers et al., 2005; Zekveld et al., 2009). The amount of benefit a person receives from visual cues can be substantial, with some studies reporting about a 5 dB SNR advantage in typical adults (Middelweerd & Plomp, 1987). However, it is important to note that wide variability exits in the amount of benefit that listeners derive from visual cues. For example, in the study by MacLeod & Summerfeld (1990), researchers found that normal hearing adult listeners gained anywhere from a 2.7 to 9.5 dB SNR improvement with the

addition of visual cues, equating a 22% to 75% improvement—quite a wide range in performance.

Some deaf subjects may derive greater benefit from visual cues compared to normal hearing subjects (Arnold & Murray, 1998; Bergeson et al., 2005; Bernstein et al., 2000; Ellis et al., 2001; Mitchell et al., 2013; Rouger et al., 2007, 2012; Schorr et al., 2005; Stropahl et al., 2015; Stropahl & Debener, 2017). Auer & Bernstein (2007) reported that adults with early-onset deafness gained greater relative benefit from visual cues for auditory-visual speech perception compared to normal hearing adults. In their study, deaf adult participants derived about 43.55% benefit from visual cues for speechreading of sentences in quiet, while normal hearing adults showed only 18.57% benefit. However, majority of the aforementioned studies included subjects with pre-lingual deafness onset, a very different case from adults who acquire hearing loss later in life. Very few studies have investigated how clinical populations with adult-onset and lesser degrees of hearing loss functionally benefit from visual (lip-reading) cues (Clouser, 1977; Farrimond, 1959; Lyxell & Rönnberg, 1989, 1991; Owens & Blazek, 1985). It is unclear whether early-stage (mild-moderate) age-related hearing loss is associated with enhanced lip-reading benefit.

Following the cognitive framework of speech perception, it is possible that visual cues available to a listener may decrease cognitive demands in degraded listening situations. Studies by Pichora-Fuller (1996) demonstrated that the addition of visual cues may decrease the negative effects of background noise on working memory in speech perception tasks. Older adult listeners, and to a greater extent older adult listeners with age-related hearing loss, tend to perform better on working memory tasks when visual cues are available (Frtusova & Phillips, 2016). In summary, it is not clear to what extent age-related hearing loss is associated with benefit from visual (lip-reading) cues relative to age-matched, normal hearing control subjects.

1.2.2. Visual Cross-Modal Re-Organization

Electroencephalography (EEG) has proven to be a useful neuroimaging technique for evaluating cross-modal neuroplasticity in humans with hearing loss (see Glick & Sharma, 2017, for a review). While EEG has poorer spatial resolution capabilities compared to other imaging techniques (e.g. fMRI, fNIRS), EEG offers more ideal temporal resolution (millisecond level), ideal for assessing aspects of sensory perception and attention. EEG is also non-invasive and inexpensive, making it feasible for clinical and translational research on human populations (Luck et al., 2005). Further, there is increasing concern about the high acoustic noise levels generated by MRI scanners, with peak levels as high as 125-130 dB sound pressure level (SPL) (Hattori et al., 2007). Not only is this concerning as such high noise levels may contribute to noise-induced hearing loss (Bongers et al., 2017), but the acoustic noise generated by the scanner may bias results when assessment of metabolic activity in the auditory cortex is the primary region of interest (Ravicz, 2000).

Cortical Visual Evoked Potentials (CVEPs) are late-occurring event-related potentials (ERPs) time-locked to the presentation of visual stimuli (see Luck, 2005 for a review). CVEP recordings can be averaged over many stimulus presentations (trials). Analysis of CVEP data is performed by evaluating latencies and amplitudes at particular electrodes, across several electrodes (called regions of interest, or ROIs), or across the entire scalp. When using high-density (>64 channel) EEG, source modeling can also be performed to estimate sources of brain activity underlying the CVEP response with relatively low-localization error (Pascaul-Marqui, 2002).

The CVEP response averaged over many stimulus trials is comprised of 3 primary components: The P1, N1, and P2 components. These components are termed based upon their polarity (positive or negative voltage) and timing occurrence in the CVEP waveform. Each

component of the CVEP waveform represents the summed electrical activity generated by postsynaptic potentials of many simultaneously active pyramidal cells in the cortex in response to the visual stimulus, thus reflecting the underlying cortical and cognitive activity associated with the processing of visual stimuli (Luck et al., 2005).

In the visual cortex, there are two different streams or networks responsible for processing visual stimuli: the dorsal pathway and the ventral pathway. The dorsal pathway ('where' pathway) primarily processes magnocellular inputs such as visual motion, whereas the ventral pathway ('what' pathway) processes both magnocellular and parvocellular inputs such as visual form (Haxby et al., 1991; Rauschecker & Tian, 2000). As the complexity of the visual stimulus increases, both the dorsal and ventral streams may be involved in visual processing (Ptito et al., 2003; Tse, 2006). The first two components in the CVEP response to visual motion stimuli, the P1 and N1 responses, reflect pattern-related activity of the parvocellular system (Doucet et al., 2005; Whittingstall et al., 2007), with cortical sources localized regions of the dorsal extrastriate cortex (e.g. middle occipital gyrus and fusiform gyrus) (Herrmann & Knight, 2001; Natale et al., 2006). Both the P1 and N1 components appear to be modulated by attention (Gazzaley et al., 2008; Hackley et al., 1990; Luck et al., 1990; Zanto et al., 2010). The later P2 component is thought to reflect higher level visual processing, involving both the parvocellular and magnocellular systems, with cortical sources localized to regions of the extrastriatal visual cortex, sharing feed-forward connections with inferior temporal cortex and fusiform gyrus, as well as temporal-occipital and parietal cortical generators (Bach & Ullrich, 1997; Kubová et al., 1990; Kuba & Kubová, 1992; Probst et al., 1993; Skrandies et al., 1998). In contrast to the P1 and N1 CVEP responses, which reflect attentional operations, the P2 component is considered an index of higher level working memory function and encoding (Lefebvre et al., 2005; Wolach & Pratt, 2011). Thus, the CVEP

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components reflect visual sensory processing, attentional processing, and working memory at a cortical level.

The earliest evidence of visual cross-modal re-organization of the auditory cortex in deafness was described by Neville and colleagues (1983, 1987). In these studies, single-channel CVEP recordings to visual stimuli were recorded in a group of congenitally deaf adults and a group of normal hearing controls. Results indicated significantly larger CVEP amplitudes over the auditory cortex in deaf adults relative to normal hearing control subjects, suggestive of cross-modal recruitment of the auditory cortex by vision. Subsequent EEG studies support these findings, where earlier visual CVEP latencies and/or larger visual EEG amplitudes over regions of the auditory cortex are considered to be markers of visual cross-modal re-organization in deafness (Buckley & Tobey, 2010; Doucet et al., 2006; Karns et al., 2012; Kim et al., 2016; Sandmann et al., 2012; Shiell et al., 2014). Earlier latencies and higher amplitudes tend to reflect increased synaptic strength and connectivity (Driver & Spence, 2004), and may be an indirect measure of enhanced cross-modal interaction to sensory stimuli.

Visual cross-modal re-organization has also been described in deaf children using high-density EEG techniques. For example, in a recent study by Campbell & Sharma (2016), CVEPs were recorded using 128-channel high-density EEG in deaf cochlear implanted children (n=14) and an age-matched group of normal hearing children (n=41). Deaf children exhibited earlier N1 CVEP latencies over a right temporal ROI in deaf compared to normal hearing children, suggestive of cross-modal re-organization. Further, cortical source modeling patterns indicated increased cortical activity over auditory cortical regions for the higher-order N1 and P2 CVEP components (e.g. right inferior, middle, and superior temporal gyrus) in the deaf children, relative to normal hearing children, in which cortical activity was

restricted to occipital cortical areas (e.g. cuneus, lingual gyrus, Broadman area 18, 19) traditionally associated with visual motion processing.

Increasingly, it has become apparent that cross-modal plasticity is not just restricted to deafness but is also apparent in lesser degrees of hearing loss, including age-related hearing loss. Campbell & Sharma (2014) provided the first evidence of visual cross-modal re-organization in mild-moderate age-related hearing loss. CVEPs were recorded to a visual motion stimulus in a small group of adults with normal hearing (n=9, M=50.5 years, SD=6.2) and a group of adults with mild-moderate age-related hearing loss (n=8, M=56.9 years, SD=8.9 years). Similar to the Campbell & Sharma (2016) study, earlier N1 CVEP latencies were observed in the age-related hearing loss group relative to the normal hearing group, suggestive of visual cross-modal re-organization. Further, cortical source modeling patterns indicated increased activity over auditory cortex for the later N1 and P2 CVEP components (e.g. inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus) in the age-related hearing loss group, whereas the normal hearing group exhibited expected activation restricted to occipital and cerebellar regions typically associated with visual motion processing (e.g. cerebellum, fusiform gyrus, lingual gyrus). Evidence of visual cross-modal re-organization in age-related hearing loss was recently replicated in an EEG study by Stropahl & Debener (2017), where adults with age-related hearing loss exhibited similar cross-modal findings to those reported in Campbell & Sharma (2014).

The neural mechanisms underlying visual cross-modal re-organization are still disputed. In adults, it is possible that unmasking of 'silent' multi-modal inputs (e.g. auditory-visual or auditory-somatosensory inputs) or non-auditory (e.g. visual, somatosensory) inputs, the stabilization of transient neuronal connections, the sprouting of new axons, the strengthening of existing multi-sensory connections between higher-order sensory cortices, or some combination of these processes may facilitate cross-modal re-organization of the

auditory cortex by other sensory systems (Allman et al., 2009; Falchier et al., 2002; Meredith & Lomber, 2017; Rauschecker et al., 1995; Rockland & Ojima, 2003).

The functional implications of visual cross-modal re-organization are also disputed. From one perspective, visual cross-modal re-organization may serve an adaptive purpose, helping to facilitate more efficient integration auditory-visual speech information. For example, Strophal and colleagues (2015) found that amplitude of auditory cortex activation to visual stimuli correlated with lip-reading benefit in and auditory-visual speech perception task in deaf adults, where earlier latencies over auditory cortex (indicative of cross-modal re-organization) were associated with higher auditory-visual speech perception scores, suggesting that cross-modal re-organization may serve an adaptive purpose for real-world communication. Stropahl & Debener (2017) observed similar findings in post-lingually deafened adults, whereby greater activation of auditory cortex was associated with greater benefit from lip-reading cues. However, while Strophal & Debener (2017) also observed visual cross-modal re-organization in a group of adults with less severe hearing loss (mild-moderate sensorineural hearing loss), researchers observed no association between visual neuroplastic changes and lip-reading benefit in the mild-moderate hearing loss group.

From another perspective, visual cross-modal re-organization may have 'maladaptive' effects in the auditory modality. This idea is related to the load theory of selective attention that operates under the assumption that information and attentional processing resources are limited (Broadbent, 1954; Lavie & Fockert, 2003; Lavie et al., 2004, 2005; Norman & Bobrow, 1975). If a large proportion of auditory cortical resources are devoted to perceptual processing during one task (e.g. visual processing), this may limit the available resources available for other tasks (e.g. auditory processing). There may be no downstream negative consequences when the perceptual load of the primary task is low (Lavie, 1995; Lavie et al.,

2004, 2005, 2014; Lavie & Tsal, 1994; Rees et al., 1997), but when the perceptual demands of the primary task are high, perceptual capacity may be exhausted.

For example, in the study by Campbell & Sharma (2016) in deaf cochlear implanted children, auditory-only speech perception performance in background noise was negatively correlated with N1 CVEP latency over the right temporal ROI. In other words, earlier CVEP latency (an index of more cross-modal recruitment of the auditory cortex by vision) was associated with poorer auditory speech perception outcomes in background noise. Similarly, in the study by Campbell & Sharma (2014) in adults with age-related hearing loss, N1 CVEP latency was negatively correlated with auditory speech perception in noise performance, where earlier latencies (considered a marker of cross-modal re-organization) were associated with poorer auditory speech perception outcomes. Other studies in deaf subjects have observed similar negative correlations between auditory cortex recruitment for visual processing and auditory-only speech perception performance in quiet or noise (Doucet et al., 2006; Buckley & Tobey, 2010; Chen et al., 2016; Lee et al., 2001, Sandmann et al., 2012; Strelnikov et al., 2013). Further, several investigations indicate that even after hearing loss has been 'restored' with a cochlear implant, visual cross-modal re-organization of the auditory cortex persists in some subjects. Further, this persistent visual cross-modal re-organization is correlated with poorer auditory speech perception outcomes following cochlear implant intervention (Doucet et al., 2006, Lee et al., 2001, Sandmann et al., 2012).

To our knowledge, no studies have evaluated the association between visual cross-modal re-organization and cognitive outcomes in listeners with hearing loss. However, in line with the cognitive load theory, it could be theorized that cross-modal re-organization of the auditory cortex for visual processing may deplete spare capacity for auditory processing under multi-modal contexts if the demands of the tasks are high. For example, in a real-world adverse listening environment where a hearing impaired listener is trying to perceive speech

in background noise and has visual cues at their disposal, greater cortical resources may be devoted toward visual processing (e.g. recruitment of attentional networks, cross-modal recruitment of the auditory cortex for visual processing), depleting spare capacity available for auditory processing or for other cognitive tasks downstream (e.g. working memory). In the case of a deaf listener struggling with their cochlear implant, for example, if a significant portion of cognitive resources are being devoted to visual processing, this may deplete the available cortical resources that can be allocated to listening. While this association has never been evaluated in hearing impaired populations, cross-modal distraction tasks in normal hearing listeners support the idea that working memory, executive function, and processing speed performance may deteriorate when the cognitive load on the system (e.g. due to perceptual or cognitive factors) increases (Konstantinou et al., 2012, 2014; Konstantinou & Lavie, 2013; Regenbogen et al., 2012; Simon et al., 2016). The implications of visual cross-modal re-organization on cognitive function in deafness or hearing loss have not been investigated.

1.2.3. Cognitive Function in Age-Related Hearing Loss

Several recent meta-analyses have established an independent association between age-related hearing loss and risk for and cognitive impairment, cognitive decline, and dementia (Loughrey et al., 2018; Thompson et al., 2017; Wei et al., 2017; Yuan et al., 2018; Zheng et al., 2017). For example, in a recent meta-analysis by Yuan et al. (2018) which analyzed dementia risk across 11 research studies, moderate age-related hearing loss (PTA >40 dB HL) was associated with a 29% higher risk for dementia over a follow-up period ≤6 years and 57% higher risk over a follow-up period >6 years. In fact, elevated risk for dementia was significant even when mild age-related hearing loss (>25 dB HL) was included in the analysis. Another meta-analysis across 7 different research studies by Wei et al. (2017)

concluded that age-related hearing loss is associated with significantly increased risk for mild cognitive impairment (MCI), a precursor to dementia.

Dementia describes a progressive neurocognitive disorder that impairs cognitive function in one or more cognitive domains and affects daily function (DSM-5), of which Alzheimer's disease (AD) is the most common form (Hebert et al., 2003). Mild cognitive impairment (MCI) refers to modest impairments in cognitive function in one or more cognitive domains, where daily functioning remains largely intact, albeit with greater effort (DSM-5). Clinical diagnosis of MCI and dementia are made through neuropsychological assessment across 6 cognitive domains: Attention, executive function, learning/memory, language, perceptual-motor function, and social cognition (DSM-5). Broad definitions of these sub-domains of cognition in accordance with DSM-5 criteria are outlined in Table 1. For a complete review of the epidemiology, diagnosis, and treatment of dementia and MCI, see Hugo and Ganguli (2014).

Age-related hearing loss is associated with poorer cognitive function in many sub-domains overlapping with the DSM-5 diagnostic criteria for dementia and MCI diagnoses. For example, in a recent meta-analysis by Loughrey et al. (2018) researchers quantitatively assessed the effects of age-related hearing loss on cognitive function across several domains across 26 cross-sectional studies and 9 cohort studies where data were collected between 1970 and 2012. In their analyses, age-related hearing loss was associated with significant impairments in global cognitive function, as well as impairment in other cognitive sub-domains including attention, delayed recall, fluency, immediate recall, processing speed, reasoning, semantic memory, visuospatial ability, and working memory.

It is important to note that audibility-related factors may confound or overestimate the strength of the association between age-related hearing loss and cognitive impairment. One of the known issues with neuropsychological tests is that many measures rely on verbal

presentation. Thus, it is possible that audibility-related factors (e.g. inability to hear test instructions or items presented on the test) may lead to poorer cognitive performance, or overestimate level of cognitive impairment (Dupuis et al., 2015; Jorgensen et al., 2016; Pratt et al., 2016; Scheneider, Daneman, & Murphy, 2005). That stated, the association between age-related hearing loss and cognitive impairment appears to remain significant when using cognitive tests with non-verbal presentation (Lin et al., 2011; Lin et al, 2013; Wong et al., 2014), when test items with requiring verbal presentation are removed (Dupuis et al., 2015; Panza et al., 2015a; Wayne & Jonhstrude, 2015), and when alternative non-verbal adaptations of cognitive tests are used (Uhlmann et al., 1989).

Sub-Domain	Broad Definition
Attention	Ability to attend and concentrate for execution of tasks. May include selective attention, divided attention, sustained attention and processing speed
Executive Function	Cognitive management of tasks. May include planning, decision-making, and working memory, feedback utilization, inhibition, and cognitive flexibility
Learning and Memory	Information retrieval. May include immediate memory, recent memory, episodic memory, semantic memory, autobiographical memory, and implicit memory
Language	Expressive and receptive communication, including naming, fluency, grammar, syntax, and comprehension
Perceptual-Motor Function	Visual-motor perception and construction, visuo-spatial skills
Social Cognition	Social-emotional recognition and theory of mind

Table 1. Sub-Domains of Cognitive Function for Diagnosis of Mild Cognitive Impairment and Dementia. These six sub-domains are specified by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM–5).

1.2.4. Mechanisms of Cognitive Decline in Age-Related Hearing Loss

The causal mechanisms linking age-related hearing loss to neurocognitive decline are unclear. It is possible that age-related hearing loss and dementia share a common etiology (a "common cause") that may lead to neurodegeneration (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994). However, even after controlling for presence of co-morbid health conditions and health-related risk factors (e.g. cardiovascular disease, diabetes, hypertension, smoking, high cholesterol, stroke), the association between age-related hearing loss and dementia remains significant (Deal et al., 2015, 2017; Gurgel et al., 2014; Lin et al., 2011b, 20011c, 2013, 2014; Tomioka et al., 2015).

Another hypothesis is that psychosocial factors associated with age-related hearing loss may precipitate neurodegeneration. There is some evidence to support this hypothesis. For example, age-related hearing loss is associated with increased depressive symptoms and decreased levels of social support (Dawes et al., 2015; Fratiglioni et al., 2000). However, even after controlling for depressive status in multiple studies (Amieva et al., 2015; Deal et al., 2015; Lin et al., 2013; Tomioka et al., 2015; Uhlmann et al., 1989; Wen et al., 2016), the independent association between age-related hearing loss and dementia remains significant, suggesting that hearing loss itself may contribute to neurocognitive degeneration. Other hypotheses have proposed that age-related hearing loss contributes to non-specific physical frailty, increasing risk to stressors (inflammation, vascular issues, and hormonal stressors) leading to neurodegeneration (Panza, 2015a, 2015b).

Another emerging theory linking age-related hearing loss to neurocognitive decline is the cognitive reserve theory (Lindenberger & Baltes, 1994; Schneider & Pichora-Fuller, 2000). Under this theory, it is hypothesized that peripheral-central impairment from age-related hearing loss depletes cognitive reserve, initiating long-term neurodegeneration (Lin

et al., 2011). Cognitive reserve refers to individual differences in cognitive processing, allowing some people to better cope or withstand greater resiliency to neuropathology compared to others (Stern, 2009). For example, in study by Savva and colleagues (2009), a proportion of patients with post-mortem physical indicators of dementia (e.g. neuritic plaques, neurofibrillary tangles, hippocampal atrophy) showed no detectable pre-mortem clinical signs of dementia on cognitive assessments before they died. This finding suggests that the expression of dementia may be (at least in part) determined by differences in cognitive reserve or compensation strategies.

1.2.5. Evidence of Neurocognitive Benefit from Treatment

It remains unclear whether audiological intervention with hearing aids or cochlear implants may modify the risk between age-related hearing loss and cognitive decline. Outcomes from epidemiological studies evaluating effects of hearing aid use on cognitive function are mixed. Some studies provide evidence that hearing aid use is associated with improved cognitive performance. For example, in a large cross-sectional sample of adults with age-related hearing loss (n=65, ages 60-69 years), Lin and colleagues (2011a) observed a significant positive association between hearing aid use and processing speed (Lin et al., 2011a), though only a small sample reported hearing aid use (n=13). In the cohort study by Maharani et al. (2018), significant positive effects of hearing aid use on episodic memory scores were reported in adults who used hearing aids compared to those who did not over the course of 18 years of hearing aid use (n=2040, M=62.8 years). Smaller studies by Acar et al. (2011) and Amieva et al. (2005) observed significant positive effects of hearing aid use on global cognitive functioning. In an investigation by Dawes et al. (2015), researchers found significant effects of hearing aid use on cognitive function (reaction time, pairs matching, and fluid intelligence) (n=164,770, age range 40-49 years).

Despite positive effects of hearing aid use reported in some studies, other studies found no effect of hearing aid use on cognitive abilities. For example, in a cross-sectional cohort study by Lin et al. (2011b) (n=347, age>55 years), there was no effect of hearing aid use across a battery of 10 cognitive tests evaluating global cognitive function, memory, executive function, and processing speed (Lin et al., 2011b). Similarly, in a prospective cohort study (n=1984, average age=77.4 years), Lin et al. (2013) observed no effect of hearing aid use on global cognitive function or processing speed over a 6-year follow up period (Lin et al., 2013). Insignificant effects of hearing aid use have also been reported in smaller longitudinal studies of short duration (Deal et al., 2015; Kalluri & Humes, 2012; Lin et al., 2013; Valentijn et al., 2005).

The lack of robust research evidence in this area likely exists for several reasons. First, important hearing aid factors were not accounted for in many of the aforementioned studies. For example, duration of hearing aid use, average daily hearing aid use, verification of the hearing aid fitting, and other relevant variables were not documented. Second, uncontrolled audibility factors were not accounted for in majority of these studies. Researchers did not describe whether or not hearing aids were utilized during cognitive testing. Finally, differences between hearing aid users and non-users (e.g. demographic factors) were not accounted for. All of these different factors could confound cognitive results and over or underestimate the effects of hearing aid use. Systematic review of the literature demonstrates a lack of experimental research evidence evaluating the impact of hearing aid use on cognitive outcomes.

Evidence from longitudinal studies in cochlear implant recipients sheds some light onto possible neurocognitive benefits of clinical intervention. For example, a recent study by Mosnier et al. (2015a) examined cognitive function before, 6 months, and 1 year after treatment in elderly cochlear implant recipients (n=94, age range 65-85 years). Several

cognitive domains were assessed using 6 different outcome measures assessing global cognitive function, memory, orientation, executive function, mental flexibility, and fluency. In this study, participants were provided with both verbal and written instructions on cognitive tests in efforts to ensure test instructions were clearly understood. Results from this study indicated that 81% of participants whose baseline cognitive test results were below average exhibited significant improvements in global cognitive function within 1 year after cochlear implantation. Further, improvements in cognitive function were evident as early as 6 months after cochlear implantation. In the remaining 19% of participants whose baseline cognitive function was normal, cognitive abilities remained stable over the year-long follow-up. In a smaller longitudinal study by Mosnier et al. (2018b), cognitive function was measured in an elderly cohort of cochlear implant recipients over the course of 7 years (n=70). While a relative high percentage of participants demonstrated signs of MCI at baseline evaluation (47%) (a significantly higher statistic than the 3-19% reported prevalence of MCI in the general population), only 6% of these participants developed dementia in the 7-year follow-up (as compared to 50% of the general MCI population who progress to dementia diagnosis in 5 years). While this study lacked a control group, good prognostic outcomes in participants at the 7-year follow-up suggest that audiological intervention may provide lasting neurocognitive benefit.

There is very limited experimental evidence evaluating the effects of hearing aid or cochlear implant use on neurocognitive function. However, the few studies that do exist show promising results. In a pilot study (n=40, age range 70-84 years) by Deal et al. (2017) which randomly assigned age-related hearing loss participants to a treatment (hearing aid treatment using gold-standard audiology treatment procedures) or control group (successful aging intervention program), researchers found significant improvements in cognitive function across memory, language, and processing speed sub-domains over the course of 6

months, with the greatest improvements in the treatment group observed in the sub-domain of delayed memory. In this study, researchers collected hearing aid fitting and verification data and logged hearing aid use. In a series of small, randomized controlled studies by Karawani et al. (2018a) (n=32, age range 52-82 years), researchers recently investigated cognitive outcomes in two groups of age-related hearing loss participants with normal-mild sloping to moderately-severe hearing loss who were randomly assigned to a hearing aid treatment or no treatment group. After 6 months of hearing aid use, significant improvements in working memory performance were observed. In this study, hearing aid verification and data logging information were also documented.

There exists a paucity of research examining neurocognitive benefit from hearing aid treatment from a neurophysiological perspective. In the randomized controlled study by Karawani et al. (2018a) reported above, researchers additionally measured cortical auditory evoked potential (CAEP) responses in the same hearing loss participants in response to a speech syllable /ga/ in quiet and in 6-talker babble noise (Karawani et al., 2018b). Critically, the hearing aid group exhibited a significant increase in N1 and P2 amplitude after 6 months of hearing aid use, suggestive of changes auditory attention (Näätänen & Winkler 1999; Suzuki & Amaral, 1994). However, researchers observed no association between N1 CAEP amplitudes post-treatment and working memory abilities, suggesting that changes in auditory cortical plasticity due to hearing aid use were not associated with cognitive outcomes. Overall, there exists a lack of robust research evidence as to whether audiological intervention with hearing aids may improve neurocognitive function.

In this thesis, we investigated the effects of untreated, age-related hearing loss on visual cortical neuroplasticity, as they relate to speech perception and cognitive outcomes (Study 1). Further, we evaluated the effect of clinical treatment with hearing aids on visual cortical cross-modal neuroplasticity and neurocognitive outcomes within the hearing loss

group (Study 2). To our knowledge, this is the first investigation of its kind to assess treatment effects with hearing aids on visual cortical cross-modal re-organization.

CHAPTER 2

STUDY 1: EFFECTS OF UNTREATED, AGE-RELATED HEARING LOSS ON

NEUROCOGNITIVE FUNCTION

2.1.   Specific Aims

Aim 1: To examine the effects of untreated, age-related hearing loss on visual cortical cross-modal neuroplasticity, by assessing group differences in visual cortical evoked potentials (CVEPs) between normal hearing adults and adults with untreated, age-related hearing loss.

Hypothesis 1: Consistent with previous studies, the hearing loss group will exhibit evidence of greater cross-modal re-organization of the auditory cortex by vision, as indexed by earlier CVEP latencies over a right temporal ROI and current density source reconstruction patterns indicative of cross-modal recruitment of the auditory cortex for the higher-level N1 and P2 CVEP components, as compared to the normal hearing group.

Aim 2: To evaluate group differences in speech perception outcomes between normal hearing adults and adults with untreated, age-related hearing loss.

Hypothesis 2: The hearing loss group will exhibit poorer auditory speech perception in noise performance and greater dependence on visual (lip-reading) cues for auditory-visual speech perception in noise, relative to normal hearing listeners.

Aim 3: To evaluate group differences in cognitive outcomes between normal hearing adults and adults with untreated, age-related hearing loss.

Hypothesis 3: The adults with hearing loss will exhibit poorer cognitive function across the domains of global cognitive function, executive function, processing speed, and working memory, relative to the normal hearing group.

Aim 4: To examine the association between neurophysiological outcomes and degree of hearing loss, speech perception, and cognitive outcomes in age-related hearing loss.

Hypothesis 4: CVEP latencies over the right temporal region of interest will be negatively associated with auditory speech perception in background noise, negatively associated with degree of hearing loss, positively associated with dependence on lip-reading cues, and negatively associated with cognitive function across the cognitive sub-domains of global cognitive function, executive function, processing speed, and working memory.

2.2. Study Design

A non-randomized, controlled experimental design was used to address the Specific Aims 1-3 for Study 1, allowing for comparison of CVEPs, speech perception, and cognitive function between the normal hearing and age-related hearing loss groups, as well as correlational analyses between the neurophysiological and behavioral and cognitive outcome variables.

Study participants were non-randomized into normal hearing and age-related hearing loss groups based absence or presence of clinically significant hearing loss determined through an audiological evaluation (see section 2.5.1. for more details). Baseline CVEP testing, auditory speech perception in noise, auditory-visual speech perception in noise, and cognitive function were assessed over the course of 1-2 test sessions within 2 weeks of the initial audiological assessment. For participants in the hearing loss group, CVEPs and auditory speech perception in noise were assessed in an unaided condition, while cognitive assessment and auditory-visual speech perception in noise were assessed in an acutely aided

condition (immediately following hearing aid fitting and verification). Acute aided testing was selected to negate potential confounding effects of audibility on cognitive outcomes.

2.3.   Human Subjects Assurances and Protection

This study was conducted in accordance with University of Colorado Institutional Review Board (IRB) guidelines. All participants provided written consent approved under protocol 18-0087.

2.4.   Participants

A total of 41 participants ranging between ages 57-74 years took part in this study (M=64 years, SD=4.68). All participants were native speakers of English, with no reported neurological impairment and reported normal or corrected-to-normal visual acuity. Of these participants, 13 participants comprised the normal hearing control group (M=62.62 years, SD=4.91) and 28 participants comprised the experimental group of untreated, age-related hearing loss (M=65.4 years, SD=4.23). Independent samples t-tests were conducted to confirm that groups did not significantly differ in terms of age (t(39)=1.621, p=0.980) or gender (t(39)=0.394, p=0.356). It should be noted that it is difficult to recruit subjects in this age-range with normal hearing given the high prevalence of hearing loss in older adults.

Because pure tone average (PTA) thresholds (0.5, 1, 2 kHz) (t(39)=-2.44, p=0.81) and high frequency pure tone average (HFPTA) thresholds (2, 4, 6 kHz) (t(39)=-1.516, p=0.137) between the right and left ears were not statistically different among study participants, averaged audiometric thresholds across the two ears were computed and used in subsequent analyses. Average PTA thresholds were approximately 16.5 dB HL poorer in the hearing loss group (M=27.08 dB HL, SD=10.41) compared to the normal hearing group (M=10.58 dB HL, SD=5.23) (t(39)=5.386, p<0.001). Average HFPTA thresholds were approximately 33.5 dB HL

poorer in the age-related hearing loss group (M=47.44 dB HL, SD=11.54) compared to the normal hearing group (M=13.91 dB HL, SD=3.77) (t(39)=10.17, p<0.001). Average pure tone air conduction thresholds for each group and corresponding 95% confidence intervals are depicted in Figure 1.

Demographic variables collected through a case history questionnaire indicated no difference between groups on a variety of known risk factors for hearing loss including smoking (t(39)=1.508, p=0.140), noise exposure (t(39)=1.643, p=0.109), or hypertension (t(39)=-0.116, p=0.908). None of the participants reported history of diabetes, another known risk factor for hearing loss. The two groups did not differ in terms of education level (t(39)=-0.975, p=0.335) or handedness (t(40)=1.030, p=0.309). None of the participants in the study reported clinical depression. As expected with the presence of hearing loss, report of tinnitus was significantly higher in the hearing loss group than the normal hearing group (t(39)=4.210, p<0.001), with 68% of hearing loss participants reporting tinnitus as compared to 15% of normal hearing participants. Interestingly, self-report of balance problems was also significantly higher in the hearing loss group (t(39)=2.030, p=0.049), with 25% of hearing loss participants reporting balance disturbances and/or falls in the past year as compared to 0% of normal hearing participants.
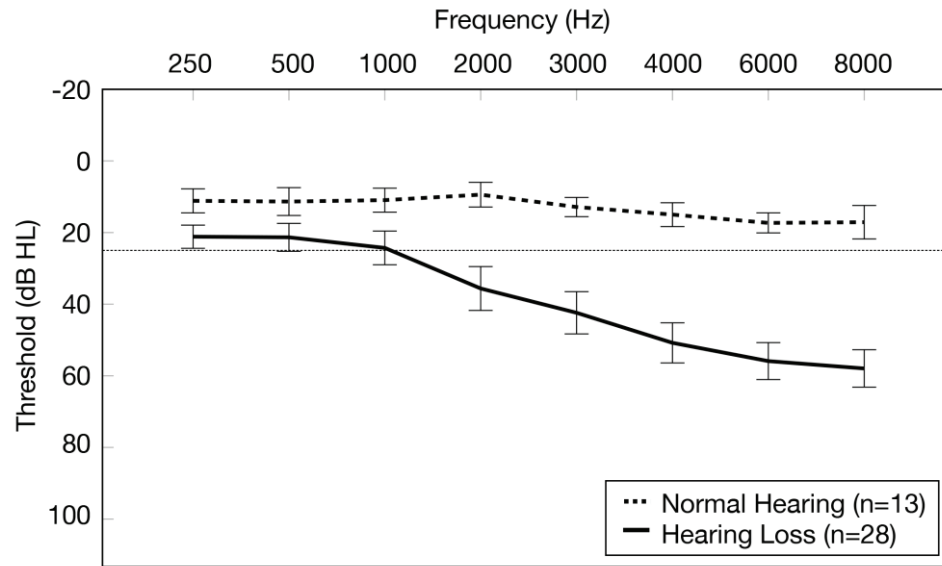
Figure 1. Average Pure Tone Air Conduction Thresholds for the Normal Hearing and Age-Related Hearing Loss Groups. Average pure tone air conduction thresholds across the two ears (0.25-8.0 kHz) are displayed for the normal hearing group (n=13) (dashed line) and the group with age-related hearing loss (n=28) (solid line). Frequency (Hz) is displayed on the horizontal axis and pure tone air conduction thresholds in decibels hearing level (dB HL) are displayed on the vertical axis. The dotted line on the y-axis indicates the clinical cutoff for normal hearing thresholds (25 dB HL). The bars display 95% confidence intervals at each threshold for each group.

2.5.   Methods

2.5.1. Case History & Audiological Assessment Additional Questionnaires

Study participants completed a case history form, allowing for assessment of candidacy inclusion criteria and the collection of relevant demographic data. For inclusion in the study, participants must have reported English as a native language, corrected-to-normal visual acuity, no neurological impairment, and no history of clinical depression on the case history questionnaire. Other relevant demographic variables including age, gender, handedness, tinnitus, education level, and presence of co-morbid health conditions and risk factors for hearing loss and cognitive decline (hypertension, diabetes, smoking, depression) were gathered.

Study participants then received a comprehensive audiological assessment to assess audiological candidacy inclusion criteria. The audiological assessment included otoscopy, ear-specific pure tone air and bone conduction thresholds (0.25-8 kHz), speech recognition thresholds, suprathreshold word recognition assessment, tympanometry (226 Hz probe tone), and acoustic reflex measurements (0.5, 1, 2, 4 kHz). These measures provided important audiological information regarding laterality/symmetry, type, degree, and configuration of hearing loss, allowing for assignment of study participants into normal hearing and hearing loss groups. Inclusion criteria for the normal hearing group was defined as pure tone thresholds for both ears ≤25 dB HL from 0.25-8.0 kHz, with no presence of an air-bone gap ≥15 dB HL at two or more adjacent frequencies, and no sign of interaural asymmetry ≥15 dB HL at two or more frequencies. Audiologic inclusion criteria for the hearing loss group was defined as HFPTA (2, 4, 6kHz) >25 dB HL for both ears, with no presence of an air-bone gap ≥15 dB HL at two or more adjacent frequencies, and no sign of interaural asymmetry ≥15 dB HL at two or more frequencies.

2.5.2. Cortical Visual Auditory Evoked Potential Testing

Participants were fit with a 128-channel, high-density EEG net (GSN-Hydrocel 128, Electrical Geodesics, Inc.) and seated in an electro-magnetically shielded sound booth. CVEPs were recorded in response to a visual motion stimulus (radially modulated grating or star-circle pattern), providing the percept of apparent motion. An example of the visual stimulus is depicted in Figure 2. The visual stimulus was adapted from Doucet et al. (2006) and used in several previous studies in our laboratory (Campbell & Sharma, 2014, 2016, Sharma et al., 2016; Glick & Sharma, 2017). 300 trials were presented (150 star, 150 circle stimulus presentations) at an inter-stimulus interval of 495 ms and pre-stimulus interval of 100 milliseconds. Participants were instructed to focus on the black dot in the center of the pattern without shifting their gaze. Stimuli were presented via E-Prime 2.0 stimulus presentation software and displayed on a flat screen LCD television at a viewing distance of approximately 42 inches. CVEPs were recorded using NetStation 5 software (Electrical Geodesics, Inc.) at a sampling rate of 1000 Hz with a band-pass filter set at 0.1-200 Hz.
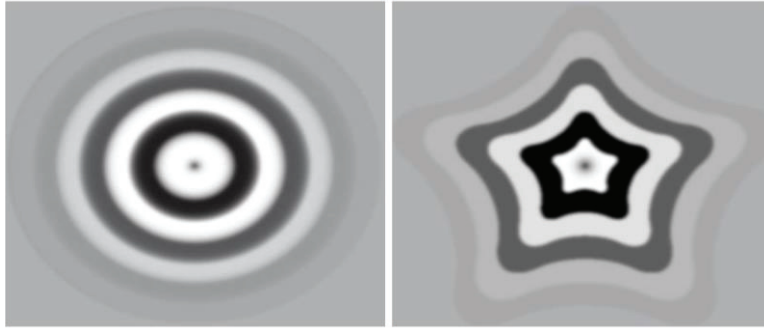
Figure 2. Central Visual Motion Stimulus. Visual motion stimulus (radially modulated grating) used to elicit the cortical auditory evoked potential (CVEP) response. The star-circle pattern provides the percept of apparent visual motion.

2.5.3. Hearing Aid Fitting

Hearing loss participants were acutely fit with bilateral receiver-in-the-ear Oticon OPN 1 mini receiver-in-the-ear (miniRITE) hearing aids prior to auditory-visual speech perception in noise testing and cognitive testing to negate potential confounding effects of audibility on test performance for the speech perception and cognitive tests.

The receiver size most appropriate for the degree of hearing loss (60-power receiver for thresholds <60 dB HL 0.25-8 kHz; 85-power receiver: thresholds ≥60 dB HL 0.25-8 kHz) was selected for each hearing loss participant. In addition, proper non-custom acoustic coupling (open dome, double vent (1.44mm) dome, single vent (0.88mm) dome, or double (closed vent) dome) was selected for each hearing loss participant. Hearing aids were then initially programmed with patients' audiometric thresholds using the Oticon Genie 2™ fitting software. Advanced signal processing features were set using the Oticon OpenSound Navigator™ in the Genie 2™ fitting software. Efforts to minimize advanced signal processing features were selected to promote generalizability of study findings across hearing aid manufacturers. Settings for noise reduction (0 dB simple environments, -7 dB complex environments, open sound transition set to medium), microphone mode (open automatic), transient noise management (off), and binaural broadband controls (on) were set to manufacturer defaults (LeGoff et al., 2016). Feedback reduction algorithms were not applied, since algorithms can affect ideal frequency-gain characteristics and vary between manufacturers. Instead, modifications to the acoustic coupling were made (e.g. selecting a more occlusive dome) if significant feedback was present.

After initial fitting of the hearing aids, probe-microphone measures were performed to verify the hearing aid fitting for each participant. These measures were taken using the Audioscan™ probe-microphone verification system in response to soft (55 dB SPL), medium

(65 dB SPL) and loud (75 dB SPL) speech inputs, where hearing aid gain was adjusted to match to NAL-NL2 prescriptive fitting targets from 0.25-4.0 kHz. NAL-NL2 is a commonly used prescriptive fitting formula used for fitting adults with age-related hearing loss, with the goal of making speech intelligible and ensuring comfort of overall loudness (Keidser et al., 2011). Maximum Power Output (MPO), or the maximum dB SPL that that the hearing aid can deliver in response to a steady narrow band input, was also measured to avoid loudness discomfort and to approximate uncomfortable loudness levels (UCL) for each ear. Based on verification testing, probe microphone measurements were all ±5 dB of NAL-NL2 targets (0.25-4.0 kHz), indicating adequate audibility. The average difference between actual and prescriptive gain for the 65 dB SPL input was +1.76 dB in the right ear (sd=2.58) and +0.96 dB in the left ear (sd=3.16) from 0.25-4.0 kHz.

2.5.4. Speech Perception Testing

Baseline auditory-only speech perception in noise was assessed in an unaided condition for all study participants using the QuickSIN™. The QuickSIN™ is a standardized assessment of sentence-level auditory speech perception in background noise and is routinely used in the clinical audiology setting (Etymotic Research, 2001; Killion et al., 2004). 2 randomly selected recorded lists of 6 sentences (5 key words per sentence) spoken by a target speaker were presented in the context of 4-talker babble noise. Stimuli were presented in a binaural condition via a speaker located at 0° azimuth at a level of 60 dB SPL (conversational speech level). The sentences in each list vary in signal-to-noise ratio (SNR), beginning at 25 dB SNR (easiest) for the first sentence and decreasing in 5 dB steps with each subsequent sentence (most difficult). Participants were instructed to repeat what the heard the target talker say. The test is scored in terms of the dB SNR loss, or the dB SNR required for the participant to score 50% of the words correct (threshold), relative to normal hearing adult

listeners. Reliability of the QuickSIN™ is accurate to 1.9 dB SNR (95% confidence interval) when averaging performance across 2 lists (Bentler, 2000).

Auditory-visual speech perception in background noise was assessed using the Arizona Auditory-Visual Test (AzAv) (Dorman et al., 2016). The AzAv test is a multi-modal speech perception in noise assessment adapted from sentence materials in Macleod & Summerfield (1987, 1990) and developed using methodology of Spahr et al. (2012) in creation of the AzBio, a routinely used auditory-only clinical assessment of speech perception in background noise. The AzAv Test has been validated in normal hearing and cochlear implant listeners in a series of previous studies reported in Dorman et al. (2016). The test was administered in an unaided condition for the normal hearing group and in an acutely aided condition for the hearing loss group to negate potential confounding effects of audibility on test performance. The test contains 10 lists, with each list comprised of 15 sentences (3 key words per sentence). Sentences spoken by a target talker are presented in the context of multi-talker babble. The test was administered in a binaural condition via a speaker located 0° azimuth, with target sentences presented at a level of 60 dB SPL (conversational speech level). Visual (lip-reading) stimuli were presented on an LCD television at a viewing distance of approximately 42 inches. Several practice lists were first administered in an auditory-only condition, varying the SNR in 2 dB increments (starting at the SNR determined by the QuickSIN™ test) to determine the level at which the participant repeats approximately 40-50% of words correct (to prevent ceiling effects). Next, 2 randomly selected lists were presented in an auditory-only condition and 2 randomly selected lists are presented in an auditory-visual condition. Performance on the AzAv test is scored in terms of visual (lip-reading) benefit, by subtracting average performance (in percent key words correct) in the auditory-only condition from the auditory-visual condition, providing a percent benefit score from the addition of visual (lip-reading) cues.

2.5.5. Cognitive Testing

Cognitive assessments probing several sub-domains were administered to all study participants. Cognitive tests were administered in an unaided condition for the normal hearing group and in an acutely aided condition for the hearing loss group to negate potential confounding effects of audibility on test performance. Tests were also administered in a quiet room to prevent negative effects of noise (Dupuis et al., 2015). The cognitive measures utilized in this study were selected based on previous investigations where impairments in specific cognitive sub-domains were observed (Lin et al., 2011a, Lin et al., 2011b; Lin et al., 2013; Loughrey et al., 2018), as well as theoretical predictions regarding which cognitive sub-domains may be most affected by hearing loss. A neuropsychologist was consulted in the formulation of this test battery and he provided comprehensive training to the test administrator in delivery of all cognitive tests. A list of cognitive measures assessed and the corresponding sub-domains of each measure are described in Table 2.

Sub-Domain	Assessment
Global Cognitive Function	Montreal Cognitive Assessment (MoCA)
Executive Function	Behavioral Dyscontrol Scale (BDS)
Processing Speed	Symbol Digit Modalities Test (SDMT)
Working Memory	Reading Span Test (RST) (Visual Working Memory)
	Word Auditory Recognition and Recall Measure (WARRM) (Auditory Working Memory)

Table 2. Cognitive Test Battery. The table describes the cognitive tests administered in this study and the associated cognitive sub-domain being evaluated.

Global cognitive status was assessed using the Montreal Cognitive Assessment (MoCA), a cognitive screening measure that was developed for detecting MCI. The MoCA assesses cognitive function sub-domains: Attention and concentration, executive function, memory, language, visuospatial skills, conceptual thinking, calculations, and orientation (Nasreddine et al., 2005). Performance on the MoCA is scored out of a possible 30 points. The MoCA has been shown to have high sensitivity to MCI compared with other global cognitive screening measures such as the Mini-Mental State Examination (MMSE) (Nasreddine et al., 2005). Test-retest reliability (r=0.96) has been established when tested 2 weeks apart (Wong et al., 2009), with slightly lower test-retest reliability (r=0.75-0.92) over a range of 4-8 weeks or longer (Lee et al., 2008). While a score below ≤26 is recommended as the original cutoff score for MCI, recent meta-analyses indicate that a cutoff score ≤23 yields may yield better diagnostic accuracy (better sensitivity and specificity) (Carson et al., 2018).

Executive function was measured using the Behavioral Dyscontrol Scale (BDS-2). The BDS-2 is a 9-item multidimensional test (Grigsby & Kaye, 1996) that is strongly predictive of executive function abilities (Suchy et al., 1997) and functional independence (Grigsby et al., 2002a, 2002b). More recent investigations indicate that the BDS-2 is useful for differentiating neurocognitive impairment (MCI and dementia, including Alzheimer's disease) from healthy aging (Belanger et al., 2005). Each test item asks participants to perform a dynamic behavioral control or regulation task, such as executing alternating hand sequences (e.g. tap twice with right hand, once with left hand), inhibition tasks (e.g. tap right when tester says "red", do nothing when tester says "green"), complex motor sequences (e.g. fist-edge-palm), alphanumeric sequencing, and awareness of deficit or insight ratings by the tester. Each item is scored on a 3 points scale (0-2) out of a total score of 27 points. High reliability (r=0.8) and validity (r=0.5-0.8) is reported for this test (Suchy et al., 2005). Test-retest reliability is also high (r=0.8) at 8 week and 6-month follow-up intervals (Grigsby et

al., 1992; Grigsby, Kaye, & Robbins, 1992). Normative data for young adults, cognitively normal elderly, and average elderly have been previously reported (Grigsby et al., 1992), where a score >19 falls within the 90th percentile for young cognitively normal adults.

Processing speed was assessed using the Symbol Digit Modalities Test (SDMT) (Smith, 1982). In this test, participants are presented with a key at the top of the page, depicting 9 different symbols, each symbol paired with single digits (1-9). Below the key are empty rows containing only symbols. Participants are instructed to fill in the number (1-9) that corresponds each symbol as fast and accurately as possible in an allotted 90 seconds. Test-retest reliability of the SDMT is high (r=0.7-0.9) when administered over the course of 2 weeks, 1 month, or 2-year intervals (Benedict et al., 2017). Construct validity is also high for this test (Benedict et al., 2017). The SDMT is reportedly sensitive to the detection of MCI and cognitive impairment (Pascoe et al., 2018). Further, impairments in processing speed using the CES-D measure were apparent 13.0-17.9 years before the onset and clinical diagnosis of dementia in a study of older adults (Rajan et al., 2015).

Visual working memory was measured using the Reading Span Test (RST). The RST is designed to measure individual working memory capacity (Daneman & Carpenter, 1980; Rönnberg et al., 1989). The RST consists of a training set of 3 sentences and a test set of 54 sentences presented in recall set sizes of 3, 4, 5, or 6 sentences. Words in each sentence are presented one at a time, at a rate of 0.8 seconds on an LCD television screen in serial order. Half of the sentences do not make sense (e.g. "The train sang a song.") and half of the sentences do make sense (e.g. "The captain saw his boat."). During a 1.75 second interval after each sentence, participants are asked to respond "yes" or "no" based on whether or not the sentence makes sense. At the end of each set, participants are instructed to recall the first or last word of each sentence in correct serial order (first or last order is randomized). The RST is scored in terms of the percent of words correctly recalled (alternative scoring

formats, such as an average span score are also possible). High reliability and validity of the RST have been reported (r=0.7-0.8) (Kane et al., 2004), as well as high test-retest reliability over minutes (Turley-Ames & Whitfield, 2003), weeks (Friedman & Miyake, 2004; Klein & Fiss, 1999), and months (Klein & Fiss, 1999).

Auditory working memory was assessed using the Word Auditory Recognition and Recall Measure (WARRM) (Smith et al., 2016). The WARRM test consists of 100 monosyllabic words presented in recall set sizes of 2, 3, 4, 5, or 6 items, with 5 trials in each set size. Half of the words begin with a letter falling in the first half of the alphabet (A-M) and half of the words begin with a letter falling in the second half of the alphabet (N-Z). Participants are instructed to repeat the target word, and to recall whether the first letter of each target word belonged to the first half of the alphabet or the second half of the alphabet (N-Z). Each word in the set is preceded by the carrier phrase, "You will cite." Between each set of words, participants hear a 500 Hz, 500 ms tone, serving as the prompt to recall. A training set of 2 recall set sizes of 2 items is administered before beginning the test. Stimuli were presented in quiet via a speaker located at 0° azimuth at a level of 60 dB HL (conversational speech level). The WARRM test is scored in terms of percent correct, based on the number of words the participant repeats correctly out of the 54 total words on the test (alternative scoring formats, such as an average span score are also possible). Current testing is underway to evaluate the reliability and test-retest reliability of the WARRM test, but preliminary data show high intra-session and inter-session and test-retest reliability (r>0.8). Some practice effects have been observed in preliminary testing of the WARRM, so effort was taken to ensure that participants understood the test procedures, and re-instruction and re-administration of the practice set of sentences was provided for participants if necessary. The rationale for including both the RST and WARRM measures in the cognitive assessment battery was to evaluate working memory capacity under both domain-general conditions (e.g.

in the visual modality presumably "uncontaminated" by the effects of hearing loss with the RST) and domain-specific conditions (e.g. in the affected auditory modality under ecologically-relevant conditions with the WARRM) (Smith et al., 2016).

2.6.   Analysis

2.6.1. Cortical Visual Evoked Potential Analysis

Following CVEP testing, data were pre-processed offline by applying a high-pass filter (1 Hz). Continuous data were then segmented around each stimulus presentation (595 millisecond recording window). Data were then exported from NetStation 5 to MATLAB™ (The MathWorks®, Inc.) via EEGLab (Delorme & Maekig, 2004), where baseline correction (to the 100 millisecond pre-stimulus recording window), bad channel rejection (±100 μV), bad epoch rejection, re-referencing (to the common average reference), and down sampling (from 1 kHz to 0.25 kHz, to reduce processing time) were performed. Average CVEP responses for each participant were then computed by averaging CVEP responses across several electrodes corresponding to cortical regions of interest (ROIs) on the scalp: Occipital, right temporal, and left temporal ROIs. Figure 3 shows a schematic of the pre-selected regions of interest and electrode numbers corresponding to the 128-channel GSN Hydrocel Net used in this study (Electrical Geodesics®, Inc.). After computing average CVEP responses for each participant across each region of interest, peak latencies and amplitudes were extracted.
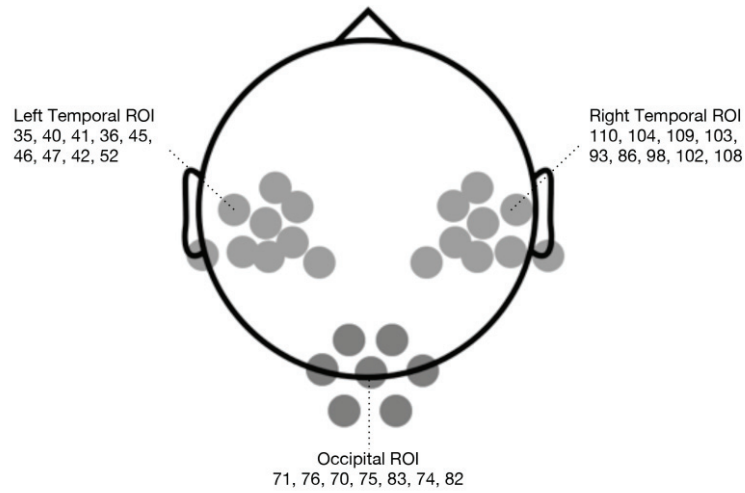
Figure 3. Cortical Regions of Interest and Corresponding Electrode Numbers. Schematic visualization of the 3 regions of interest (occipital, right temporal, and left temporal) are displayed. Electrode numbers correspond to the 128-channel GSN Hydrocel Net (Electrical Geodesics, Inc.) used in this study.

After CVEP pre-processing steps, an independent components analysis (ICA) was applied to identify spatially fixed and temporally independent components underlying each component (P1, N1, P2) in the CVEP response for each participant according to the timeframe in which the component occurred (Delorme et al., 2012; Makeig et al., 1997). ICA components accounting for the greatest percent variance for each of the CVEP component were kept, while remaining ICA components were regarded as artifact/noise and discarded.

ICA-pruned CVEP data for each participant were then exported from Matlab™ into Curry7™ Neuroimaging Suite (Compumedics Neuroscan™), where cortical source modeling occurred. Here, grand average ICA-pruned CVEP waveforms for the normal hearing and hearing loss groups were computed and current density source reconstruction (CDR) was performed to visualize differences in cortical activation patterns between the two groups. To achieve this, a second ICA was performed on the grand averaged data for each group to identify components with the highest SNR. A head model was then created and standardized using the boundary element method (BEM) (Fuchs et al., 2002). Next, CDRs were computed via standardized low-resolution electromagnetic tomography (sLORETA). sLORETA is a statistical method that estimates current densities with low localization error (Grech et al., 2008; Pascaul-Marqui, 2002). The resultants CDRs for each group were projected onto an average adult structural MRI (provided by the Montreal Neurological Institute). CDRs are depicted by a graded color scale (F-statistic) indicating the statistical likelihood of cortical activity in each region. This described protocol has been used in our laboratory to observe changes in visual cross-modal plasticity in adults and children with hearing loss at the single-subject and group level (Campbell & Sharma, 2014, 2016; Glick & Sharma, 2017; Sharma et al., 2016; Sharma, Campbell, & Cardon, 2015).

2.6.2. Statistical Analyses

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 25. Histograms, Q-Q plots, and significance tests (Shapiro Wilk test, Levene test) were first computed to assess potential violation in assumptions of normality and homogeneity of variance for all variables. Visual inspection and outlier analyses were also performed.

A series of two-tailed independent sample t-tests were used to assess differences in the cortical, speech perception, and cognitive outcome variables between groups. Because comparisons of CVEP latencies were made across 3 ROIs, a Bonferroni correction was applied to reduce chance of Type I error, reducing the alpha level from $\alpha=0.05$ to $\alpha=0.017$. The same correction was applied for assessing differences in CVEP (P1, N1, P2) amplitudes across the 3 ROIs between groups.

To assess the association between CVEP latencies over the right temporal ROI and degree of hearing loss, speech perception, and cognitive outcomes within the group of adults with untreated, age-related hearing loss, Pearson's correlation coefficients were computed in the hearing loss group. Pearson's correlations provide information about the association (strength) of the relationship between two variables, where a correlation coefficient (r) of 0 indicates no linear relationship between two continuous variables, and a correlation coefficient of -1 or +1 indicates a strong negative or positive linear relationship, respectively. Because comparisons were made between the 3 different CVEP components and cognitive outcomes, a Bonferroni correction was applied to reduce chance of Type I error, reducing the alpha level from $\alpha=0.05$ to $\alpha=0.017$.

2.7.   Results and Discussion

2.7.1.   Cortical Visual Evoked Potential Latencies and Amplitudes

Plots of the grand average CVEP waveforms for the normal hearing and hearing loss groups across the occipital, right temporal, and left temporal ROIs are depicted in Figure 4. CVEP responses in each group are marked by the presence of all 3 obligatory CVEP components (P1, N1, P2) elicited by the visual motion stimulus. Morphological patterns are similar to the findings reported in Campbell & Sharma (2014) using the same stimulus in a smaller group of adults with normal hearing and mild-moderate sensorineural hearing loss.

Independent samples t-tests indicated no significant differences in P1, N1, or P2 peak latencies or amplitudes over the occipital or left temporal region of interest. However, significant differences in CVEP P1, N1 and P2 latencies were observed in the right temporal ROI ($\alpha<0.0055$ level). As can be seen in Figure 4 and corresponding Table 3, the hearing loss group exhibited significantly earlier P1 (t(39)=-4.65, p<0.001), N1 (t(39)=-5.36, p<0.001), and P2 CVEP latencies (t(39)=-3.42, p=0.001) in the right temporal ROI, relative to the normal hearing group.

Results are consistent with the Hypothesis 1 outlined in Specific Aim 1 (Section 2.1). Earlier CVEP latencies have been reported in deafness and adult-onset hearing loss in previous studies (Buckley & Tobey, 2011; Campbell & Sharma, 2014; Doucet et al., 2006; Fine et al., 2005; Finney et al., 2003; Hauthal et al., 2013; Neville & Lawson, 1987; Sandman et al., 2012). Earlier CVEP latencies are considered an index of visual cross-modal re-organization, reflecting increased synaptic strength and connectivity (Driver & Spence, 2004). Our observations of visual cross-modal re-organization in the right temporal ROI are also consistent with findings from Cardon & Sharma (2018) where researchers

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somatosensory cross-modal plasticity in right temporal areas in adults with age-related hearing loss.
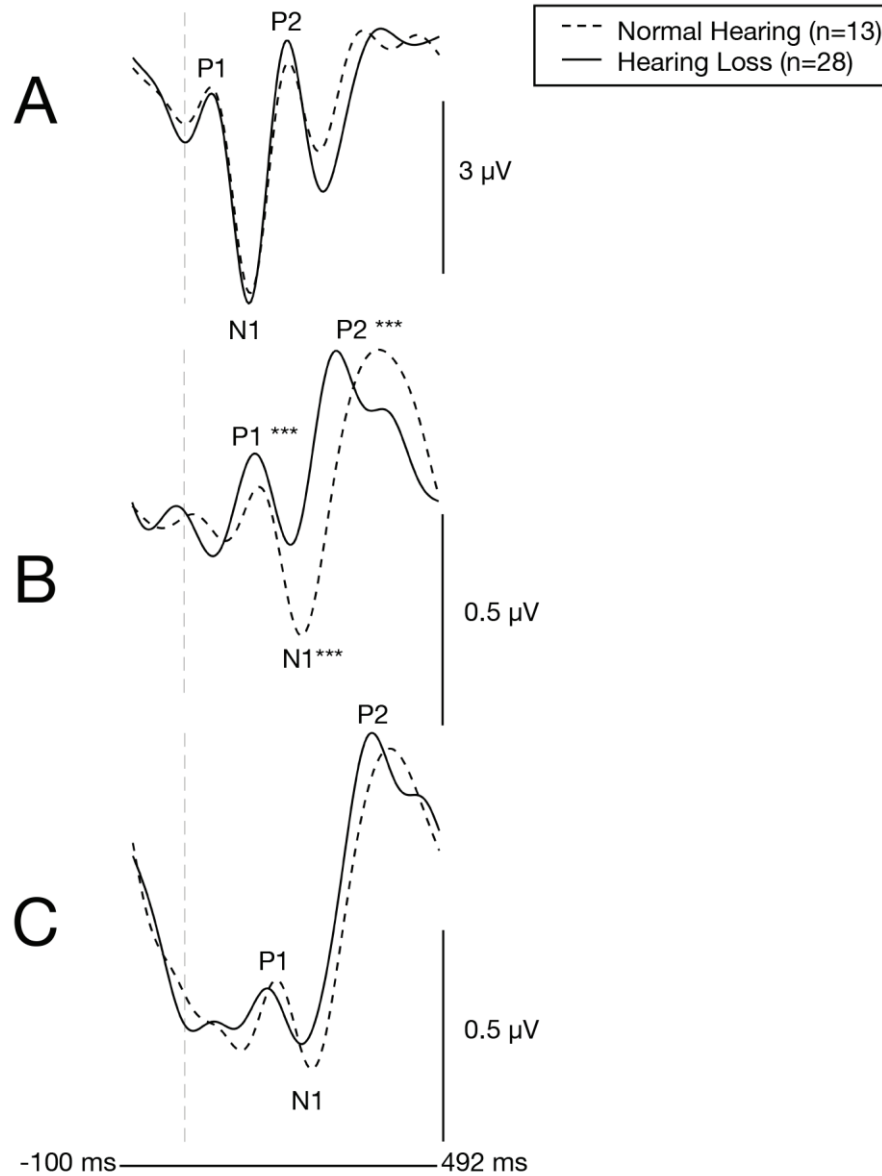
Figure 4. Baseline Group Differences in Cortical Visual Evoked Potentials Across an Occipital, Right Temporal, and Left Temporal Region of Interest. Grand-averaged CVEP waveforms for the normal hearing group (n=13) and the age-matched group of adults with early-stage, age-related hearing loss (n=28) are depicted for the occipital (**Panel A**), right temporal (**Panel B**), and left temporal (**Panel C**) regions of interest. Time (milliseconds) is displayed on the horizontal axis and amplitude (μV) is displayed on the vertical axis. Asterisks indicate level of significance (***p≤0.001) for differences in CVEP latencies between the two groups. The hearing loss group exhibited significantly earlier CVEP P1, N1, and P2 latencies over the right temporal region compared to the normal hearing group.

Component	Average Latency		Peak Standard Deviation		95% Interval	Confidence	Statistic t(39) (p-value)
	HL	**NH**	**HL**	**NH**	**HL**	**NH**	
P1	99 ms	128 ms	19.10	15.62	92-106	118-137	-4.65 (<0.001)
N1	134 ms	175 ms	24.42	20.38	124-143	163-187	-5.36 (<0.001)
P2	203 ms	242 ms	38.42	24.62	188 218	228-258	-3.42 (0.001)

Table 3. Baseline Cortical Visual Evoked Potential Latencies Over a Right Temporal Region of Interest. Average peak latencies, standard deviations, 95% confidence intervals, and statistical significance values are provided for the age-related hearing loss (HL) (n=28) group and the normal hearing (NH) group (n=13) in a right temporal region of interest. Significantly earlier P1, N1, and P2 latencies are observed in the HL group.

2.7.2. Cortical Visual Evoked Potential Source Reconstruction

CDRs for each CVEP component (P1, N1, and P2) are shown in Figure 5. 3D CDRs are displayed on a Maximum Intensity Projection (MIP) (a 2D depth-buffered MRI), providing visualization of the voxels with the highest likelihood of activation. The gradient color scale to the right of each figure indicates the statistical likelihood of activation (F-statistic), from lowest (red) to highest (yellow) probable current density computed via sLORETA. Table 4 lists the cortical regions of activity for each component in the CVEP response in order of highest to lowest likelihood of activation.

The visual motion stimulus elicited activity in bilateral occipital and cerebellar cortical regions for all CVEP components in the normal hearing group (Figure 5, Table 4). These areas activation are in consistent with results reported in previous visual motion studies in typical adult samples (Dupont et al., 2003; Kellerman et al., 2012). In the hearing loss group, the visual motion stimulus elicited similar activation patterns in the occipital and cerebellar cortex for the P1 CVEP component (Figure 5, Table 4). However, for the later N1 and P2 CVEP components, the hearing loss group exhibited distinct differences from the normal hearing group. Consistent with the Hypothesis 1 outlined in Specific Aim 1 (Section 2.1), the hearing loss group showed additional activity over regions of auditory cortex (e.g. superior, middle, and inferior temporal gyrus) for the later N1 and P2 CVEP components (Figure 5, Table 4). This finding replicates results from a previous study in a smaller group of adults with mild-moderate sensorineural hearing loss (Campbell & Sharma, 2014). Further, this finding is congruent with animal investigations (Kral et al., 2017) and human investigations (Doucet et al., 2006; Sandmann et al., 2012) where deafness is associated with recruitment of auditory cortex for visual processing, indicative of visual cross-modal re-organization.

While the mechanisms underlying cross-modal re-organization are poorly understood, it is possible that auditory deprivation may upset typical balance in excitation and inhibition in the auditory cortex, where the downregulation of inhibition makes auditory cortex more sensitive to latent or 'silent' multi-modal or non-auditory inputs (e.g. visual and somatosensory inputs), resulting in cross-modal recruitment of auditory cortex for visual processing (Mao & Pallas, 2013).

We observed an additional unexpected finding via cortical source localization analyses in the hearing loss group. In addition to evidence of cross-modal recruitment of auditory cortex in the hearing loss group, we also observed activation of pre-frontal and frontal cortex for the N1 and P2 CVEP components (Figure 5, Table 4). Regions of activity included orbital gyrus, inferior frontal gyrus, and middle frontal gyrus, predominately in the left hemisphere.

The mechanisms underlying alterations in frontal and pre-frontal cortical resource allocation for visual processing in age-related hearing loss have not been studied. Frontal cortex recruitment (including recruitment of orbitofrontal gyrus and Broadmann area 11) for visual processing has been reported in healthy elderly adults presumably reflecting age-related changes in visual attention or other forms of cognitive compensation (Kaufman et al, 2016). Further, recruitment of a broader network of cortical areas (including frontal and pre-frontal cortex) during perceptual, attentional, and cognitive tasks in healthy older adults suggests that normal aging may be associated with inhibitory control or attentional deficits (Gazzaley et al., 2005; Hasher & Zachs, 1988).

Similarly, recruitment of frontal cortex (e.g. middle and inferior frontal gyrus) was recently reported in deafness during a visual processing task (Bola et al., 2017). Recruitment of frontal and pre-frontal cortex is also apparent in age-related hearing loss during auditory tasks, especially in difficult tasks such as background noise (Obleser et al., 2007, 2009; Wong et al., 2009). It is possible that recruitment of additional attentional and cognitive networks

in hearing loss may reflect top-down cognitive compensation strategies to facilitate sensory processing (Li et al., 2013; Paneri & Gregoriou, 2017; Reuter-Lorenz & Cappell, 2008). While the aim of the current study was focused on assessing cross-modal re-organization in the auditory cortex, evidence of frontal and pre-frontal cortical recruitment for visual processing in hearing loss warrants further investigation. Based on our neurophysiological findings, however, hearing loss appears to alter normal cortical network dynamics between the visual and auditory systems, as well as attentional and cognitive networks, in order to facilitate sensory processing.
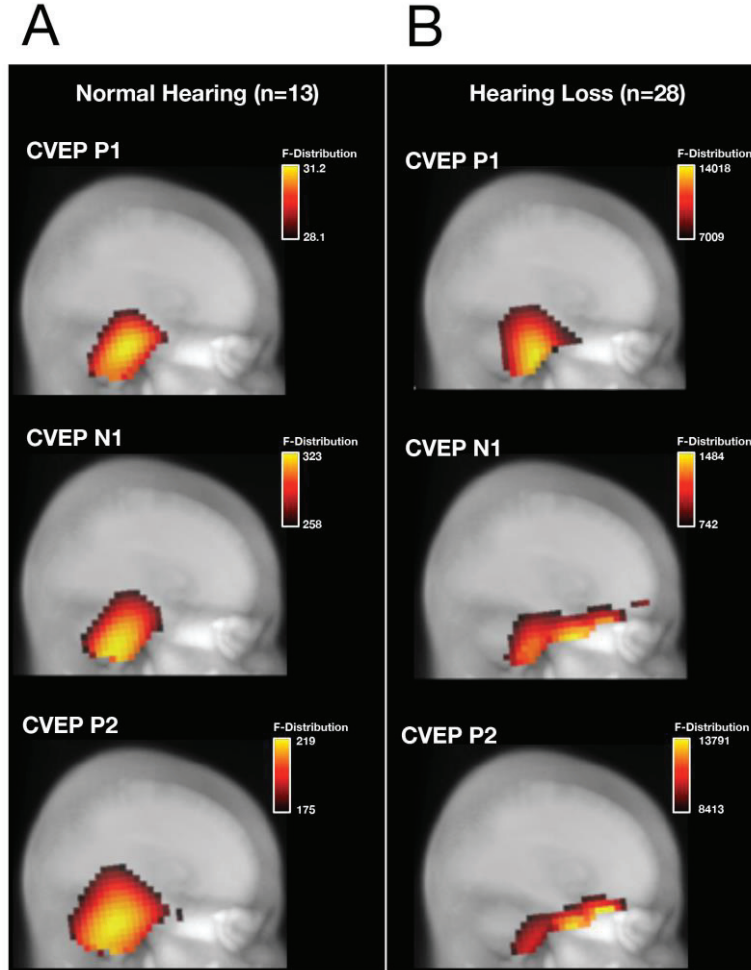
Figure 5. Baseline Group Differences in Cortical Source Activation Patterns Elicited by Visual Motion Stimuli. Current density source reconstructions (CDR) for the P1, N1, and P2 cortical visual evoked potential components are depicted for the normal hearing group (n=13) and the group of adults with untreated age-related hearing loss (n=28). 3D current density source reconstructions obtained via standardized low-resolution brain electromagnetic tomography (sLORETA) are projected on a 2D depth-buffered structural magnetic resonance image (Maximum Intensity Projection), providing visualization of the voxels with the highest likelihood of activation. The color scale to the right of each figure indicates the statistical likelihood of activation (F-statistic), from lowest (red) to highest (yellow) probable current density.

Component	Normal Hearing (n=13)		Hearing Loss (n=28)	
	Right Hemisphere	**Left Hemisphere**	**Right Hemisphere**	**Left Hemisphere**
P1	Cerebellar tonsil, culmen, cerebellar lingual	Cerebellar tonsil, culmen, cerebellar lingual	Cerebellar tonsil, culmen, fusiform gyrus, BA 20, middle temporal gyrus, uncus, BA 36, cerebellar lingual	Cerebellar tonsil
N1	Cerebellar tonsil, culmen, cerebellar lingual	Cerebellar tonsil, culmen, cerebellar lingual	Cerebellar tonsil, inferior temporal gyrus, BA 20, middle temporal gyrus, BA 21, superior temporal gyrus, BA 38, uncus, BA 28, fusiform gyrus, culmen	Inferior temporal gyrus, BA 20, middle temporal gyrus BA 21, superior temporal gyrus, BA 38, inferior frontal gyrus, orbitofrontal gyrus BA 11, cerebellar tonsil, middle frontal gyrus, BA 25, BA 47, fusiform gyrus, BA 20, uncus, BA 28, culmen
P2	Cerebellar tonsil, inferior semi lunar lobule, uvula, pyramis, culmen, dentate, cerebellar lingual	Cerebellar tonsil, uvula, culmen, uncus, dentate cerebellar lingual	Cerebellar tonsil, middle temporal gyrus, BA 21, inferior temporal gyrus, BA 20, superior temporal gyrus, BA 38, middle frontal gyrus, orbitofrontal gyrus, BA 11, inferior frontal gyrus, BA 47	Middle temporal gyrus, BA 21, orbital gyrus, cerebellar tonsil, superior temporal gyrus, BA 28, inferior temporal gyrus, BA 20, inferior frontal gyrus, orbitofrontal gyrus, BA 11, middle frontal gyrus, BA 47, uncus

Table 4. Baseline Group Differences in Cortical Regions of Activation Elicited by Visual Motion Stimuli. Regions of cortical source activity, including Broadmann areas (BA), are provided for normal hearing group (n=13) and the group of adults with untreated, age-related hearing loss (HL) (n=28). Regions of activity are ranked in order of highest to lowest likelihood of activation (F-statistic) obtained via current density source reconstruction (CDR).

2.7.3. Group Differences in Speech Perception

As expected, significant differences in binaural suprathreshold auditory speech perception in noise were observed between the normal hearing and hearing loss groups. The QuickSIN™ test yields a dB SNR loss score, indicating the dB SNR required for an individual to understand 50% of keywords in sentences in background noise, compared to normal hearing adult listeners. A lower dB SNR loss score on the QuickSIN™ indicates better suprathreshold auditory speech perception in noise outcomes, while a higher dB SNR loss score indicates poorer suprathreshold auditory speech perception in noise outcomes. Average auditory speech perception scores with corresponding 95% confidence intervals are depicted in Figure 6A. Average QuickSIN™ scores for the hearing loss group (M=5.89 dB SNR loss, SD=4.55) indicate a mild dB SNR loss (3-7 dB SNR), while average scores for the normal hearing group (M=0.92 dB SNR loss, SD=2.31) indicate normal functioning in background noise (0-3 dB SNR) (Killion et al., 2004). QuickSIN™ scores were significantly poorer in the hearing loss group compared to the normal hearing group (t(39)=3.703, p=0.001). Average speech perception in noise scores on this test in the hearing loss group are comparable to results in adults with similar degree of sensorineural hearing loss reported in previous studies (Killion et al., 2004; Wilson et al., 2007).

Average visual (lip-reading) benefit scores on the auditory-visual speech perception in noise test (AzAv) are shown in Figure 6B. Contrary to Hypothesis 2 outlined in Specific Aim 2 (Section 2.1), group differences in benefit from visual (lip-reading) was not statistically different (t(39)=0.517, p=0.608). Average benefit from visual cues across both groups was approximately 37.21% (SD=10.24). This finding is comparable with previously reported visual benefit using the same AzAv test materials in cochlear implant recipients, where average benefit from visual cues was 32-44% (Dorman et al., 2016), and investigations in

older adult listeners (Cienkowski & Carney, 2002; Sommers et al., 2005) using similar experimental designs but different test materials. The relative benefit from visual (lip-reading) cues described in our study is also comparable to benefit described in younger adult populations under acoustically degraded listening situations (Grant and Seitz, 2000; Ross et al., 2007; Schwartz et al., 2004; Sumby and Pollack, 1954). Based on our data, results indicate that adults with early-stage (mild-moderate) untreated hearing loss do not derive greater relative benefit from visual (lip-reading) cues compared to age-matched normal hearing control participants.
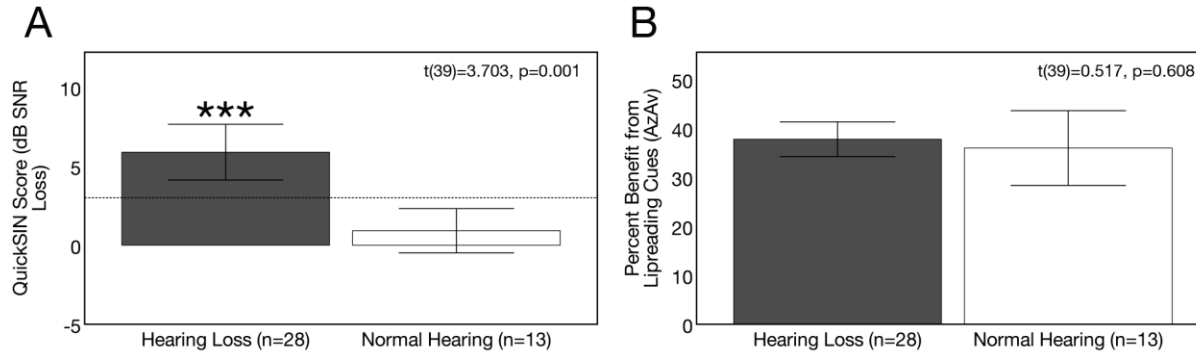
Figure 6. Baseline Group Differences in Speech Perception in Noise. Average scores on speech perception measures in the age-related hearing loss group (n=28) are depicted in gray and average scores for the normal hearing group (n=13) are depicted in white. Black bars indicate 95% confidence intervals for each group. Asterisks indicate level of significance (***p≤0.05). **Panel A. Average binaural auditory speech perception in noise scores (QuickSIN™).** Scores are plotted in terms of the dB signal-to-noise ratio loss (dB SNR), representing the dB SNR required for the participant to score 50% of words in a sentence correct relative to normal hearing listeners. A higher score indicates poorer auditory speech perception in noise performance. The dotted line indicates the cutoff score (3 dB SNR) for normal function in background noise. The hearing loss group performed significantly poorer on the QuickSIN™ test. **Panel B. Average benefit from visual (lipreading) cues on a binaural auditory-visual speech perception in noise test (AzAv).** Scores indicate the percent difference score in an auditory-only condition relative to an auditory-visual condition, where a higher score indicates greater benefit from the addition of visual (lip-reading) cues. No significant difference was observed between groups in terms of lip-reading benefit.

2.7.4. Group Differences in Cognitive Function

Significant differences in cognitive function were observed between the two groups. Average global cognitive scores with corresponding 95% confidence intervals are depicted in Figure 7A. Average MoCA score was 1.69 points lower in the hearing loss group (M=24.93, SD=2.801) compared to the normal hearing group (M=26.62, SD=1.193). A paired samples t-test indicated poorer global cognitive function (MoCA) in the hearing loss group compared to the normal hearing group (t(39)=-2.074, p=0.045). Poorer global cognitive outcomes have been reported in previous cross-sectional studies (Baltes & Lindenerger, Deal et al., 2015; Dupuis et al., 2015; Gussekloo et al., 2005; Harrison Bush et al., 2015; Lin et al., 2011b; Lin et al., 2013; Lindenberger & Baltes, 1994) and cohort studies (Deal et al., 2015; Gallacher et al., 2012; Hong et al., 2016; Lin et al., 2013) in age-related hearing loss.

Average executive function scores (BDS-2) with corresponding 95% confidence intervals are depicted in Figure 7B. Executive function scores were 3.06 points lower on average in the hearing loss group (M=20.79, SD=2.80) compared to the normal hearing group, and this group difference was statistically significant (t(39)=-3.087, p=0.004). These findings are consistent with previous cross-sectional and cohort studies showing impairments in tests of executive functioning in cohorts of comparable age to our hearing loss group (Gates et al., 1996, 2010; Lin et al., 2013).

Average processing speed scores (SDMT) with corresponding 95% confidence intervals are depicted in Figure 7C. Hearing loss participants (M=43.96, SD=7.42) performed 7.81 points poorer on the processing speed task compared to the normal hearing participants, and this difference was significantly significant (M=51.77, SD=6.06) (t(39)=-3.310, p=0.002) on average. Slower processing speeds have been reported in several previous cross-sectional studies (Anstey et al., 2001; Clark, 1960; Valentijn et al., 2005; Lin et al., 2011a, 2011b; 2013;

Bucks et al., 2016) and in cohort studies (Anstey et al., 2003; Deal et al., 2015; Deal et al., 2016; Gallacher et al., 2012; Lin et al., 2013; Linberger & Ghisletta, 2009) in adults with age-related hearing loss.

Average visual working memory percent recall scores (RST) and auditory working memory percent recall scores (WARRM) with corresponding 95% confidence intervals are depicted in Figure 7D and 7E. Percent recall scores on the visual working memory task (RST) were 6.92% poorer in the hearing loss group (M=39.61%, SD=10.81) compared to the normal hearing group (46.53%, sd=7.25). The difference in RST scores was poorer in the hearing loss group (t(39)=-2.091, p=0.043). Percent recall scores on the auditory working memory task (WARRM) were 11.39% poorer in the age-related hearing loss group (average=71.52, sd=13.36) compared to the normal hearing group (M=82.01, SD=5.69) and this result was significantly different (t(39)=-2.937, p=0.006, α<0.01) between groups. These results are consistent with previous cross-sectional studies, where adult-onset sensorineural hearing loss is associated with significantly poorer working memory performance (Anstey & Smith, 1999; Bucks et al., 2016; Hofer et al., 2003; Harrison Bush et al., 2015; MacDonald et al., 2004).

In summary, the hearing loss group performed significantly poorer across all cognitive sub-domains assessed (global cognitive function, executive function, processing speed, visual working memory, and auditory working memory), relative to the normal hearing group.
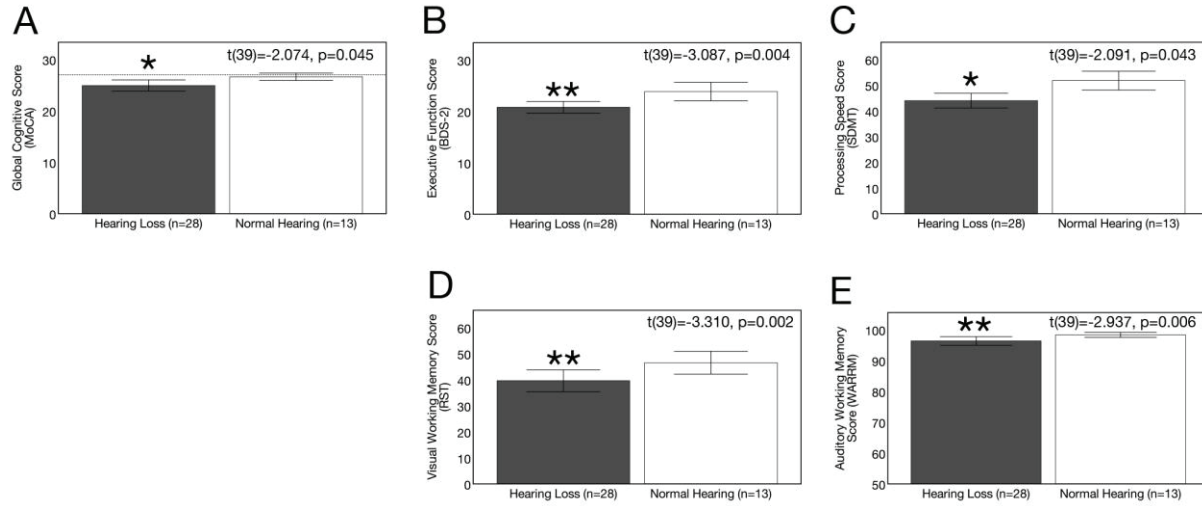
Figure 7. Baseline Group Differences in Cognitive Function. Average scores on cognitive measures in the age-related hearing loss group (n=28) are depicted in gray and average scores for the normal hearing group (n=13) are depicted in white. Black bars indicate 95% confidence intervals for each group. Asterisks indicate level of significance (**p≤0.01, *p≤0.05). **Panel A. Average global cognitive function on a screening measure (MoCA) for mild cognitive impairment.** Higher scores in indicate higher global cognitive function, out of a total possible score of 30 points. The dotted reference line on the y-axis indicates the cutoff score (≤27) indicating risk for mild cognitive impairment. **Panel B. Average executive function score (BDS-2).** Higher scores in indicate better executive functioning, out of a total possible score of 27 points. **Panel C. Average processing speed score (SDMT).** Higher scores in indicate faster processing speeds in a timed, 90-second digit-symbol matching task. **Panel D. Average visual working memory score (RST) in percent words correctly recalled.** Higher scores indicate higher visual working memory performance in a dual-task paradigm. **Panel E. Average auditory working memory score (WARRM) in percent words correctly recalled.** Higher scores indicate higher auditory working memory performance in a dual-task paradigm. The hearing loss group performed more poorly than the normal hearing group across all cognitive outcome measures assessed. **Note:** Cognitive testing in the hearing loss group was administered in an acutely aided condition to negate confounding effects of audibility on cognitive performance.

2.7.6. Correlational Analyses Among Neurophysiological and Behavioral Measures

We examined the association of neurophysiological outcomes with behavioral and cognitive outcomes in the untreated hearing loss group using Pearson's correlation analyses. CVEP latencies over the right temporal ROI were predictive of auditory speech perception in noise performance. Correlations between auditory speech perception in noise performance (QuickSIN™ score) and CVEP latencies are shown in Figure 8A-8C. As predicted, we observed a significant negative correlation with auditory speech perception in noise on the QuickSIN™ and CVEP peak latencies for the P1 (r=-743, p<0.001) (Figure 9A) N1 (r=-0.643, p<0.001) (Figure 9B), and P2 (r=-0.532, p<0.001) (Figure 9C) components. This finding is consistent previous studies in adults in adult-onset mild-moderate sensorineural hearing loss (Campbell & Sharma, 2014), deaf children (Campbell & Sharma, 2016; Lee et al., 2001), and deaf adults (Buckley & Tobey, 2010; Chen et al., 2016; Doucet et al., 2006; Sandmann et al., 2012; Strelnikov et al., 2013), where a significant negative correlation was observed between visual cortical evoked potential components and auditory performance outcomes. These findings suggest that earlier CVEP latencies (an index of greater visual cross-modal re-organization of auditory cortex) are associated with poorer auditory outcomes.

No significant association between benefit from visual (lip-reading) cues for auditory-visual speech perception in noise and CVEP latencies over the right temporal ROI were detected in the untreated hearing loss group (P1 (r=0.070, p=0.724), N1 (r=-0.123, p=0.532), P2 (r=-0.41, p=0.837)). While a significant association between visual cross-modal neuroplasticity and face processing benefit has been observed in deaf adults (Stropahl et al., 2015 Stropahl & Debener, 2017), based on our results it does not appear that visual cross-modal recruitment of auditory cortex is related to dependence on visual (lip-reading) in mild-moderate, age-related hearing loss. This finding is consistent with Stropahl & Debener

(2017), where visual (lip-reading) benefit for auditory-visual speech perception was not correlated with strength (amplitude) of visual evoked potential responses to facial stimuli in adults with mild-moderate sensorineural hearing loss. It is possible that visual cross-modal recruitment of auditory cortex may be related to auditory deprivation itself and the general reliance on faces rather than skill in lip-reading.
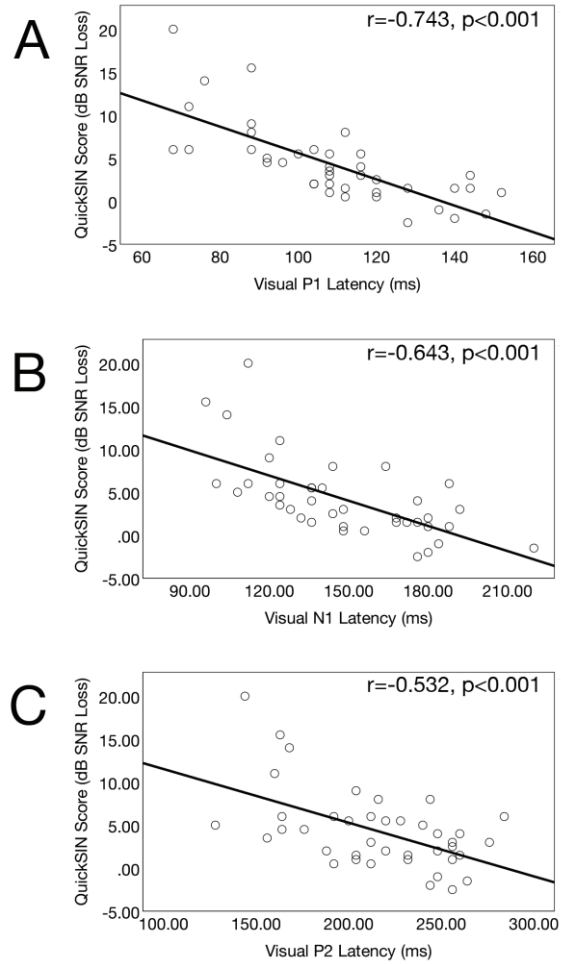
Figure 8. Association Between Cortical Visual Evoked Potential Latencies and Auditory Speech Perception in Noise Performance in the Hearing Loss Group. CVEP peak latencies (in milliseconds) for the P1 (**Panel A**), N1 (**Panel B**) and P2 (**Panel C**) components over the right temporal region of interest are displayed on the horizontal axis and binaural auditory speech perception in noise (QuickSIN™) score is displayed on the vertical axis. QuickSIN™ performance is described in terms of a dB HL loss, where higher scores indicate greater auditory deficits (poorer performance) in background noise. Earlier P1, N1, and P2 CVEP latency (an index of visual cross-modal re-organization) in the hearing loss is associated with poorer auditory outcomes.

CVEP latencies over right temporal ROI were also predictive of high frequency pure tone average. Correlations between high frequency pure tone averages and CVEP latencies are shown in Figure 9A-9C. A significant negative correlation with between high frequency pure tone average and P1 (r=-0.672, p<0.001) and N1 (r=-0.741, p<0.001) and P2 (r=-0.572, p<0.001) CVEP latencies were observed. This result is consistent with findings from Stropahl & Debener (2017) who found an association between degree of hearing loss and strength of visual cross-modal re-organization in the auditory cortex to visual stimuli in adults with mild-moderate hearing loss. These results indicate that visual cross-modal re-organization depends on degree (and possibly duration, though this is hard to document in age-related hearing loss) of auditory deprivation. Greater degree of hearing loss is associated with more visual cross-modal recruitment of the auditory cortex. Based on our findings, even early-stage (mild-moderate) auditory deprivation alters typical sensory cortical functioning.
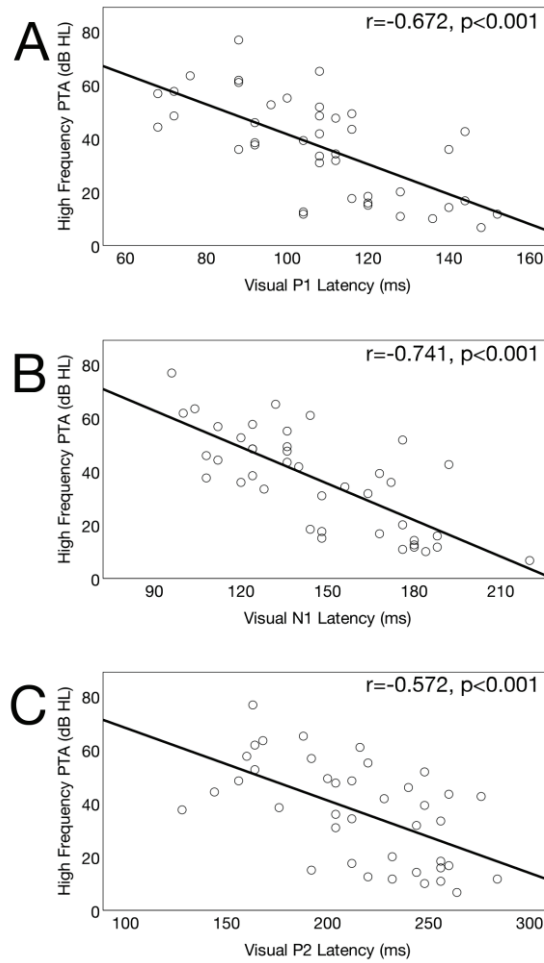
Figure 9. Association Between Cortical Visual Evoked Potential Latencies and Degree of Hearing Loss in the Hearing Loss Group. CVEP peak latencies (in milliseconds) for the P1 (**Panel A**), N1 (**Panel B**) and P2 (**Panel C**) components over the right temporal region of interest are displayed on the horizontal axis and high frequency pure tone averages (averaged across the right and left ears) are displayed on the vertical axes in the hearing loss group, where higher PTA (measured in dB hearing level, or dB HL) indicates more severe hearing loss. Earlier P1, N1, and P2 CVEP latency (considered an index of visual cross-modal re-organization) is associated with greater degrees of hearing loss.

Significant positive correlations were observed between CVEP latencies over the right temporal ROI and all of the cognitive outcome measures, with the exception of the visual working memory test (RST), in which no significant correlations with CVEP latencies were observed. Correlations between P1 CVEP latency and the 5 cognitive outcome measures are depicted in Figure 10A-E. P1 (r=0.391, p=0.011) CVEP latency was significantly positively correlated with global cognitive function (MoCA) score. P1 (r=0.391, p=0.010) CVEP latency was significantly positively correlated with executive function (BDS-2) score. P1 (r=0.397, p=0.010) CVEP latency was significantly positively correlated with processing speed (SDMT) performance. Significant positive correlations between N1 CVEP latency (r=0.379, p=0.015) and auditory working memory (WARRM) performance were also observed. Consistent with the load theory of selective attention and the load theory of speech perception, the strong correlations between visual cortical evoked potential latencies and cognitive outcomes suggest that auditory deprivation may induce compensatory changes in cortical resource allocation (e.g. cross-modal re-organization), correlated with negative impacts on cognitive functioning (Broadbent, 1954; Lavie & Fockert, 2003; Lavie et al., 2004, 2005; Norman & Bobrow, 1975).

The association between sensory cortical resource allocation (e.g. cross-modal re-organization) and cognitive performance may indicate deficits in inhibitory control in age-related hearing loss. For example, both older adults with normal hearing and older adults with hearing loss exhibit greater errors in cognitive P300 oddball paradigms (Andrés et al., 2006; Hong et al., 2016) and auditory gating tasks (Friedman, 2008), suggesting that peripheral hearing loss and aging may suppress ability to disregard task-irrelevant or distraction stimuli. The widespread cross-modal and frontal and pre-frontal cortex recruitment for sensory processing that we observed in the hearing loss group (Figure 5) may reflect decreased inhibitory control associated with peripheral hearing loss. While the

primary focus of this study was to examine the association between hearing loss, cross-modal re-organization, and cognitive functioning, 68% of hearing loss participants in our study reported symptoms of tinnitus. Similar alterations in top-down executive control of attention have been reported in tinnitus (Heeren et al., 2014). Thus, it appears that peripheral deprivation from cochlear hearing loss (and tinnitus) may contribute to alterations in typical sensory processing and other cognitive processes such as attention, executive function, processing speed, and working memory.
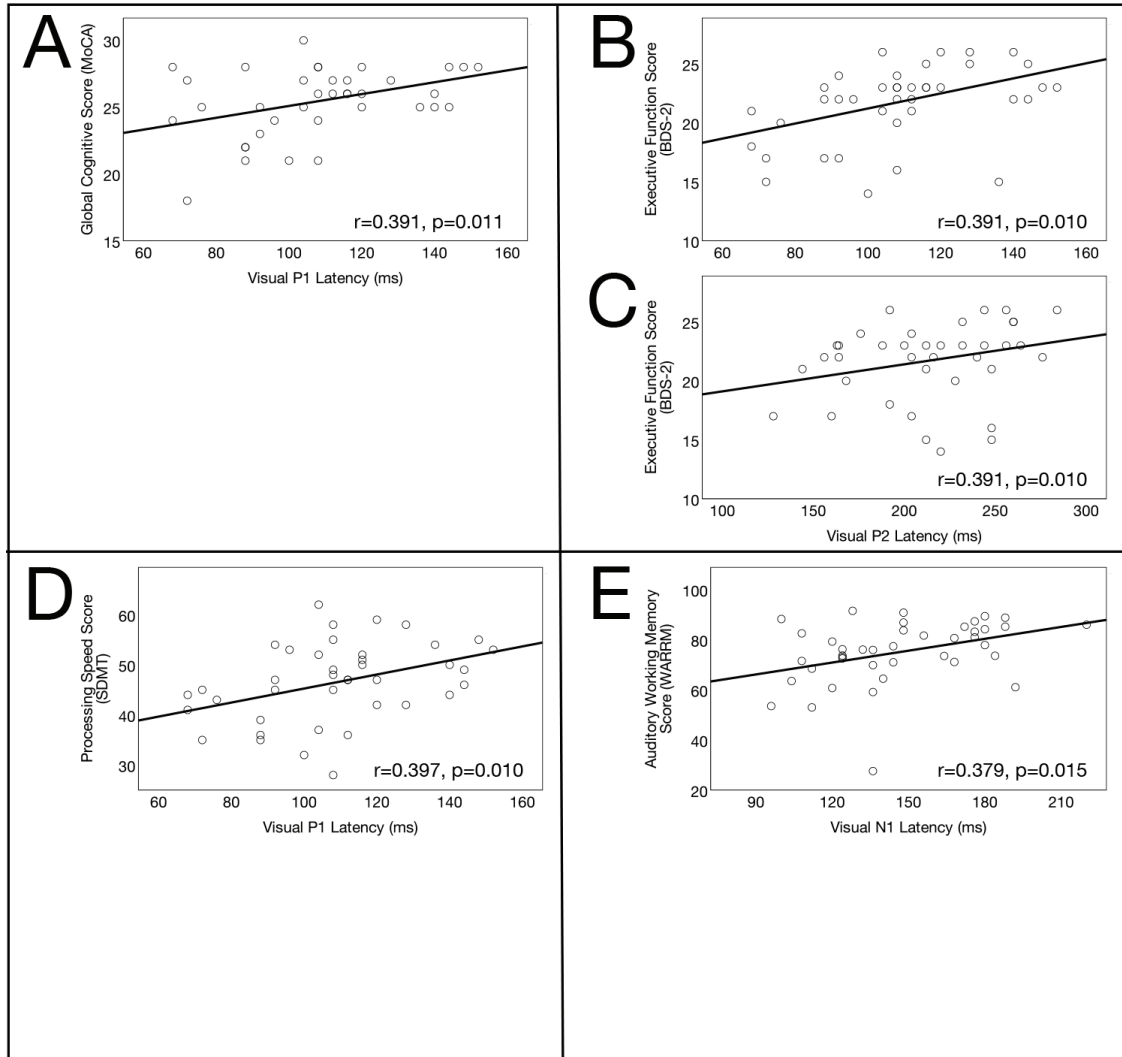
Figure 10. Significant Associations Between Cortical Visual Evoked Potential Latencies and Cognitive Function in the Hearing Loss Group. Significant correlations (p≤0.017) between P1, N1, and P2 CVEP peak latencies (in milliseconds) and global cognitive function on the MoCA test (**Panel A**), executive function score on the BDS-2 test (**Panel B, Panel C**), processing speed score on the SDMT test (**Panel D**), and auditory working memory percent recall on the WARRM test (**Panel E**). Higher scores on the cognitive measures indicate better cognitive performance. Earlier CVEP latencies (considered an index of visual cross-modal re-organization) are associated with poorer cognitive functioning across the domains of global cognitive function, executive function, processing speed, and auditory working.

CHAPTER 3

STUDY 2: TREATMENT EFFECTS ON NEUROCOGNITIVE FUNCTION IN AGE-
RELATED HEARING LOSS

3.1.   Specific Aims

Specific Aim 1: To examine pre-post treatment differences in visual cortical cross-
modal neuroplasticity in adults with age-related hearing loss, over the course of 6 months of
hearing aid use.

Hypothesis 1: The hearing loss adults will exhibit a reduction in cross-modal re-
organization of the auditory cortex by vision post-treatment, as indexed by a shift to
significantly later CVEP latencies over a right temporal region of interest and current density
source reconstruction patterns indicative of reduction in cross-modal recruitment of the
auditory cortex for visual processing for the higher-level N1 and P2 CVEP components. This
reduction in visual cross-modal re-organization will provide evidence that restored audibility
with hearing aids promotes more typical visual cortical functioning.

Specific Aim 2: To examine pre-post treatment differences in speech perception
outcomes in adults with age-related hearing loss, over the course of 6 months of hearing aid
use.

Hypothesis 2: The hearing loss adults will exhibit significant improvements in
auditory speech perception in noise performance after treatment with hearing aids and a
significant reduction in dependence on visual (lip-reading) cues for auditory-visual speech
perception in noise, providing evidence that restored audibility with hearing aids promotes

better auditory performance outcomes in background noise and decreased reliance on lip-reading cues for auditory-visual speech perception.

Specific Aim 3: To evaluate pre-post differences in cognitive outcomes in adults with age-related hearing loss, over the course of 6 months of hearing aid use.

Hypothesis 3: The adults with hearing loss will exhibit significant improvements in cognitive function across the domains of global cognitive function, executive function, processing speed, and working memory after 6 months of hearing aid use. Improvements in cognitive function will provide evidence of neurocognitive benefit from early treatment with hearing aids.

Aim 4: To examine whether pre-treatment neurophysiological measures are predictive of post-treatment behavioral and cognitive outcomes in adults with age-related hearing loss.

Hypothesis 4: Pre-treatment CVEP latencies over the right temporal ROI will be negatively associated with auditory speech perception in noise outcomes after treatment with hearing aids, positively associated with dependence on lip-reading cues, and negatively associated with cognitive function across the all cognitive sub-domains of global cognitive function, executive function, processing speed, and working memory. These findings will provide evidence that pre-treatment visual cross-modal neuroplasticity in auditory cortex predicts post-treatment hearing aid outcomes in early-stage, age-related hearing loss.

3.2.   Study Design

A pretest-posttest design was used to evaluate the effects of treatment with hearing aids on neurophysiological, speech perception, and cognitive outcomes in adults with age-related hearing loss over the course of 6 months of hearing aid use. Outcome measures assessed at pre-treatment/acute treatment (baseline visit) and a post-treatment visit after 6-months of hearing aid use included the following: Cortical visual evoked potentials (CVEPs),

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sentence-level auditory speech perception in noise performance (QuickSIN™), benefit from visual (lip-reading) cues for sentence-level auditory-visual speech perception (AzAv), and cognitive outcomes across the domains of global cognitive function (MoCA), executive function (BDS-2), processing speed (SDMT), and working memory (RST, WARRM). In addition, several subjective questionnaires were administered to the hearing loss group to assess self-perceived benefit and satisfaction with hearing aids at the post-treatment 6-month follow-up.

Hearing loss participants were required to wear their hearing aids at least 5 hours per day over the 6-month duration of the study to remain enrolled in Study 2. Participants returned at 2 week, 1 month, 3 month, and 6 months follow-up intervals for routine hearing aid checks and to assess daily average hearing aid usage data.

It was not feasible to have all normal hearing participants (n=13) outlined in Study 1 (Chapter 2) return for 6-month follow-up testing given the time constraints of completing the study. However, a sub-group of the normal hearing participants in Study 1 returned for 6-month follow-up testing to assess replicability of the CVEP measures over the time course of 6 months.

3.3.   Human Subjects Assurances and Protection

This study was conducted in accordance with University of Colorado Institutional Review Board (IRB) guidelines. All participants provided written consent approved under protocol 18-0087.

3.4.   Participants

The 28 participants with age-related hearing loss described in Study 1 (Chapter 2, Section 2.2) were enrolled in Study 2. The average age of this hearing loss group was 65.04 years (SD=4.23). All participants were native speakers of English, with no reported neurological impairment and reported normal or corrected-to-normal visual acuity.

To remain enrolled in the study, participants were required to wear the hearing aids at least 5 hours per day on average for the entire 6-month duration of the study. Of these 28 participants initially enrolled in Study 2, a total of 21 participants successfully completed the entire 6-month duration of the study and are included in the final analyses. The 7 hearing loss participants excluded from final analyses were excluded for justifiable reasons. 5 of the 7 excluded participants were removed from the study between 2 weeks and 3 months post-treatment due to inability to adjust to hearing aids and/or insufficient hearing aid use (<5 hours per day on average). 2 of the 7 excluded participants experienced changes in health status and could not complete the 6-month follow-up visit.

The 21 hearing loss participants (10 female, 11 male) included in final analyses for Study 2 ranged between the ages of 75 and 71 years (M=64.38 years, SD=4.03). Average PTA in the right ear was 26.67 dB HL (SD=10.97) and average PTA in the left ear was 26.34 dB HL (SD=10.34). Average HFPTA in the right ear was 46.90 dB HL (SD=12.20) and average PTA in the left ear was 47.86 dB HL (SD=11.17). There was no statistical difference in PTA (t(20)=0.253, p=0.803) or HFPTA (t(20)=-0.760, p=0.456) between the two ears. Thus, average pure tone air conduction thresholds across the two ears were computed for subsequent analyses. Average pure tone air conduction thresholds and corresponding 95% confidence intervals are depicted in Figure 11.

In addition to the hearing loss participants, a small sub-group of normal hearing participants described in Study 1 (Chapter 2, Section 2.2) returned for 6-month follow-up testing to ensure reliability of CVEP results over 6 months. This sub-group (n=4, 1 male, 3 female) ranged in age from 61 years to 74 years of age (SD=5.85).
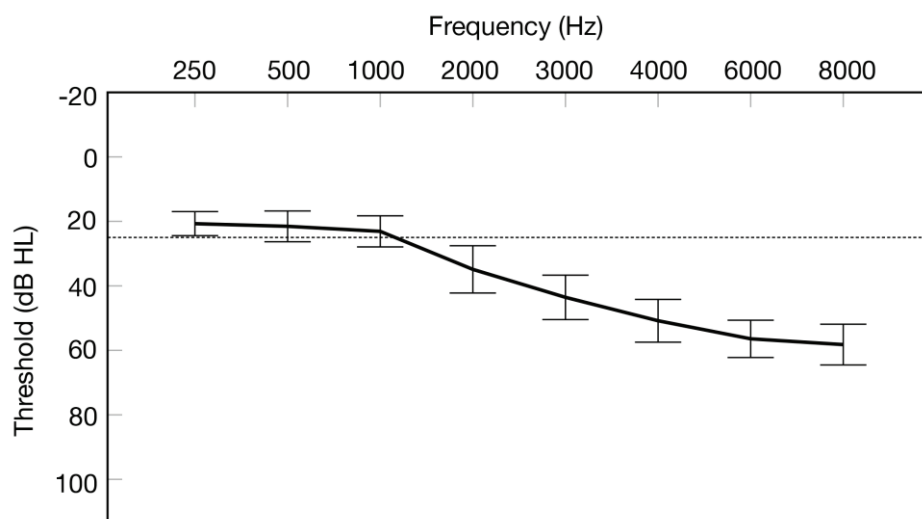
Figure 11. Average Pure Tone Air Conduction Thresholds for the Age-Related Hearing Loss Group. Average pure tone air conduction thresholds across the two ears (0.25-8.0 kHz) are displayed for the group of adults with age-related hearing loss (n=21) (solid line). Frequency (Hz) is displayed on the horizontal axis and pure tone air conduction thresholds in decibels hearing level (dB HL) are displayed on the vertical axis. The dotted line on the y-axis indicates the clinical cutoff for normal hearing thresholds (25 dB HL). The bars display 95% confidence intervals at each threshold.

3.5. Methods

3.5.1. Baseline Testing

Complete methodology for pre-treatment/acute treatment (baseline) assessment of cortical visual evoked potentials (CVEPs), auditory- and auditory-visual speech perception in noise (QuickSIN™, AzAv), and cognitive outcomes (MoCA, BDS-2, SDMT, RST, WARRM) are described in Study 1 (Chapter 2, Section 2.5). Pre-treatment CVEP and auditory speech perception in noise testing (QuickSIN™) was performed in an unaided condition. Baseline auditory-visual speech perception in noise testing (AzAv) and cognitive testing (MoCA, BDS-2, SDMT, RST, WARRM) were administered in an acutely aided condition. The purpose of administering these tests in an acutely aided condition at baseline was to negate potential confounding effects of audibility on test performance, and to ensure equal audibility between pre- and post-test sessions.

3.5.2. Hearing Aid Fitting

As described in Study 1 (Chapter 2, Section 2.5.3), hearing loss participants were fit with bilateral receiver-in-the-ear Oticon OPN 1 mini receiver-in-the-ear (miniRITE) hearing aids at the baseline evaluation before administration of the AzAv and cognitive tests. Hearing aid fittings for each participant were verified against NAL-NL2 prescriptive fitting targets from 0.25-4.0 kHz, adjusting gain within ±5 dB of prescriptive targets for soft (55 dB SPL), medium (65 dB SPL) and loud (75 dB SPL) via probe microphone measures. Efforts to minimize advanced signal processing features were selected to promote generalizability of study findings across hearing aid manufacturers. Settings for noise reduction (0 dB simple environments, -7 dB complex environments, open sound transition set to medium), microphone mode (open automatic), transient noise management (off), and binaural

broadband controls (on) were set to manufacturer defaults (LeGoff et al., 2016). Feedback reduction algorithms were not applied, since algorithms can affect ideal frequency-gain characteristics and vary between manufacturers. Instead, modifications to the acoustic coupling were made (e.g. selecting a more occlusive dome) if significant feedback was present. See Study 1 (Chapter 2, Section 2.5.3) for complete details on hearing aid fitting and verification procedures. Participants were instructed on use, care, and maintenance of the hearing aids and they were instructed to wear the hearing aids at least 5 hours per day to remain enrolled in the study.

3.5.3. Hearing Aid Checks and Data Logging

After baseline testing and hearing aid fitting, hearing loss participants returned for routine hearing aid maintenance checks and data logging procedures approximately 2 weeks, 1 month, 3 months, and 6 months post-treatment. The purpose of these monitoring visits was to ensure hearing aids were functioning properly and to document average daily hearing aid use over the course of the study. The Oticon Genie 2™ fitting software was used to log average daily hearing aid use at each visit. At the final follow-up visit, cumulative usage time over each visit was assessed to compute average hearing aid use over the course of 6 months. All participants whose average accumulated hearing aid use across 6 months were >5 hours per day were included in final analyses. Average daily hearing aid use in the hearing loss participants (n=21) after 6 months of hearing aid use was 9.84 hours (SD=2.96). Average hearing aid use ranged from 5.10 to 14.02 hours per day.

3.5.4. 6-Month Follow-Up Testing

The same exact methodology used for pre-treatment assessment of cortical, speech perception, and cognitive outcomes was administered 6 months post-treatment, with one

exception. While pre-treatment evaluation of auditory speech perception in noise (QuickSIN™) was measured in an unaided condition at baseline, 6-month post-treatment QuickSIN™ evaluation occurred in an aided condition. The purpose of evaluating aided auditory speech perception performance at the post-treatment test was to evaluate treatment effects (e.g. the effects of increased audibility) with hearing aids on auditory speech perception in noise functioning, compared to an unaided condition. See Study 1, Chapter 2, Section 2.5 for a comprehensive description of the methodology used to assess cortical (CVEPs), speech perception (QuickSIN™, AzAv), and cognitive outcomes (MoCA, BDS-2, SDMT, RST, WARRM).

3.5.5. Hearing Aid Outcome Questionnaires

Several questionnaires were selected to validate hearing aid outcomes after 6-months of hearing aid use, providing self-report measures of benefit and satisfaction. These questionnaires include the Client Oriented Scale of Improvement (COSI) (Dillon et al., 1997), the International Outcome Inventory for Hearing Aids (IOI-HA) (Cox et al., 2002, 2003), and the Satisfaction with Amplification in Daily Living (SADL) (Cox & Alexander, 2003). The purpose of including these questionnaires was to document subjective outcomes and self-perceived benefit and satisfaction in mild-moderate, age-related hearing loss.

The COSI is a subjective hearing aid outcome measure that is administered before and after hearing aid fitting. The COSI test consists of a pre-treatment step and post-treatment step. During the pre-treatment step (at the baseline visit prior to hearing aid fitting), hearing loss participants were instructed to identify up to 5 specific listening situations where they wanted to see improvements with hearing aids. They were asked to rank these situations in order of importance to them. During the post-treatment evaluation, participants were asked to rate the degree of change in hearing ability in each specific

listening situation on a 5-point scale (1=worse, 2=no difference, 3=slightly better, 4=better, and 5=much better). At the post-treatment evaluation, participants were also asked to rank their final hearing ability to hear with hearing aids in each specific listening situation on a 5-point scale (1=hardly ever, 2=occasionally, 3=half the time, 4=most of the time, and 5=almost always). An averaged degree of change score and final ability score were calculated for each participant by summing their outcome ratings across the listening situations identified and dividing by the total number of situations identified. While the COSI is not a standardized measure, outcomes reported on the COSI are highly correlated with standardized outcome measures such as the SADL (Dillon et al., 1999). The benefit of incorporating the COSI measure is that it probes self-perceived benefit from hearing aids in the situations most important to each individual patient, rather than general situations that may or may not be applicable to each person's life.

The IOI-HA is a standardized 7-item survey that targets several different outcome domains: Daily use, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others, and quality of life. The questionnaire was administered at the post-treatment 6-month follow-up visit. Participants were asked to provide a rating for each item on a 5-point scale, where a lower score indicates poorer outcome and a higher score indicates higher outcome for each item (Cox et al., 2003; Cox et al., 2002a, 2002b; Noble, 2002; Kramer et al, 2002; Stephens et al., 2002). Since the original English version of the questionnaire was published, Cox et al. (2003) added an 8th item to the questionnaire which gauged patient's self-reported hearing difficulty on a 5-point scale (1=severe, 2=moderately-severe, 3-moderate, 4=mild, 5=none), where a higher score indicates less self-perceived difficulty and developed normative data for each of these items for self-perceived difficult that is mild-moderate (rating of a 2 or 3) or moderately-severe to severe (1 or 2). The benefit of the IOI-HA measure is that is has international applicability, available in many different

languages. Normative data for this measure is also available. A global score averaged across all 7 test items was computed, as well as sub-scores for each of the 7 test items across the 7 different domains of daily use, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others, and quality of life, and the 8th added item of self-reported hearing difficulty.

The SADL is a standardized 15-item survey targeting elements most important to patient satisfaction. Participants are asked to indicate the relative importance each item on a 7-point scale. The questionnaire was administered at the 6-month post-treatment assessment visit. The questionnaire yields a global satisfaction score as several sub-scores across the following domains: Positive effects, service and cost, negative features, and personal image (Cox & Alexander, 1999; Cox & Alexander, 2001). Per the test administration instructions, the item related to cost of the devices was not included in analyses since this was a research study. An average score was calculated for each sub-score category by summing ratings for each item in that category and dividing by the total number of items in that category. A global score was also computed by averaging ratings across all items and dividing by the total number of items.

3.6.   Analysis

3.6.1. Cortical Visual Evoked Potential Analysis

The same data analysis procedures described in Study 1 (Chapter 2, Section 2.6.1.) were applied to analyze the pre-treatment and post-treatment CVEP data for the hearing loss participants in Study 2. As described in Chapter 2 Section 2.6.1, peak CVEP latencies and amplitudes for the P1, N1, and P2 components were extracted for each participant across 3 a-priori cortical ROIs (Occipital, right temporal, and left temporal regions of interest) for pre-treatment and post-treatment test sessions. A schematic illustration of the 3 regions of interest (ROIs) are depicted in Chapter 1, Figure 3. Following pre-processing and post-processing CVEP analysis procedures, cortical source modeling was performed pre-treatment and 6-months post treatment (See Chapter 1, Section 2.6.1 for cortical source modeling methodology), yielding group CDRs for the hearing loss each test session. Resultant CDRs are superimposed on an average adult structural MRI, where a corresponding graded color scale (F-statistic) indicates the probable current density in each cortical (statistical likelihood). Complete methodology for CVEP analysis is described in Chapter 1, Section 2.6.1.

3.6.2. Statistical Analysis

Pre-treatment and Post-treatment statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 25. Histograms, Q-Q plots, and significance tests (Shapiro Wilk test, Levene test) were first computed to assess potential violation in assumptions of normality and homogeneity of variance for all variables for the hearing loss group at pre- and post-treatment sessions for the 21 hearing loss participants included in final analyses for Study 2.

A series of two-tailed, paired samples sample t-tests were then applied assess pre-post treatment effects with hearing aid treatment on the cortical, speech perception, and cognitive variables. Because multiple comparisons were made to assess CVEP (P1, N1, P2) latencies across the different 3 ROIs across the test sessions, a Bonferroni correction was applied (alpha error divided by number of tests) to reduce chance of Type I error, reducing the alpha level from $\alpha=0.05$ to $\alpha=0.017$. The same correction was applied for assessing CVEP (P1, N1, P2) amplitudes across the 3 ROIs.

To assess whether pre-treatment CVEP latencies over the right temporal ROI were predictive of post-treatment behavioral and cognitive outcomes, Pearson's correlation coefficients were computed. Pearson's correlations provide information about the association (strength) of the relationship between two variables, where a correlation coefficient (r) of 0 indicates no linear relationship between two continuous variables, and a correlation coefficient of -1 or +1 indicates a strong negative or positive linear relationship, respectively. Because comparisons were made between the 3 different CVEP components pre-treatment and cognitive outcomes post-treatment, a Bonferroni correction was applied to reduce chance of Type I error, reducing the alpha level from $\alpha=0.05$ to $\alpha=0.017$.

3.7.   Results and Discussion

3.7.1. Treatment Effects on Evoked Potential Latencies and Amplitudes

Plots of the grand average CVEP waveforms for hearing loss group (n=21) at pre-treatment and 6-month post-treatment test sessions across the occipital, right temporal, and left temporal ROIs are depicted in Figure 13. Paired samples t-tests indicated no significant pre-post treatment effects of hearing aid use on P1, N1, or P2 peak latencies or amplitudes over the occipital or left temporal region of interest. However, significant pre-post treatment

differences in CVEP P1, N1 and P2 latencies were observed in the right temporal ROI (α<0.055 level). As can be seen in Figure 12 and corresponding Table 5, the age-related hearing loss group exhibited a significant late-ward shift in P1 (t(20)=4.148, p<0.001), N1 (t(20)=5.193, p<0.001), and P2 CVEP peak latencies (t(20)=4.300, p<0.001) 6 months post-treatment. While amplitudes appear reduced in the right temporal ROI in the hearing loss group post-treatment upon visual inspection, pre-post differences in peak amplitudes in the right temporal ROI (P1 (t(20)=-0.784, p=0.442), N1 (t(20)=-0.476, p=0.639), P2 (t(20)=-0.460, p=0.650)) were not statistically significant.

Results are consistent with the Hypothesis 1 outlined in Specific Aim 1 (Section 3.1). To our knowledge, no prior studies have examined the effects audiological intervention with hearing aids or cochlear implants on visual cross-modal plasticity in clinical populations with adult-onset, mild-moderate hearing loss. Post-hoc group comparisons of right temporal CVEP latencies in the normal hearing group in Study 1 assessed at baseline (n=13) and latencies observed in the hearing loss group (n=21) assessed at 6-months post-treatment, showed no difference in P1 (t(32)=1.339, p=0.190), N1 (t(32)=1.010, p=0.320, or P2 latencies (t(32)=0.814, p=0.422), suggesting that treatment with hearing aids may restore typical cortical visual evoked potential processing, comparable to normal hearing adults. Since earlier CVEP latencies are considered a marker of visual cross-modal re-organization, these findings indicate that restored audibility from amplification with hearing aids may promote more typical cortical visual processing patterns.
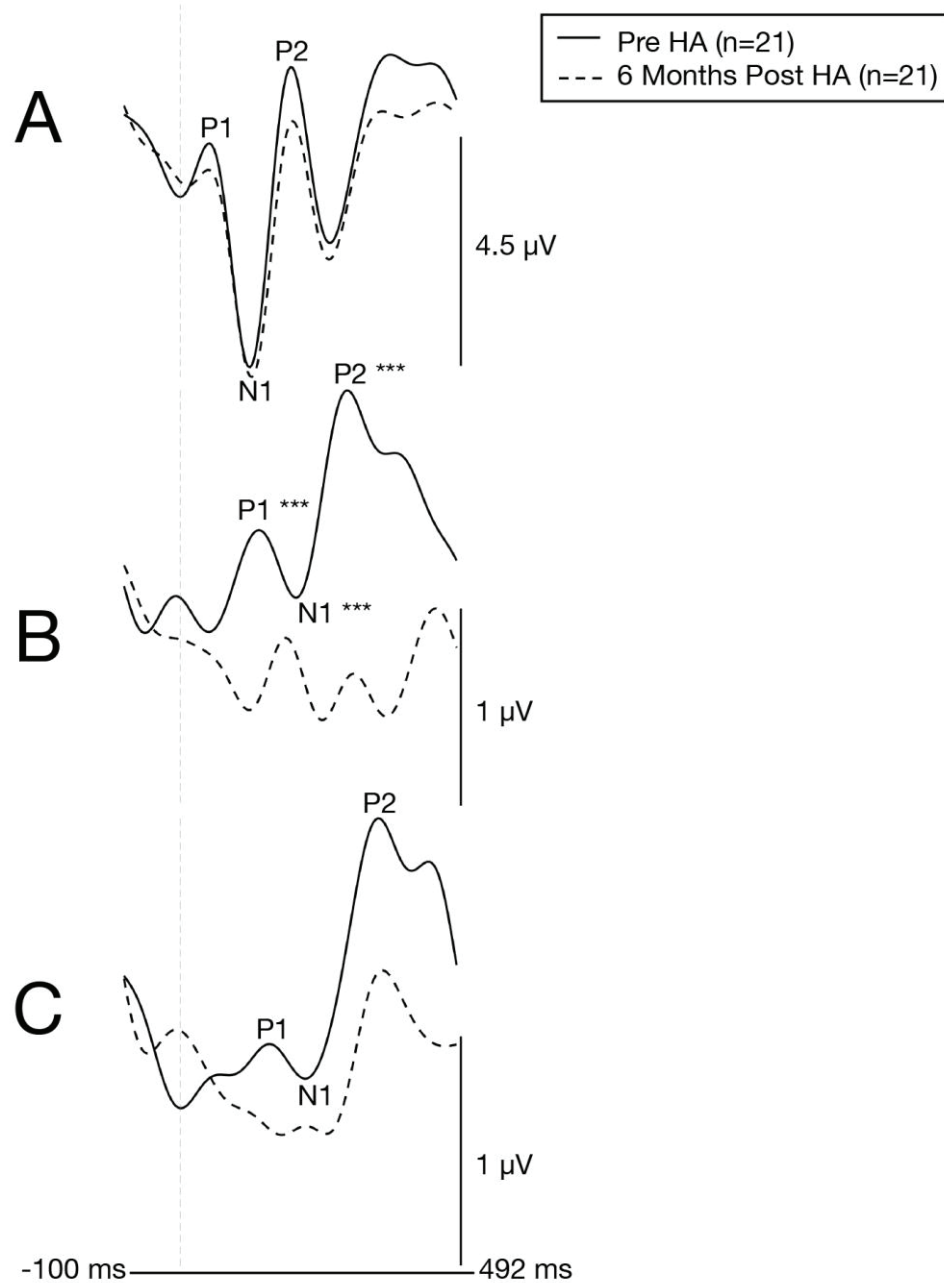
Figure 12. Cortical Visual Evoked Potentials across the Occipital, Right Temporal, and Left Temporal Regions of Interest Before and 6-Months After Intervention with Hearing Aids. Grand-averaged CVEP waveforms for a group of adults with early-stage, age-related hearing loss (n=21) are depicted for the occipital (**Panel A**), right temporal (**Panel B**), and left temporal (**Panel C**) regions of interest before (solid black line) and 6 months after hearing aid use (dashed black line). Time (milliseconds) is displayed on the horizontal axis and amplitude (μV) is displayed on the vertical axis. Asterisks indicate level of significance (***$p \leq 0.001$). The hearing loss group exhibits significantly earlier CVEP P1, N1, and P2 latencies over the right temporal ROI compared to the normal hearing group.

Component	Average Peak Latency		Standard Deviation		95% Confidence Interval		Statistic t(39) (p-value)
	Pre-HA	Post-HA	Pre-HA	Post-HA	Pre-HA	Post-HA	
P1	101 ms	118 ms	19.40	23.78	92-110	108-129	4.148 (<0.001)
N1	33 ms	166 ms	26.90	27.75	121-145	154-179	5.193 (<0.001)
P2	196 ms	231 ms	41.18	44.55	178-216	212-252	4.300 (<0.001)

Table 5. Cortical Visual Evoked Potential Latencies Over a Right Temporal Region of Interest in Adults with Age-Related Hearing Loss Before and After 6 Months of Hearing aid Use. Average peak latencies, standard deviations, 95% confidence intervals, and statistical significance values are provided for the age-related hearing loss group pre-treatment and 6-months post-treatment (n=21). A significant late-ward shift in P1, N1, and P2 latencies are observed with hearing aid use.

A small sub-group of normal hearing adults (n=4) who were assessed at baseline returned for 6-month follow-up testing to ensure replicability of CVEP test results over the course of 6 months. Plots of the grand average CVEP waveforms for the normal hearing sub-group group at baseline (pre-test) and at 6-month follow-up (post-test) across the occipital, right temporal, and left temporal ROIs are depicted in Figure 13. As can be seen in Figure 13, morphology of the CAEP response was similar across test sessions in the normal hearing group. Additionally, paired-samples t-tests revealed no pre-posttest difference in peak P1, N1, or P2 CVEP latencies or amplitudes across any of the 3 ROIs assessed. While only a small sub-group, test-retest replicability of CVEP responses over the course of 6 months is quite good in this small sample. This is in contrast to results observed in the hearing loss, where clear changes in CVEP morphological patterns can be observed across pre-treatment and post-treatment test sessions (Figure 12). This findings suggests that changes in CVEP latency over the right temporal ROI in the hearing loss group are true treatment effects of restored audibility with hearing aids, rather than 'normal' variance in test-retest replicability.
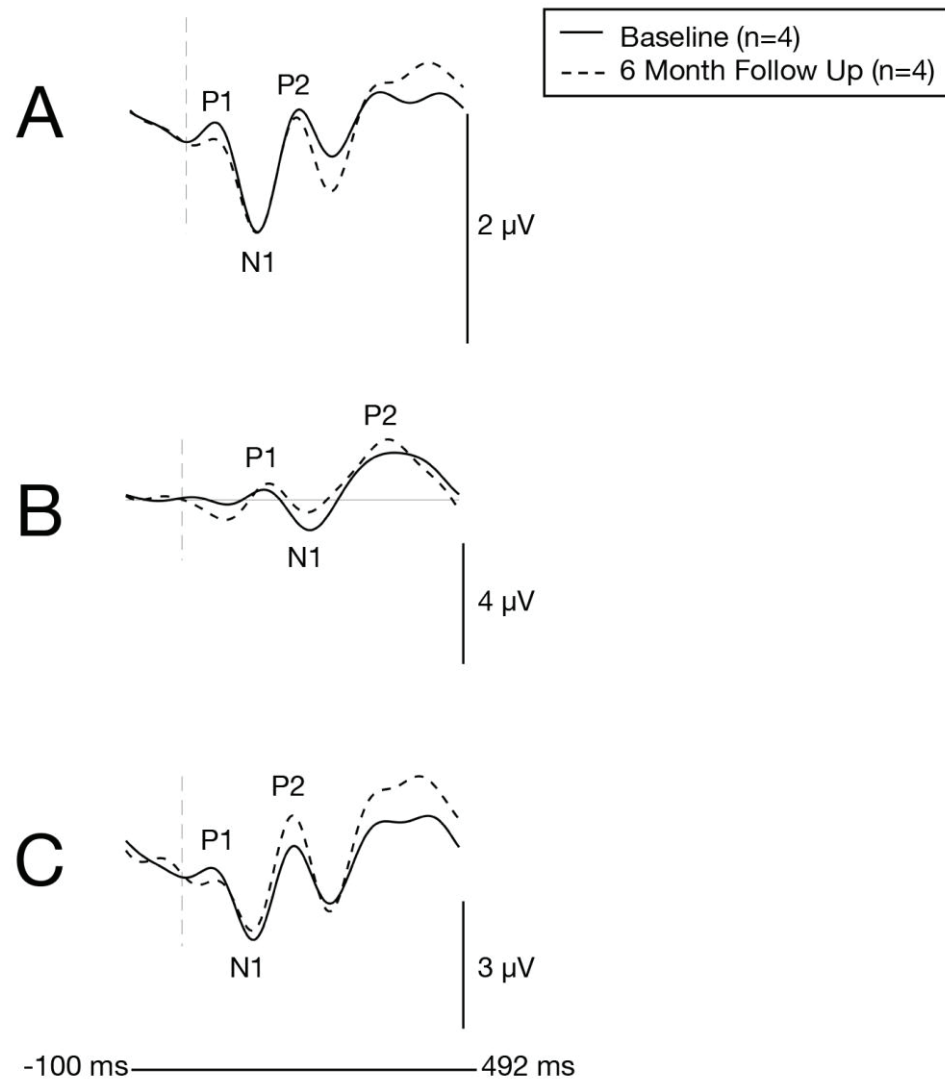
Figure 13. Cortical Visual Evoked Potentials across the Occipital, Right Temporal, and Left Temporal Regions of Interest in a Sub-Group of Normal Hearing Adults Assessed at Baseline and 6-Month Follow-Up Visits. Grand-averaged CVEP waveforms for a normal hearing sub-group (n=4) are depicted for the occipital (**Panel A**), right temporal (**Panel B**), and left temporal (**Panel C**) regions of interest at baseline evaluation (solid black line) and at 6-month follow-up (dashed black line). Time (milliseconds) is displayed on the horizontal axis and amplitude (μV) is displayed on the vertical axis. No significant differences in CVEP P1, N1, and P2 latencies over the right temporal ROI were observed across test sessions.

3.7.2. Treatment Effects on Cortical Source Activation Patterns

Pre-treatment and 6-months post-treatment cortical source localization patterns for each CVEP component (P1, N1, and P2) are displayed for the hearing loss group in Figure 14. Please note that since stability of cortical sources localization (and SNR) increases with larger subject numbers, all 28 hearing loss participants who were initially assessed pre-treatment at baseline in Study 1 were compared to the 21 hearing loss participants who successfully completed the study and were assessed 6-months post-treatment in Study 2. 3D CDRs are displayed on a Maximum Intensity Projection (MIP) (a 2D depth-buffered MRI), providing visualization of the voxels with the highest likelihood of activation. The gradient color scale to the right of each figure indicates the statistical likelihood of activation (F-statistic), from lowest (red) to highest (yellow) probable current density computed via sLORETA. Table 6 lists the cortical regions of activity for each component in the CVEP response in order of highest to lowest likelihood of activation.

Pre-treatment, the visual motion stimulus elicited activity in occipital and cerebellar cortex for the P1 response, consistent with results reported in previous visual motion studies in typical adult samples (Dupont et al., 2003; Kellerman et al., 2012). However, the hearing loss group exhibited additional activity over regions of auditory cortex (e.g. superior, middle, and inferior temporal gyrus) for the later N1 and P2 CVEP components at pre-treatment evaluation, evidence of visual cross-modal re-organization. This finding is consistent with previous reports of cross-modal recruitment of auditory cortex for visual processing in adults with mild-moderate hearing loss using the same stimulus (Campbell & Sharma, 2014), in adults with mild-moderate hearing loss using a different visual paradigm (Stropahl & Debener, 2017), and in deaf adults (Doucet et al., 2006; Sandmann et al., 2012). In addition to pre-treatment evidence of visual cross-modal re-organization, the hearing loss group also

exhibited unexpected left pre-frontal and frontal cortex (including orbitofrontal gyrus, Broadmann area 11) for the N1 and P2 CVEP components. Frontal and pre-frontal cortex recruitment has been reported in deaf subjects in one previous study (Bola et al., 2017), and may reflect alterations in visual attention and cognitive processing (Li et al., 2013; Paneri & Gregoriou, 2017; Reuter-Lorenz & Cappell, 2008).

Within 6 months of hearing aid use, however, we observed a reduction in auditory cortex recruitment for higher-level N1 and P2 CVEP components, suggestive of a reversal in visual cross-modal re-organization. This result is consistent with the Hypothesis 1 outlined in Specific Aim 1 (Section 3.1). In addition, we observed a decrease in frontal and pre-frontal cortex activation at post-treatment testing. Post-treatment CDR results in the hearing loss group are comparable those results observed in the normal hearing group at baseline evaluation (Study 1, Chapter 2, Figure 5), and indicating that restored audibility from hearing aids may promote more typical visual cortical processing patterns.

To our knowledge, this study is the first to document reduction in cross-modal re-organization of auditory cortex following clinical intervention with hearing aids in adult-onset, mild-moderate, age-related hearing loss. This finding is consistent with pediatric case study evidence in a pediatric case of single-sided deafness (Sharma et al., 2016), where treatment with a cochlear implant resulted in partial reversal in cross-modal recruitment of auditory cortex by vision within approximately 2 years of audiological intervention. Our results are also consistent with unpublished data from our laboratory, in which some adults with single-sided deafness exhibit restoration of more typical visual cortical processing patterns following clinical intervention with cochlear implants. This finding is also supported by the deaf adult cochlear implant literature. For example, deaf cochlear implanted adults with good auditory speech perception outcomes exhibit less diffuse activity in auditory cortex for visual motion processing, compared to deaf cochlear implanted adults with poorer

auditory speech perception outcomes who exhibit more diffuse activity in auditory and visual cortex for visual motion processing (Doucet et al., 2006).

Evidence of a reversal in cross-modal re-organization following audiological intervention in our study is in previous studies in cochlear implant recipients, where pre- and post-lingually deafened adults exhibit persistent visual cross-modal re-organization even after cochlear implantation (Chen et al., 2016; Rouger et al., 2012; Sandmann et al., 2012; Stropahl et al., 2015). However, our study sample of adults with age-related hearing loss have substantially less severe hearing loss (and likely much shorter duration of hearing loss) compared to deafness. Because we observed a correlation between amount of visual cross-modal re-organization and degree of hearing loss (Figure 10), it is possible that visual cross-modal re-organization may be less 'reversible' in greater degrees of hearing loss.

While the mechanisms underlying reversal in cross-modal re-organization observed in our hearing loss group is poorly understood, it is possible that increased audibility may restore more typical balance in excitation and inhibition in the auditory cortex, where upregulation of inhibition may decrease sensitivity of auditory cortical neurons to multi-modal or non-auditory inputs (e.g. visual and somatosensory inputs), thus decreasing cross-modal recruitment of auditory cortex for visual processing (Mao & Pallas, 2013). Taken together, cortical source localization patterns from our study provide objective neurophysiological evidence that restored audibility may promote more typical visual cortical processing patterns, reversing cross-modal re-organization in mild-moderate hearing loss.
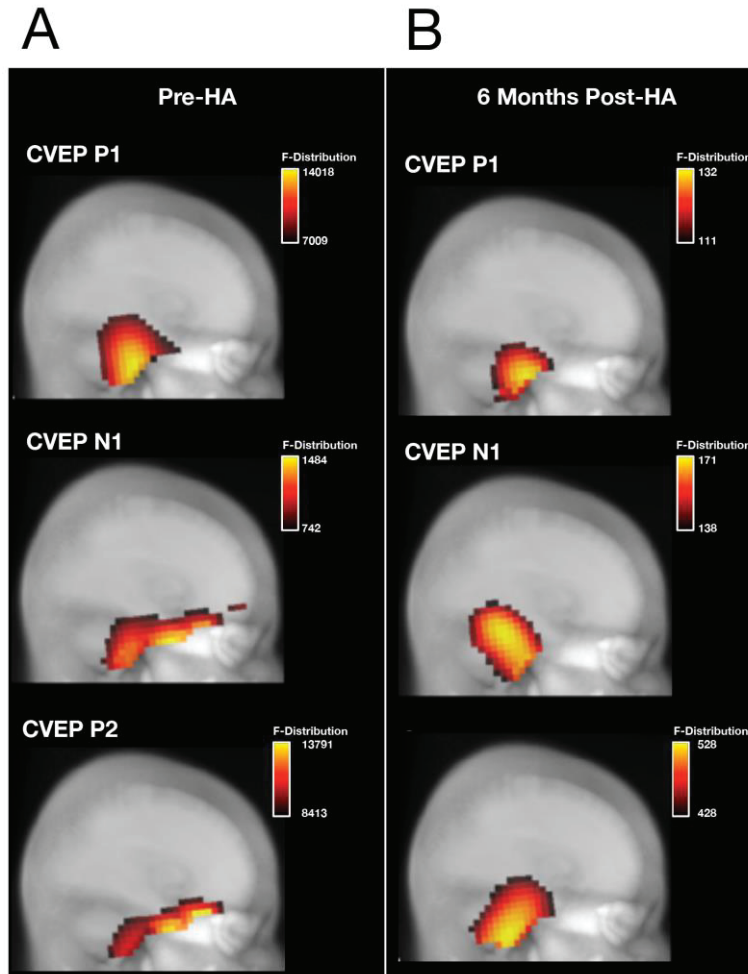
Figure 14. Effects of Treatment with Hearing Aids on Cortical Source Activation Patterns Elicited by Visual Motion Stimuli in Age-Related Hearing Loss. Current density source reconstructions (CDR) for the P1, N1, and P2 cortical visual evoked potential components are depicted for the group of adults with untreated age-related hearing loss assessed pre-treatment before hearing aid fitting (pre-HA) (n=28) and a sub-group of these adults (n=21) assessed post-treatment after 6 months of hearing aid use (post-HA). 3D current density source reconstructions obtained via standardized low-resolution brain electromagnetic tomography (sLORETA) are projected on a 2D depth-buffered structural magnetic resonance image (Maximum Intensity Projection), providing visualization of the voxels with the highest likelihood of activation. The color scale to the right of each figure indicates the statistical likelihood of activation (F-statistic), from lowest (red) to highest (yellow) probable current density.

Component	Pre-HA		Post-HA	
	Right Hemisphere	**Left Hemisphere**	**Right Hemisphere**	**Left Hemisphere**
P1	Cerebellar tonsil, culmen, fusiform gyrus, BA 20, middle temporal gyrus, uncus, BA 36, cerebellar lingual	Cerebellar tonsil	Cerebellar tonsil, culmen, uncus, BA 20, parahippocampal gyrus, BA 36 Left Hemisphere: Cerebellar tonsil	Cerebellar tonsil
N1	Cerebellar tonsil, inferior temporal gyrus, BA 20, middle temporal gyrus, BA 21, superior temporal gyrus, BA 38, uncus, BA 28, fusiform gyrus, culmen	Inferior temporal gyrus, BA 20, middle temporal gyrus BA 21, superior temporal gyrus, BA 38, inferior frontal gyrus, orbitofrontal gyrus BA 11, cerebellar tonsil, middle frontal gyrus, BA 25, BA 47, fusiform gyrus, BA 20, uncus, BA 28, culmen	Culmen, cerebellar tonsil, declive, cerebellar lingual dentate, fusiform gyrus, BA 37, sub gyrus	Culmen, cerebellar tonsil
P2	Cerebellar tonsil, middle temporal gyrus, BA 21, inferior temporal gyrus, BA 20, superior temporal gyrus, BA 38, middle frontal gyrus, orbitofrontal gyrus, BA 11, inferior frontal gyrus, BA 47	Middle temporal gyrus, BA 21, orbital gyrus, cerebellar tonsil, superior temporal gyrus, BA 28, inferior temporal gyrus, BA 20, inferior frontal gyrus, orbitofrontal gyrus, BA 11, middle frontal gyrus, BA 47, uncus	Cerebellar tonsil, culmen	Cerebellar tonsil, culmen, parahippocampal gyrus, BA 35

Table 6. Cortical Regions of Activation Elicited by Visual Motion Stimuli in Age-Related Hearing Loss Before and After 6 Months of Hearing Aid Use. Regions of cortical source activity, including Broadmann areas (BA), are provided for the group of adults with untreated, age-related hearing loss assessed at pre-treatment with hearing aids at baseline (pre-HA) (n=28) and 6 months post-treatment with hearing aids (Post-HA) (n=21). Regions of activity are ranked in order of highest to lowest likelihood of activation (F-statistic) obtained via current density source reconstruction.

3.7.3. Treatment Effects on Speech Perception Outcomes

Consistent with Hypothesis 2 outlined in Specific Aim 2 (Section 3.1), the adults with hearing loss exhibited significant auditory speech perception benefit from clinical treatment with hearing aids. Figure 15A depicts sentence-level auditory speech perception in noise scores on the QuickSIN™ test with corresponding 95% confidence intervals at pre-treatment and post-treatment test sessions. Treatment with hearing aids resulted in a significant improvement in auditory speech perception in noise performance with hearing aid treatment $(t(20)=4.643, p<0.001)$. Unaided QuickSIN™ scores for the hearing loss group assessed pre-treatment at baseline indicated a mild dB SNR loss (M=6.05 dB SNR, SD=5.11), while aided QuickSIN™ scores assessed post-treatment at 6-month follow-up indicated a 3.6 dB SNR improvement (M=2.40 dB SNR, SD=2.15). While the average pre-treatment QuickSIN™ score is indicated a mild dB SNR loss (3-7dB SNR), or a mild auditory deficit in background noise, the post-treatment score is considered a normal threshold (0-3 dB SNR), indicative of 'normal' auditory speech perception in background noise comparable to normal hearing adult subjects. The improvement of auditory outcome with hearing aid treatment provides objective evidence of restored audibility with hearing aids in terms of real-world speech perception outcomes in background noise.

Contrary to the hypothesis outlined in Hypothesis 2 in Specific Aim 2 (Section 3.1), we observed no effect clinical treatment with hearing aids on auditory-visual integration. Figure 15B depicts sentence-level visual (lip-reading) benefit for auditory-visual speech perception in noise on the AzAv test, as well as corresponding 95% confidence intervals at pre-treatment and 6-month post-treatment test sessions in the hearing loss adults. Hearing loss adults performed similarly across pre- and post-treatment test sessions on the AzAv test $(t(20)=-0.203, p=0.841)$. Average benefit from visual cues pre-treatment at the baseline

evaluation (acutely aided condition) was 36.93% (SD=9.69) and average benefit from visual cues at 6-month post-treatment follow-up (aided condition) was 37.66% (SD=13.92). Based on this finding, hearing aid treatment did not modify auditory-visual integration in age-related hearing loss. However, given that adults with hearing loss did not have an advantage in lip-reading at the pre-treatment baseline compared to normal hearing listeners, it was not entirely unexpected that there would be no change in their results after treatment.
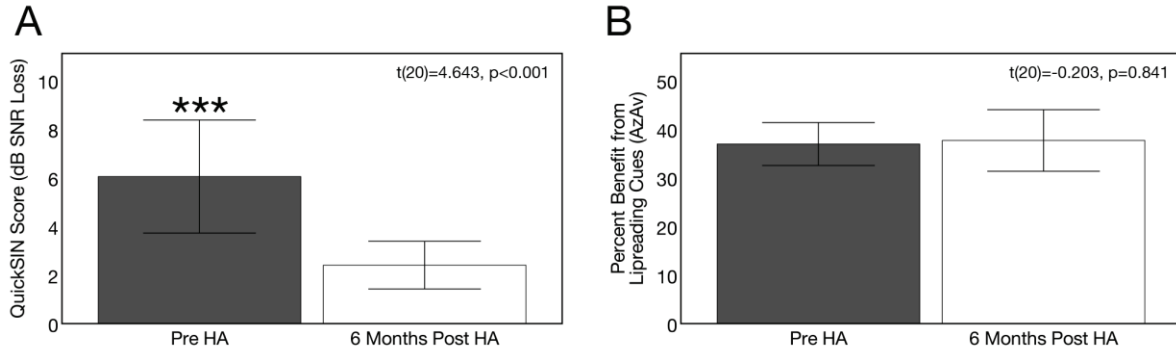
Figure 15. Effects of Treatment with Hearing Aids on Auditory Speech Perception in Noise. Average scores on speech perception measures in the age-related hearing loss group pre-treatment (gray) and 6-months post-treatment with hearing aids (Post HA) (white). Black bars indicate 95% confidence intervals for each group. Asterisks indicate level of significance (***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.05$). **Panel A.** Average binaural auditory speech perception in noise scores (QuickSIN™) before and after hearing aid treatment. Scores are plotted in terms of the dB signal-to-noise ratio loss (dB SNR), representing the dB SNR required for the participant to score 50% of words in a sentence correct relative to normal hearing listeners. A higher score indicates poorer auditory speech perception in noise performance. The dotted line indicates the cutoff score (3 dB SNR) for normal function in background noise. The hearing loss group exhibited significant improvements in auditory speech perception in noise after treatment with hearing aids. **Panel B.** Average benefit from visual (lip-reading) cues on a binaural auditory-visual speech perception in noise test (AzAv). Scores indicate the percent difference score in an auditory-only condition relative to an auditory-visual condition, where a higher score indicates greater benefit from the addition of visual (lip-reading) cues. No significant difference in lip-reading benefit was observed between pre-post intervention test sessions in the hearing loss group.

3.7.4. Treatment Effects on Cognitive Outcomes

Hearing aid use was associated with significant improvements in specific domains of cognitive function across 6 months of hearing aid use, consistent with Hypothesis 3 outlined in Specific Aim 3 (Section 3.1). Results are depicted in Figure 16. A 1.62 point improvement in global cognitive function (MoCA) score was observed after 6 months of hearing aid use compared to pre-treatment, and this improvement was statistically significant ($t(20)=2.878$, $p=0.009$). Average improvement in executive function (BDS-2) after 6 months of hearing aid use was 3.09 points higher than pre-treatment scores, and this improvement was also significant at the $\alpha=0.01$ level ($t(20)=5.253$, $p<0.001$). Significant improvements in processing speed (SDMT) by 4.52 points ($t(20)=4.209$, $p<0.001$) and visual working memory (RST) by 5.30 percentage points ($t(20)=4.121$, $p=0.001$) were observed. The only measure where a significant improvement in cognitive outcomes was not observed post-treatment was on the auditory working memory (WARRM) measure ($t(20)=1.072$, $p=0.296$). It is possible that treatment effects on the WARRM test were not observed due to participant fatigue, as the WARRM test was the final test administered in the cognitive test battery at pre-test and post-test sessions. Anecdotally, many hearing participants reported fatigue during the WARRM test at both the pre-treatment and post-treatment test sessions due to its length and difficulty with increased set side. The creators of the WARRM test are currently working on developing a shortened version of the WARRM test, which may prove more feasible in a clinical setting.

In summary, clinical treatment with hearing aids in our study sample yielded significant improvements in the domains of global cognitive function, executive function, processing speed, and visual working memory over 6 months of hearing aid use. These results

indicate that early-intervention with hearing aids in the mild-moderate stages may enhance neurocognitive function.

Our findings are in contrast to reported results in a randomized crossover pilot study by Nkyekyer et al. (2019), in which a group of adults with hearing loss (n=40) fit with hearing aids did not show improvements in cognitive function with over 3 months of hearing aid use. However, cognitive function in that study was assessed across a much shorter duration of hearing aid use, and researchers assessed different cognitive sub-domains (reaction times, immediate and delayed recall, spatial working memory, and contextual memory) compared to our study. Our findings are supported by experimental evidence by Deal et al. (2017) and Karawani et al. (2018a), where hearing aid treatment over longer durations (>6 months) in similar age-related hearing loss populations resulted in significant improvements in cognitive function the cognitive domains of global cognitive abilities and processing speed (Deal et al., 2017) and working memory (Karawani et al., 2018). Further, our findings are supported by longitudinal evidence documenting long-term neurocognitive benefit in deaf adult cochlear implant recipients at 6-months and 1-year post treatment in the domains of global cognitive function, memory, and executive function (Mosnier et al., 2015a).
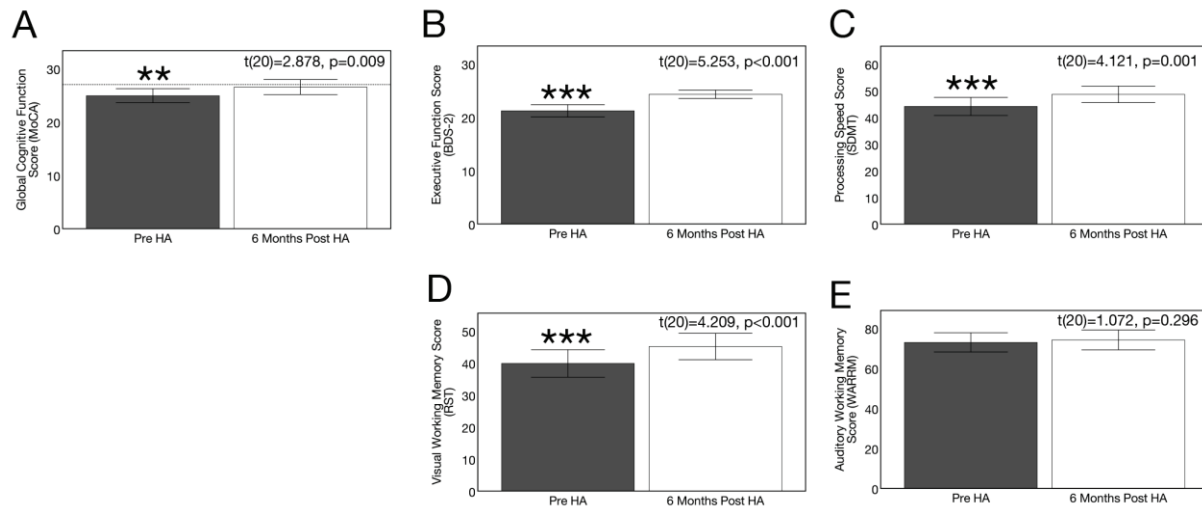
Figure 16. Effects of Treatment with Hearing Aids on Cognitive Function in Age-Related Hearing Loss Across 6 Months of Hearing Aid Use. Average scores on cognitive measures in the age-related hearing loss group (n=21) are depicted pre-treatment (gray) and 6-months post-treatment with hearing aids (white). Black bars indicate 95% confidence intervals for each group. Asterisks indicate level of significance (***$p \leq 0.001$, **$p \leq 0.01$, *$p \leq 0.01$). **Panel A. Average global cognitive function on a global cognitive screening measure (MoCA).** Higher scores in indicate higher global cognitive function, out of a total possible score of 30 points. The dotted reference line on the y-axis indicates the cutoff score (≤ 27) indicating risk for mild cognitive impairment. A significant improvement in MoCA score was observed post-treatment in the hearing loss group. **Panel B. Average executive function score (BDS-2).** Higher scores in indicate better executive functioning, out of a total possible score of 27 points. A significant improvement in executive function score was observed post-treatment in the hearing loss group. **Panel C. Average processing speed score (SDMT).** Higher scores in indicate faster processing speeds in a timed, 90-second digit-symbol matching task A significant improvement in processing speed was observed post-treatment in the hearing loss group. **Panel D. Average visual working memory score (RST) in percent words correctly recalled.** Higher scores indicate higher visual working memory performance in a dual-task paradigm. A significant improvement in visual working memory recall was observed post-treatment in the hearing loss group. **Panel E. Average auditory working memory score (WARRM) in percent words correctly recalled.** Higher scores indicate higher auditory working memory performance in a dual-task paradigm. No significant improvement in auditory working memory recall was observed post-treatment in the hearing loss group. **Note:** Cognitive testing in the hearing loss group was administered in the same condition across pre-treatment (acutely aided) and post-treatment (aided) test sessions to ensure similar pre-post test conditions and to reducing potential confounding effects of audibility on cognitive performance at the pre-treatment visit.

3.7.5. Correlational Analyses

We examined the association of pre-treatment neurophysiological outcomes with post-treatment speech perception and cognitive outcomes using Pearson's correlation analyses to examine whether CVEP latencies over the right temporal ROI pre-treatment were predictive of behavioral outcomes after 6 months post-treatment with hearing aids. Figure 17 depicts the association between pre-treatment CVEP latencies and post-treatment QuickSIN™ scores in the hearing loss group. As predicted Hypothesis 4 in Specific Aim 4 (Section 3.1), a significant negative correlation was observed between pre-treatment CVEP latencies in the right temporal ROI and auditory speech perception in noise outcomes on the QuickSIN™ for the P1 ($r=-743$, $p<0.001$) (Figure 9A), N1 ($r=-0.643$, $p<0.001$) (Figure 9B), and P2 ($r=-0.532$, $p<0.001$) components (Figure 17). This finding suggests that pre-treatment cross-modal recruitment of auditory cortex for vision is predictive of post-treatment auditory outcomes, where poorer auditory outcomes (greater difficulty in background noise) is associated with more cross-modal re-organization.

There was no association between pre-treatment CVEP latencies over the right temporal ROI and dependence on visual (lip-reading cues) post-treatment for correlations with P1, N1, and P2 latencies. Further, there was no significant association between pre-treatment CVEP latencies over the right temporal ROI and outcomes on any of the 5 cognitive measures (MoCA, BDS-2, SDMT, RST, WARRM) for correlations with P1, N1, and P2 latencies. The fact that pre-treatment visual cross-modal re-organization was associated with post-treatment auditory outcomes but not dependence on lip-reading cues suggests that the primary driver in visual cross-modal re-organization (and the reversal in cross-modal re-organization via audiological intervention) is restored auditory input, rather than functional changes associated with alterations in dependence on lip-reading or face processing, at least in the case of adult-onset, mild-moderate hearing loss.

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Together, these results indicate that pre-treatment visual cortical cross-modal re-organization (as indexed by earlier CVEP latencies over right temporal cortex) is predictive of post-treatment auditory outcomes, but not post-treatment dependence on visual (lip-reading) cues or cognitive outcomes. Results are consistent with Strelnikov et al. (2013), which showed that pre-treatment visual-driven cortical activity over the right superior temporal gyrus (auditory cortex) was negatively associated with auditory speech perception outcomes 6 months post-treatment in post-lingually deafened adults receiving cochlear implants. That is, greater activity over the right auditory cortex pre-treatment was associated with poorer auditory outcomes in deaf adults 6-months post-treatment. This result suggests that baseline visual cross-modal re-organization may limit auditory speech recovery following intervention with hearing aids.

Further, while Strelnikov et al. (2013) observed a significant positive correlation between pre-treatment visual-driven cortical activity over the right superior temporal gyrus (auditory cortex) and post-treatment auditory-visual speech perception outcomes in their deaf subjects, we found no such association in our mild-moderate hearing loss group. While researchers in the aforementioned study maintained that the cross-modal recruitment of auditory cortex was hence an 'adaptive' strategy in deafness, helping to maximize real-world (auditory-visual) performance outcomes, this was not the case in our mild-moderate hearing loss group. Our results support the notion that deprivation-induced visual cross-modal re-organization is present in untreated, early-stage hearing loss, but is not related to functional dependence on vision. In fact, earlier pre-treatment CVEP latencies were associated with poorer cognitive outcomes in our mild-moderate hearing loss group at baseline, suggesting that alterations in sensory cortical processing (at least in early-stage, mild-moderate hearing loss) may actually have 'maladaptive' consequences on cognitive functioning, as well as auditory speech in noise outcomes.
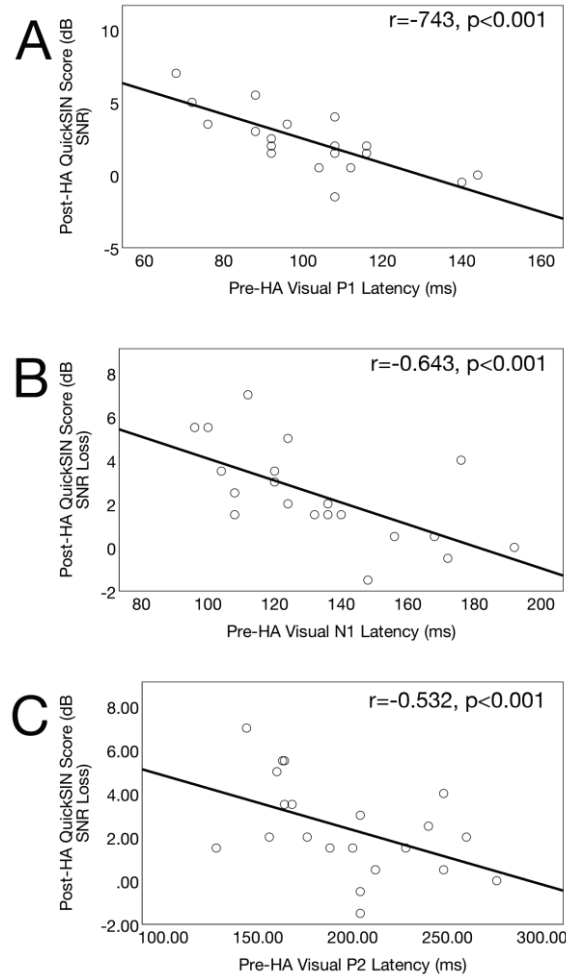
Figure 17. Association Between Pre-Treatment Cortical Visual Evoked Potential Latencies and Post-Treatment Auditory Speech Perception in Noise Outcomes in Age-Related Hearing Loss. Correlations between pre-treatment neurophysiological outcomes and post-treatment speech perception outcomes are shown for a group of adults with hearing loss (n=21) who received treatment with hearing aids. CVEP peak latencies (in milliseconds) for the P1 (**Panel A**), N1 (**Panel B**), and P2 (**Panel C**) CVEP components over a right temporal region of interest are displayed on the horizontal axis and performance 6-month post-treatment binaural aided auditory speech perception in noise outcomes (QuickSIN™ score) is depicted on the vertical axes. QuickSIN™ scores are plotted in terms of the dB signal-to-noise ratio loss (dB SNR), representing the dB SNR required for the participant to score 50% of words in a sentence correct relative to normal hearing listeners. A higher score indicates poorer auditory speech perception in noise performance. Earlier pre-treatment P1 CVEP latencies (an index of visual cross-modal re-organization) are predictive of poorer post-treatment auditory outcomes.

3.7.6. Hearing Aid Outcomes

At 6-month post-treatment follow-up testing, hearing aid outcomes were assessed in the hearing loss treatment group using several questionnaires. Results from the COSI, IOI-HA, and SADL hearing aid outcomes measures are depicted in Figures 18-20.

For the COSI hearing aid outcome measure, hearing loss participants were asked to identify 5 specific listening situations where they would like to see improvement with hearing aids. 6 months post-treatment, participants were asked to rate improvement with hearing aids in each of the situations on a 5-point scale (1=worse, 2=no difference, 3=slightly better, 4=better, and 5=much better) and their final hearing ability with hearing aids in each of the situations on a 5-point scale (1=hardly ever, 2=occasionally, 3=half the time, 4=most of the time, and 5=almost always). Average outcome ratings across all hearing loss participants and situations are depicted, with a higher average rating indicating more favorable outcome. Average improvement rating with hearing aids was 4.09 (sd=0.60) on the COSI, indicating of significant improvements with hearing aid use across the individual listening situations identified by hearing loss participants (Figure 18). Average final ability with hearing aids was 4.49 (sd=0.44) indicating that participants were able to hear most of the time (>75%) in the specific listening situations they identified as most important to them (Figure 18). Results from the COSI indicate high levels of benefit from clinical treatment with hearing aids in the areas of life most important to individual hearing loss participants.

Higher Score Indicates More Favorable Outcome
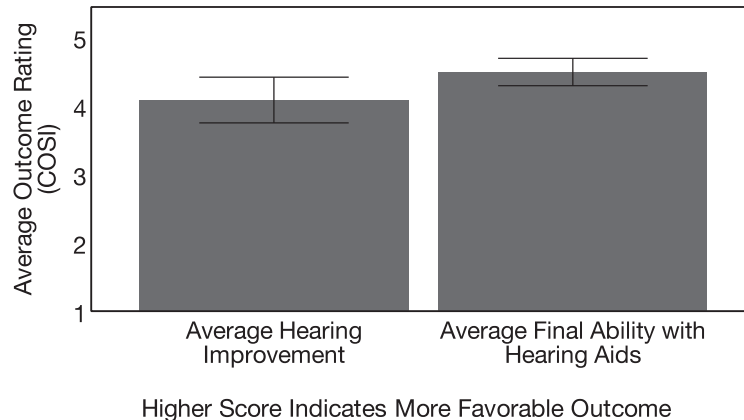
Figure 18. Hearing Aid Outcomes on the Client Oriented Scale of Improvement (COSI).
Pre-treatment, hearing loss participants (n=21) identified 5 specific listening situations where they wanted to see improvement with hearing aids. 6 months post-treatment, participants were asked to rate improvement with hearing aids in each of these situations on a 5-point scale (1=worse, 2=no difference, 3=slightly better, 4=better, and 5=much better) and their final hearing ability to hear with hearing aids in each of these situations on a 5-point scale (1=hardly ever, 2=occasionally, 3=half the time, 4=most of the time, and 5=almost always). Average outcome ratings across all hearing loss participants are depicted, with a higher average rating indicating more favorable outcomes. Hearing loss participants exhibit significant improvements with hearing aid use in the listening situations identified as most important to them, and can hear 'most of the time' (>75%) in the listening situations identified as most important to them. These results provide subjective data of benefit from clinical treatment of mild-moderate, age-related hearing loss.

For the IOI-HA hearing aid outcome measure participants were asked to provide a rating for 7-items assessing daily use of hearing aids, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others, and quality of life at the 6-month post-treatment visit. Ratings were provided on a 5-point scale, where a lower score indicates poorer outcome and a higher score indicates higher outcome for each item. Average global improvement rating was 4.33 (sd=0.38), indicating significant benefit from hearing aid use (Figure 19). An additional 8th item on the IOI-HA test probed participant's self-reported hearing difficulty on a 5-point scale (1=severe, 2=moderately-severe, 3=moderate, 4=mild, 5=none), where a higher score indicates less self-perceived difficulty. Based on the results, the average self-reported difficulty on item 8 of the IOI-HA was 3.19 (SD=0.75), indicative of moderate self-reported hearing difficulty in background noise (Figure 19). Average global score across items 1-7 on the IOI-HA was 4.33 (SD=0.38). Average scores across items 1-7 were 4.47 (SD=0.60) for the use sub-score, 4.19 (SD=0.99) for the benefit sub-score, 4.10 (SD=0.54) for the residual activity limitation sub-score, 4.67 (SD=0.67) for the satisfaction sub-score, 4.38 (SD=1.07) for the participation sub-score, 4.57 (SD=0.68) for the impact on others sub-score, and 3.95 (SD=9.92) for the quality of life sub-score (Figure 19). These results were compared to normative data in adults with moderate-severe sensorineural hearing loss reporting "moderate" hearing problems on item 8 reported in Cox, Alexander, & Byer (2003). Results from our study participants are comparable these norms across all 7 sub-scores, even though our study participants had slightly lesser degrees of hearing loss (mild-moderate in severity). Results provide evidence of real-world effectiveness of hearing aid intervention in the mild-moderate stages of age-related hearing loss.

Higher Score Indicates More Favorable Outcome
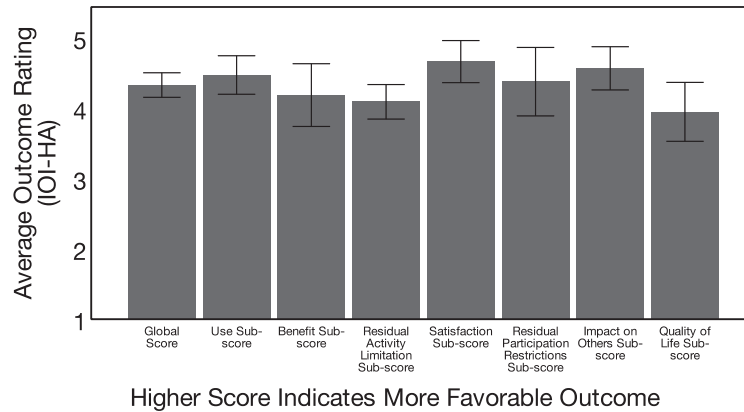
Figure 19. Hearing aid Outcomes on the International Inventory of Hearing Aids (IOI-HA). Hearing loss participants (n=21) were asked to provide a rating for 7-items assessing daily use of hearing aids, benefit, residual activity limitations, satisfaction, residual participation restrictions, impact on others, and quality of life at the 6-month post-treatment visit. Ratings were provided on a 5-point scale, where a lower score indicates poorer outcome and a higher score indicates higher outcome for each item. Average global improvement rating was 4.33 (sd=0.38) and sub-scores were also high, providing subjective evidence of benefit from hearing aid treatment.

For the SADL hearing aid outcome measure, participants are asked to indicate the relative benefit on each item assessing satisfaction with hearing aids on a 7-point scale across the domains of positive effects, service, negative features, and personal image. Higher scores indicate greater self-perceived satisfaction. Average global score on the SADL was 5.68 (SD=0.60) (Figure 20). Average positive effect sub score was 5.15 (SD=1.02), average service sub-score was 6.26 (SD=0.83), average negative feature sub-score was 5.51 (SD=1.32), and average self-image sub-score was 6.24 (SD=0.75) (Figure 20). Comparison of our results against normative data reported in Cox and Alexander (2001) indicate global scores and sub-scores above the 50th percentile, and service sub-score and negative features sub-scores falling above the 80th percentile for adults with similar degree of hearing loss. Results provide evidence of high levels of hearing aid satisfaction with hearing aid intervention. Outcomes from the hearing aid questionnaires provide evidence of high levels of satisfaction with hearing aid treatment in our group of adults with mild-moderate hearing loss.
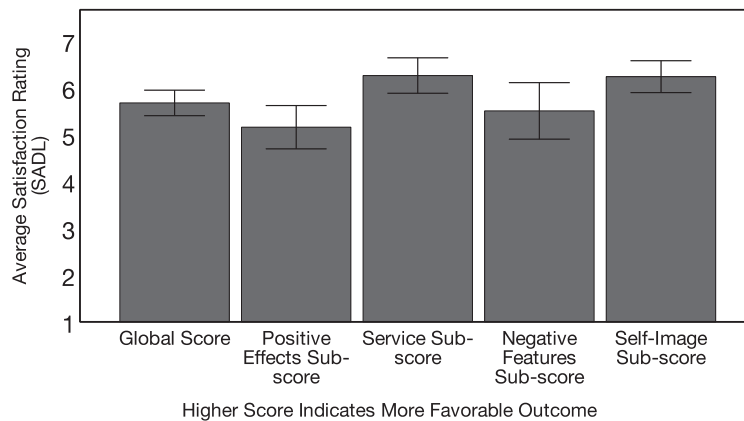
Figure 20. Hearing Aid Outcomes on the Satisfaction with Amplification in Daily Life Questionnaire (SADL). Hearing loss participants were asked to provide a rating for 15 items assessing positive effects of hearing aid use, service, negative features, and personal image on a 7-point scale at the 6-month post-treatment follow-up. Lower scores indicate poorer outcomes and higher scores indicate more favorable outcomes. Average global score was 5.68 (SD=0.60) and sub-scores were also high, indicating high levels of self-perceived satisfaction with hearing aids in early-stage, mild-moderate age-related hearing loss.

4. Summary

Overall, the goal of this investigation was to explore the relationship between cortical visual cross-modal re-organization and speech perception and cognitive outcomes in early-stage, age-related hearing loss (Study 1), and to assess treatment effects with well-fit hearing aids on these outcomes within the hearing loss group (Study 2). A main finding from Study 1 was evidence of cross-modal recruitment of auditory cortex by vision in mild-moderate, age-related hearing loss. While cross-modal re-organization was originally believed to be a phenomenon restricted to severe-profound hearing loss (e.g. deafness) (Bavalier & Neville, 2000), our results support a growing body of evidence that even mild auditory deprivation may induce compensatory changes in cortical resource allocation for sensory processing (Campbell & Sharma, 2014; Stropahl & Debener, 2017). Given recent evidence that degradation in auditory function may induce peripheral and central changes in the auditory system not detectible through conventional audiometric tests (Kujawa & Liberman, 2009, 2011), the identification of neurophysiological biomarkers (e.g. visual cross-modal re-organization) may become valuable clinical tools to detect "hidden hearing loss." Neurophysiological biomarkers of auditory dysfunction may also help audiologists determine the optimal time to recommend audiological intervention.

Second, our results indicate that untreated mild-moderate hearing loss is associated with deficits in auditory speech perception in noise and cognitive performance. Cognitive deficits were observed across the domains of global cognitive function, executive function, processing speed, visual working memory, and auditory working memory in the untreated hearing loss group. Auditory and cognitive outcomes were significantly correlated with visual cross-modal re-organization, such that earlier latencies (considered a marker of visual cross-modal recruitment of auditory cortex for visual processing) were associated with poorer

auditory speech perception and cognitive performance. This finding is consistent with the cognitive load theory, whereby decreased audibility and/or degraded auditory input in hearing loss taxes the brain, inducing alterations in compensatory cortical resource allocation (e.g. visual cross-modal re-organization) which are correlated with negative impacts on cognitive function.

Interestingly, untreated, age-related hearing loss was not associated with enhanced benefit from visual (lip-reading) cues, and further, there was no correlation between lip-reading benefit and cortical visual evoked potential latencies (considered a marker of visual cross-modal recruitment of auditory cortex for visual processing). The fact that we did not observe a correlation between visual cross-modal re-organization and dependence on lip-reading cues in the hearing loss group suggests that cross-modal re-organization may be driven by deprivation to auditory cortex itself, rather than functional reliance on lip-reading or facial cues, at least in the early stages of hearing loss. Since strong correlations between lip-reading benefit and visual cross-modal re-organization have been reported in deafness but not mild-moderate hearing loss (Strophal & Debener, 2017), it is possible that enhanced lip-reading benefit may be a 'learned' or 'acquired' skill developing only after degree of hearing loss has significantly impaired speech comprehension, or after extended duration of hearing loss. While visual cross-modal neuroplasticity has been argued as an 'adaptive' compensatory strategy in deafness (Strelnikov et al., 2013), visual cortical cross-modal re-organization was related to negative impacts on auditory speech perception and cognitive performance in our group of adults with age-related hearing loss. Future studies should systematically evaluate the relationship between visual cross-modal re-organization, lip-reading benefit, and cognitive function by degree of hearing loss.

In Study 2, we examined the effects of clinical treatment with well-fit hearing aids in age-related hearing loss over the course of 6 months of hearing aid use. A main finding in

this study was a reversal in visual cross-modal re-organization after clinical intervention with hearing aids. To our knowledge, this is the first study to provide evidence that restored audibility with hearing aids may reverse compensatory changes in cortical resource allocation and promote typical more typical visual sensory processing patterns. Further, the reversal in cross-modal re-organization we observed following treatment with hearing aids coincided with gains in auditory speech perception in noise and cognitive performance. Thus, beyond the known benefits hearing aid use in improving speech perception and communication, our results provide preliminary evidence that hearing aid use can enhance cognitive function.

The reversal in visual cross-modal re-organization that we observed following hearing aid treatment may reflect restoration of more typical excitatory-inhibitory balance in the auditory cortex once audibility is 'restored' with hearing aids. While downregulation of inhibition in auditory cortex pre-treatment may increase sensitivity to latent non-auditory or multi-modal inputs (e.g. visual input), resulting in cross-modal recruitment of auditory cortex for visual processing, restored audibility may increase inhibition in the auditory cortex, reducing take-over from non-auditory modalities.

The pre-frontal and frontal cortex recruitment for visual processing we observed in the hearing loss group pre-treatment was an unexpected finding. However, post-treatment reversal in pre-frontal and frontal cortex recruitment suggests that that restored auditory input may decrease top-down attentional or cognitive modulatory control for sensory processing, potentially reducing cognitive load.

Results from this preliminary investigation highlight the need for future randomized controlled trials that assess the impact of hearing aid intervention on cognitive outcomes in age-related hearing loss, and longitudinal studies assessing whether hearing aid use may modify long-term risk of developing dementia. Currently, less than 15% of adults who could

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benefit from hearing aids have them (Chien & Lin, 2012) and most Medicare and private insurance policies do not provide coverage for hearing aids for adults. The subjective and benefits from treatment with hearing aids in participants with mild-moderate hearing loss in this study is thus relevant from a public health perspective. Our study findings support the idea that early and timely intervention with hearing aids (e.g. in the mild-moderate stages) may provide the best chance of promoting typical cortical sensory functioning and good prognostic cognitive and behavioral outcomes.

Interestingly, the extent of visual cross-modal re-organization of auditory cortex pre-treatment (as indexed by earlier cortical visual evoked potential latencies) were predictive of auditory speech perception in noise outcomes 6-months post-treatment. This finding suggests that there may be an upper limit to reversing compensatory changes in cortical resource allocation. That is, recovery of auditory speech perception abilities after clinical intervention may be limited by the extent to which auditory cortex has become 're-purposed' by vision. For the small percentage of adults with age-related hearing loss who do seek treatment, treatment is typically delayed 7-10 years after hearing loss onset (Davis et al., 2007). Thus, audiological intervention with hearing aids is likely introduced to a central auditory system that has extensively re-organized, potentially limiting auditory outcomes post-treatment. It is possible that these alterations in visual cross-modal re-organization (or other changes in cortical resource allocation) may contribute to the wide variability in outcomes observed in adults with hearing loss who receive treatment.

Results from this study also carry important implications on innovation in aural rehabilitation for adults. In our study, participants were fit with hearing aids but received no additional rehabilitation services beyond intervention with hearing aids. Future studies should evaluate whether intervention coupled with additional rehabilitation (e.g. auditory training) may help maximize auditory function once hearing has been 'restored' with hearing

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aids. If the extent of cross-modal re-organization is a limiting factor of post-treatment auditory outcomes, then aural rehabilitation or other therapeutic techniques may help maximize auditory performance outcomes when coupled with an intervention.

Finally, study findings highlight the clinical utility of cognitive testing in the audiology setting. If treatment with hearing aids can modify cognitive function, then measuring cognitive abilities before and after intervention may be a valuable clinical tool. For example, cognitive assessment tools may help audiologists make better recommendations regarding when a patient should receive intervention, what kind of intervention or rehabilitation plan is ideal, and assessment of whether a selected intervention or rehabilitation method is providing sufficient benefit.

Perhaps the most remarkable ability of human brain is its capacity for change. Ultimately, audiological intervention relies on the principles of neuroplasticity, the ability for the brain to adapt to restored sensory input. As a profession, we are just beginning to unearth the widespread effects of hearing loss on the brain, including the impact of hearing loss on cognitive function, as well as functional changes in cortical resource allocation, including visual cortical cross-modal re-organization. With a more solid understanding of the mechanisms of neuroplasticity and cognitive function in age-related hearing loss, this may help clinicians harness neuroplasticity to optimize treatment outcomes for their patients. Further, research in this area may lead to the development of better clinical tools to detect early neural changes associated with auditory dysfunction and metrics useful in guiding clinical intervention and rehabilitation.

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