Auditory-cognitive Associations in Older Adults: Differential Effects of Sex, Test Modality, and Hearing Measures

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A Thesis
In the Department
of
Psychology

Presented in Partial Fulfillment of the Requirements
For the Degree of Doctor of Philosophy (Psychology) at
Concordia University

Montreal, Quebec, Canada
JUNE 2022

CONCORDIA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

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Entitled: Auditory-cognitive Associations in Older Adults: Differential Effects of Sex, Test M

and submitted in partial fulfillment of the requirements for the degree of

Doctor Of Philosophy Psychology

complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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ABSTRACT

Auditory-cognitive associations in older adults: Differential effects of sex, test modality, and hearing measures

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Concordia University, 2022

This dissertation presents findings that address auditory-cognitive associations in older adults with hearing loss (HL), particularly with regards to sex-related differences in said associations. Manuscript I (Chapter 2) reports the psychometric properties of the Montreal Cognitive Assessment scale (MoCA) when hearing-related items are excluded from scoring (MoCA-Modified). This involved a cross-sectional analysis of the original MoCA validation study data in healthy older adults, older adults with mild cognitive impairment (MCI), and older adults with mild Alzheimer's disease (AD). Our findings showed that, compared to the original MoCA, MCI sensitivity was substantially reduced when all auditory subtests were omitted, with the biggest contribution to the reduction coming from the delayed recall subtest. This Chapter highlights the contribution that hearing-dependent subtests have on the accuracy of the MoCA.

Manuscript II (Chapter 3) examines sex-related differences in the associations between MoCA scores and pure-tone average (PTA) in healthy older adults. MoCA-Modified scores were also calculated for all participants to assess the contribution of hearing-dependent items. Results showed that women with normal hearing were more likely to pass the MoCA compared to their counterparts with HL. In contrast, no associations were observed in men. Regression analysis

showed an interaction between sex and PTA in the worse ear. PTAs were significantly correlated with both MoCA and MoCA-Modified scores in women, but not in men. This suggests significant sex-related differences in auditory-cognitive associations even when hearing-related test items are omitted.

Manuscript III (Chapter 4) examines sex-related differences in auditory-cognitive associations in a sample of individuals with MCI. In this cross-sectional analysis, we examined sex-related differences in hearing, as measured by both PTA and the Canadian Digit Triplet Test (CDTT), and cognition, as measured by the MoCA, Rey Auditory Verbal Learning (RAVLT), and the Brief Visuospatial memory test (BVMT-R). Women with better hearing on either measure outperformed their worse hearing counterparts on the MoCA. Women with normal hearing showed correlations between CDTT SRTs and MoCA and RAVLT scores. Men but not women showed an effect of hearing on the BVMT-R. Generally, this dissertation points to the existence of sex-related differences in auditory-cognitive associations and discusses potential mechanisms that underly these observations, including the common cause and information degradation hypotheses.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my parents, who carried me on their back for 15+ years while I completed my higher education in Canada. I would not be where I am now without them. I love you mam, bab. To my reliable brother Ahmad and my fabulous sister Dana, thank you both for being in my life and indulging me in my silliness.

To my partner and wife, Averil, whom I love a lot more than I love this thesis (and I do love this thesis quite a bit), thank you for being the best person that ever happened to me. Thank you for supporting me when I'm down and congratulating me when I'm up.

To all my lab mates, especially Samantha B, Kristina C, and Sana S, thank you for all your help, ideas, and guidance over the years. Most importantly thank you for always making me laugh.

To my supervisor, Dr. Natalie Phillips, I can't even begin to describe how grateful I am that you allowed to me to be part of your lab so many years ago. It has been a life-changing experience filled with moments of learning, adaptation, laughter, joy, hard work, and everything in between. Thank you for your infinite patience, your constant humour, and most importantly, thank you for always treating me with dignity and respect.

I would also like to thank the members of the Canadian Consortium on Neurodegeneration in Aging (CCNA) Team 17 for always providing me with support and wisdom. Finally, I would like to acknowledge and thank my personal funding sources over the course of the dissertation (FRSQ, The Perform Centre, Concordia University) without which my research would not have been possible.

CONTRIBUTION OF AUTHORS

For the three studies included in this thesis, my supervisor Dr. Natalie Phillips and I collaboratively decided on the research question and experimental design, performed the necessary statistical analyses, and wrote the manuscript. Additional contributions are listed below.

Manuscript I

Dr. Natalie Phillips is an author on the original study (Nasreddine et al., 2005) from which data are used and contributed to the current study concept and design, analysis and interpretation of the data, and preparation of the manuscript. Dr. M. Kathleen Pichora-Fuller contributed to the interpretation of data and preparation of the manuscript.

Manuscript II

This study used data collected by Dr. Karen Li and Dr. Halina Bruce (see Lai et al., 2017; Bruce et al., 2017, 2019 for information on the original study). Dr. Karen Li, Dr. Halina Bruce, and Dr. M. Kathleen Pichora-Fuller additionally contributed valuable critical revisions and edits to the manuscript.

Manuscript III

This study used data collected at various Canadian sites as part of the COMPASS-ND arm of the Canadian Consortium on Neurodegeneration in Aging (CCNA). Sana Rehan and Dr. Nathalie Giroud helped with data analysis and statistical troubleshooting. Dr. M. Kathleen Pichora-Fuller, Dr. Walter Wittich, Dr. Paul Mick, Dr. Nathalie Giroud, and Sana Rehan all provided valuable critical revisions and edits to the manuscript.

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CHAPTER 1

GENERAL INTRODUCTION

In the 2016 Canadian census, the number of adults aged 65 and over (hereinafter referred to as older adults or OAs) exceeded the number of children aged 14 and under for the first time in Canada (Stats Canada, 2015). While most OAs maintain normal cognitive functioning, accurately identifying cognitive decline in this aging population is important both for research looking into causes of dementia as well as health outcomes for affected individuals. Clinical screening and subsequent neuropsychological assessment are commonly used to detect conditions associated with later development of dementia, such as Mild Cognitive Impairment (MCI), a prodromal form of dementia (Petersen, 2011). However, scores on cognitive tests to screen MCI and dementia, such as the Montreal Cognitive Assessment scale (MoCA; Nasreddine et al., 2005), as well as neuropsychological test batteries, may be influenced by changes in hearing that are common in old age (Albers et al., 2015). In addition, hearing loss may itself engender cognitive changes, and thus may be a risk factor for future declines (Livingston et al., 2017, 2020). As cognitive screening tests are often used to assess possible dementia, examining their accuracy and susceptibility to sensory changes is essential. Furthermore, few studies have looked at sex-related differences in the auditory-cognitive relationship. Another finding from the aforementioned census was that older adults were mostly women, with over 20% more women than men in the over 65 bracket (Stats Canada, 2015). Yet despite this population advantage, research into auditory-cognitive relationships has been largely uninformed by sex, with most studies controlling for these variables without any additional analyses. Therefore, in the current set of studies, I will begin by examining the psychometric properties of the MoCA and how these might potentially be impacted by hearing loss (Manuscript I). Following this, I will examine how hearing loss affects scores on the MoCA in a sample of healthy older adults, taking care to examine potential sex-related differences in this association (Manuscript II). In the third and final

study, I will examine how hearing loss impacts the cognitive performance of individuals who are at risk for the development of dementia (MCI), including differences in scores on visual and auditory tests as well as the MoCA (Manuscript III). Our aim is to shed more light on sensory-cognitive interactions and how they are differentially manifested on screening and neuropsychological tests, in men and in women.

Cognitive Decline and Early Detection

Natural aging involves some expected decline in mental capacities such as memory, attention, and processing speed (Craik & Salthouse, 2000). These declines are minor, and generally do not interfere with functional activities. Beyond normal aging, a variety of genetic, health, and environmental factors can lead to the development of dementia – an umbrella term describing a major progressive decline in cognition that impairs the individual's functional abilities. The prevalence of dementia increases with age. Alzheimer's disease (AD), named after Dr. Alois Alzheimer, is the most prevalent type of dementia, expected to impact over 1 million Canadians within the next 20 years (Dudgeon, 2010). Individuals with AD show increased beta amyloid depositions, pathologic levels of Tau protein, and brain neurodegeneration, though I note that the first two can occur in healthy individuals without AD (see Jack et al., 2010, 2018 for review). More reliably, individuals with AD show progressive cognitive decline, most commonly in the domain of episodic memory, which through the course of the disease results in an inability to carry out activities of daily living (Albert et al., 2011). The financial impact of dementia is enormous, with the global annual cost of dementia care in 2015 being estimated at US$818 billion (Prince et al., 2015). As no cure currently exists for dementia, research has focused on prevention and early detection of disease.

Because of the potential benefits of early detection and prevention of dementia, researchers have been interested in examining risk states or prodromal forms of dementia. While the term Mild Cognitive Impairment (MCI) only appeared during the late 1990's, the concept itself has been around for many decades, being referred to as incipient dementia, benign senescent forgetfulness, and age-associated memory impairment (Kral, 1962; Levy 1994). MCI is defined as a significant decline in one or more cognitive domains that does not interfere with the individual's functional activities of daily living (Albert et al., 2011; Petersen, 2011). Most commonly, the domain impaired is memory (amnestic MCI), but other impairments have been observed, such as with executive function or language (non-amnestic-MCI; Petersen, 2011; Winblad et al., 2004). MCI's prevalence increases with age and shares many of the same risk factors as AD, including lower educational attainment, vascular risk factors, and the presence of genetic risk ApolipoproteinE (APOE) e4 genotype (Langa & Levine, 2014). MCI is considered a risk state for dementia; however, the rates of progression to dementia or AD vary as a function of testing factors. Petersen and colleagues (2001) examined several studies looking at the outcomes of individuals with MCI and found that conversion to dementia varied based on the sample age, the length of time from the initial assessment to follow-up, and the clinical settings. For example, participants recruited from a memory disorders clinic showed a higher rate of dementia conversion than those recruited via community advertising. More recently, a study by Marcos and colleagues (2016) showed that conversion from MCI to dementia in a Spanish sample of community-dwelling older adults over a 4.5 years follow-up period was 10-15%. One factor that could influence the perceived conversion rate to dementia is the neuropsychological tests used to determine the individual's level of cognitive functioning.

Belleville and colleagues (2017) recently conducted a systemic review and meta-analysis of studies using neuropsychological tests to predict progression from MCI to AD. Different cognitive measures vary in their sensitivity and specificity as well as the cognitive domains that they assess. Furthermore, as mentioned previously, the delay between assessment and follow-up can also play a role, with poor performance on some tests predicting more imminent change, while others can detect subtle changes in cognition long before the actual disorder manifests. The researchers synthesized findings from over 20 studies and found that the best predictive accuracy for progression to AD came from tests of verbal episodic memory and language (Belleville et al., 2017). This study highlights how neuropsychological tests vary in their sensitivity to MCI and prediction rates of progression to AD. This issue is often circumvented in neuropsychological testing by the use of multiple measures that assess a wide range of cognitive domains, which is often costly both in terms of time and money. Consider then the case of cognitive screening.

Older adults that notice or suspect a decline in their cognitive function often attempt to resolve this by discussing it with their family doctor or someone in a primary care setting. For nurses and physicians faced with this situation, the first line of investigation includes collecting background information about the nature of the decline, such as its severity and duration, and then administering a cognitive screening test. If the results from the cognitive screening suggest impairment, the patient could be referred for full neuropsychological testing, or the physician can use their clinical judgment to make a diagnosis (e.g., Chertkow et al., 2008). Cognitive screening tests are different from neuropsychological tests in that they are short, inexpensive, and cover a wide range of cognitive domains. However, this comes at the cost of depth. This can have serious implications for the accuracy of screening results. For example, the Mini–Mental State Examination (MMSE; Folstein et al., 1975), a common cognitive screening measure, has

relatively low sensitivity for detecting MCI (60-72%; Breton et al., 2019 meta-analysis). This is an issue as these tests are regularly used in primary care settings to establish diagnoses. One study in a German primary care setting showed that over half of the older adults with a positive cognitive screening outcome received an official diagnosis of dementia without additional neuropsychological testing (Eichler et al., 2015). This poses a risk as cognitive screening might be vulnerable to other factors, aside from cognition, that influence scores on these measures. One possibility is the presence of sensory loss.

The MoCA scale is a brief screening measure for MCI, taking around 10 minutes to administer, that assesses a wide range of cognitive functions, such as memory, learning, executive functions, language, and orientation (Nasreddine et al., 2005). While originally designed for the assessment of MCI, the MoCA has been used in the assessment of cognitive function of individuals with traumatic brain injury (TBI; e.g., de Guise et al., 2014), stroke (e.g., Dong et al., 2010), HIV–associated neurocognitive disorders (e.g., Koenig et al 2016), and many others. The MoCA has relatively high sensitivity to MCI (90%) and AD (100%; Nasreddine et al., 2005). These qualities make it ideal for use in primary care settings, where clinicians need a quick assessment of the patient's cognitive functions. While domains such as planning and executive functions are mostly assessed visually, episodic memory is assessed via a word list delayed recall test, and thus relies on adequate audition. As cognitive domains are "locked" into certain sensory modalities, valid performance on the MoCA requires both adequate hearing and vision abilities, and sensory deficits can potentially influence the individual's total score as well as future healthcare decisions.

The Auditory-Cognitive Relationship

Hearing

Hearing loss is prevalent in many middle-aged and older adults. In the US, hearing loss (HL) affects over a quarter of adults in the 60-69 age bracket and over half of those in the 70-79 age bracket (Goman et al., 2016). In Canada, recent research has shown that approximately 2.7 million individuals aged 45-85 suffered from hearing loss in 2016 (Mick et al., 2021). Age related HL (sometimes referred to as presbycusis) is the result of age-related decreases in endocochlear potential which in turn reduce cochlear function at higher frequencies (Schmiedt, 2010). This peripheral hearing loss is commonly identified using pure-tone average (PTA) testing, which involves examining the audibility of tones presented at various levels and frequencies. These declines in the function of the peripheral auditory system are also thought to impact the function and structure of brain regions involved in auditory processing (e.g., Eckert et al., 2019; Xu et al., 2019).

Hearing loss has been shown to impact brain morphology both cross-sectionally and longitudinally. Previous studies have observed an association between gray matter volume in regions of the primary auditory cortex and high frequency hearing loss (Eckert et al., 2012). Other studies observed a dose-response relationship between peripheral hearing loss and hippocampal volume in a community-dwelling sample of over 2000 middle-aged and older Japanese adults (Uchida et al., 2018). That is, smaller hippocampal volume was associated with more hearing impairment at both low and high frequency ranges. Xu and colleagues (2019) observed similar cross-sectional findings of lower hippocampal and entorhinal cortex volumes in individuals with hearing loss. Furthermore, they observed longitudinal findings of increased rates of atrophy in those two regions in individuals with HL over a period of 24 months (Xu et al., 2019). Other longitudinal studies have observed similar associations between poorer hearing in

mid-life and reduced temporal lobe volume over a follow-up period of over 3 years (Armstrong et al., 2019). Specifically, poorer midlife hearing was associated with reductions in right hippocampal gray matter volume and left entorhinal cortex volume. These studies demonstrate that peripheral hearing loss, beyond impacting sensory function, has a significant impact on brain morphology in several hearing-related regions, including the hippocampus, a region commonly associated with memory function (Scoville & Milner, 1957; Smith & Milner, 1981).

Hearing and Cognition

In the last three decades, research has consistently demonstrated a bidirectional link between sensory and cognitive functions (for review see Albers et al., 2015). Starting with the work of Lindenberger and Baltes (1994), an association between sensory acuity (hearing and vision) and cognitive scores in various domains was observed. Following this, a number of research studies demonstrated that hearing loss was associated with cognitive function both cross-sectionally (e.g., Guerreiro & Van Gerven, 2017; Harrison-Bush et al., 2015; Helzner et al., 2005; Lin et al., 2011a) and longitudinally (e.g., Armstrong et al., 2020a; Gurgel et al., 2014; Kiely et al., 2012; Lin et al., 2013; Lindenberger & Ghisletta, 2009; Valentijn et al., 2005). Data from the 347 participants in the Baltimore Longitudinal Study of Aging (BLSA) helped demonstrate that pure-tone hearing loss was associated with poorer scores on multiple cognitive measures, including tests presented in the visual modality, suggesting that these effects are not solely due to perceptual difficulties during testing (Lin et al., 2011a). Interestingly, recent studies have demonstrated that the association between hearing and cognition is present even in those considered to have "normal hearing," defined as a PTA of 25 dB or less, suggesting that even subclinical hearing loss can have an adverse interaction with cognition (Golub et al., 2020). Hearing loss has also been independently associated with the development of dementia in OAs (e.g., Brenowitz et al., 2019; Deal et al., 2017; Lin et al., 2011b). Most strikingly, some studies

have been able to associate hearing loss in individuals as young as 19 years old with future risk of dementia, though I note that hearing loss at such a young age may differ in etiology from age-related hearing loss acquired in middle and old age (Osler et al., 2018). Considering this line of research, a Lancet commission on Dementia, Prevention, Intervention, and Care identified hearing loss as a potentially modifiable mid-life risk factor of dementia, suggesting that eliminating HL could reduce the future incidence of dementia by up to 8%, more so than any other modifiable risk factor for dementia (Livingston et al., 2017, 2020).

The aforementioned studies compared levels of peripheral hearing, that is the audibility of sound, to cognitive function or status. Other studies have also examined another aspect of hearing, what is sometimes referred to as central, or suprathreshold, hearing. Suprathreshold hearing refers to the intelligibility of sound and how it is processed in the auditory cortex of the brain. Older adults often have difficulties with speech intelligibility even when there is good speech audibility (Pichora-Fuller et al., 2017). Difficulties with speech understanding sometimes precede peripheral hearing difficulties (such as those identified using PTA, Vermiglio et al., 2012). Tests of suprathreshold hearing generally involve the recognition of sound in non-ideal conditions, for example listening to speech in noise (Wilson et al., 2007). These measures are thought to be more strongly related to cognition compared to PTA, as they generally involve higher functioning and cognitive processes (Humes et al., 2013). Indeed, as with peripheral hearing, suprathreshold hearing has been closely associated with brain volume in healthy older adults (e.g., Wong et al., 2010) and in those with MCI (e.g., Giroud et al., 2021). Furthermore, worse scores on suprathreshold hearing measures were associated with lower scores on cognitive tests (e.g., Gates et al., 2010; Humes et al., 2013; Ronnberg et al 2014). For example, Gates and colleagues (2010) compared performance on multiple suprathreshold measures (including a

dichotic digits test) to performance on a variety of cognitive measures, controlling for age, gender, education, and pure tone hearing. They observed that the suprathreshold measures were significantly associated with the cognitive tasks, including tests that did not rely on audition (e.g., the Stroop color and word task; Gates et al., 2010). Suprathreshold measures have also been associated with the development of dementia in longitudinal studies (Gates et al., 2011; Quaranta et al., 2014). Quaranta and colleagues (2014) assessed suprathreshold hearing levels in a population of 488 OAs with normal cognition, MCI, and AD. They found that MCI and AD were associated with suprathreshold hearing impairment relative to those with normal cognition (odds ratio = 1.6 and 4.2, respectively; Quaranta et al., 2014). Suprathreshold hearing and cognitive impairment may be more tightly linked than peripheral hearing. The aforementioned Gates et al (2010) study also looked at pure-tone averages and found no association between them and performance on cognitive measures. A recent longitudinal study in a Swedish sample found that, over a 5-year follow-up period, individuals with AD showed greater decline in their scores on a digit triplet test, a measure of suprathreshold hearing, relative to individuals with MCI (Häggström et al., 2018). These findings suggest an association between suprathreshold hearing tasks and cognitive decline, which may be stronger than the association between peripheral measures of hearing and cognition. Overall, the findings from multiple studies clearly demonstrate an association between aspects of hearing, such as audibility and intelligibility, and cognitive decline and dementia in older adults.

Mechanisms

As noted previously, the prevalence of hearing loss and the prevalence of dementia both increase with age. Yet, this is not a sufficient justification to explain the sensory-cognitive relationship considering some of the previously discussed findings in which hearing was associated with the development of dementia independently of age (e.g., Brenowitz et al., 2019;

Deal et al., 2017; Lin et al., 2011b). The works of Lindenberger and Baltes in the 1990's helped pave the way for the current outlook on the associations between hearing and cognition (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1995). In their seminal studies, the researchers observed that sensory functioning (hearing and vision) mediated the relationship between aging and intelligence, and that this relationship grew stronger with increasing age. Since then, five main hypotheses have been proposed to account for this association (for review, see Whitson et al., 2018; Wingfield et al., 2005): The Cognitive Load on Perception hypothesis, which proposes that cognitive decline precedes and causes sensory decline (Lindenberger & Baltes, 1994); The Common Cause hypothesis, which proposes that a common factor exists which leads to declines in both cognition and sensation (e.g., oxidative stress, genetics, vascular factors; Concept first proposed in Lindenberger & Baltes, 1994); The Information Degradation hypothesis, which proposes that sensory factors have short-term effects insofar as more cognitive resources are allocated to information processing in conditions where the quality of the sensory input is diminished (Schneider & Pichora-Fuller, 2000); The Sensory Deprivation hypothesis, which proposes that prolonged sensory loss results in brain atrophy and reorganization in regions associated with those senses, which in turn impacts cognitive processes (Lin et al., 2013; Schneider & Pichora-Fuller, 2000); and the Social Isolation hypothesis, which proposes an indirect route between hearing loss and cognition in that reduced sensory function likely discourages individuals from engaging in social activities, increasing their social isolation, and thus increasing their depressive symptoms, which in term has been associated with cognitive decline and dementia. It is important to note that while the strength of evidence for these hypotheses varies, they are not mutually exclusive (e.g., Pronk et al., 2019), and might in fact be

part of a larger framework of how sensation and cognition interact (Wayne & Johnsrude, 2015). I will now briefly consider some of the evidence for and against these hypotheses.

Considering the number of longitudinal studies demonstrating long-term hearing loss prior to any noticeable cognitive decline, it is unlikely that cognitive decline causes hearing loss (e.g., Gates et al., 2010; Lin et al., 2011b). While the evidence for this cognitive load on perception hypothesis is limited, note that it might be more apt when discussing the association between speech-perception-in-noise measures and cognition, as both tap into shared cognitive resources (e.g., working memory), and thus decline in cognition could result in lower scores on these suprathreshold measures, unlike pure-tone detection which is less cognitively demanding (Gordon-Salant & Cole, 2016). For the common cause hypothesis, evidence comes from studies showing concurrent decline between multiple sensory modalities (e.g., hearing, vision) and cognition, suggesting a central nervous system pathology (e.g., Brenowitz et al., 2019; Lindenberger & Baltes, 1994). Further evidence comes from studies showing that this association increases with increasing age (Baltes & Lindenberger, 1997), suggesting again the influence of some age-related factor. Some evidence against this hypothesis comes from Anstey and colleagues (2001) who observed a longitudinal association between cognitive decline and vision, but not hearing, suggesting that a dissociation between the two senses implicates different processes in their decline. The sensory deprivation hypothesis posits that hearing loss causes cognitive decline through structural and/or functional changes in the brain over a prolonged period of time (e.g., Lin et al., 2013). As previously discussed, hearing loss engenders changes in brain morphology including increased atrophy in associated regions (e.g., Eckert et al., 2012; Uchida et al., 2018). Support for this hypothesis also comes from longitudinal studies showing associations between baseline hearing loss and future cognitive decline (e.g., Lin et al., 2011b;

Osler et al., 2018). However, it should be noted that some studies have failed to find these associations (e.g., Hong et al., 2016; Lin et al., 2004). Interestingly, both of these studies defined hearing loss as a pure-tone average > 40 dB HL, which may be more conservative compared to the common definition of PTA > 25 dB HL used in other studies (e.g., Lin et al., 2011c). Regarding the social isolation hypothesis, previous research has demonstrated the negative social and affective consequences of hearing loss (e.g., Strawbridge et al., 2000). When hearing is effortful, individuals with hearing loss may avoid social gathering to reduce fatigue and embarrassment, thus increasing their social isolation. Depression, a common consequence of social isolation, may contribute to the development of dementia (e.g., Jorm, 2000). More nuanced research has also demonstrated an association between other aspects of socialization such as low social participation, less frequent social contact, and loneliness, with incident dementia (Kuiper et al., 2015 for review). Thus, this hypothesis can explain the indirect relationship between hearing loss and cognitive decline. While social factors likely play a role, they only weakly mediate or moderate the relationship (Hämäläinen et al., 2019), and many of the observed auditory-cognitive interactions tend to remain significant even after controlling for depression (e.g., Lin et al., 2011a). Further research examining the multi-faceted aspects of social interactions and their associations with depression, hearing loss, and cognition is required.

The information degradation hypothesis proposes that the cognitive decline observed in those with hearing loss results from difficulties in perceiving stimuli (perceptual degradation) and/or from increased cognitive resource allocation towards listening and speech perception, leaving insufficient resources for the cognitive task at hand (e.g., Schneider & Pichora-Fuller, 2000; Wingfield et al., 2005). If this hypothesis were true, then it would be expected that older adults with hearing loss should underperform on tests that are dependent on good audition (e.g.,

verbal memory tests), but their performance on visual tasks should be comparable to that of age-matched controls with normal hearing. Indeed, an elegant study by Wong and colleagues (2018) showed that while older adults with HL performed worse on a verbal memory task relative to NH individuals, this difference was eliminated when a visual version of the task was used. Furthermore, in those HL individuals, scores on the visual test correlated with results on several other neuropsychological tasks, while the (original) auditory version of the test did not. This suggests that hearing loss can potentially occlude cognitive function. Considering this hypothesis in terms of cognitive resources, it might be reasonable to expect that, beyond the auditory/visual dichotomy, performance in individuals with HL might differ based on the cognitive processes involved in the task, in addition to its modality. A study by Guerreiro and Van Gerven (2017) showed differences between older adults with and without HL on measures of working memory (both auditory and visual), processing speed, and inhibition. Yet, the two groups did not differ on a measure of visuospatial reasoning, suggesting that this domain is relatively spared in the auditory-cognitive decline. However, I note that other studies have found no association between hearing loss and scores on visual measures of processing speed (Trail Making Test A, Stroop Words, Stroop Colors, Symbol Digit Modalities subtest; Glick & Sharma, 2020; Hong et al., 2016; Lin et al., 2011a). Thus, the evidence for this hypothesis is mixed. Overall, the different hypotheses may have different contributions to the auditory-cognitive association. One of the goals of the current work is to further elucidate these mechanisms. Specifically, one possibility that I aim to address is whether the impact of perceptual factors may be more pronounced in the context of brief cognitive screening tests, such as the MoCA.

Hearing and Cognitive Screening

Assessing cognitive functioning in older adults with deficits in hearing presents a methodological problem: Individuals with hearing loss are likely to show deficits in cognitive

functioning, but those deficits could be representative of a number of contributing, non-mutually exclusive factors (e.g., perceptual difficulties, brain reorganization, inattention due to depression). Some of these factors may be modifiable in the short-term (e.g., using an amplifier to account for perceptual difficulties) or the long-term (e.g., treatment for depression and increased social activity), while others may be non-modifiable (e.g., brain atrophy). Similarly, some of these factors may have a more noticeable impact in certain contexts, such as screening in primary care settings.

Cognitive screening in primary care settings, which is often brief and involves a limited number of tests, may be strongly influenced by sensory loss. As these tests cover a wide variety of cognitive domains through a limited number of items, minor errors committed due to a perceptual deficit can potentially have a significant contribution to the individual's overall score, and subsequently to the patient's diagnostic outlook. This is further exacerbated by the fact that hearing status is not regularly assessed in primary care settings. A study by Jorgensen and colleagues (2014) showed that, out of 100 older adults diagnosed with dementia at a primary care setting, only 13 were asked about their hearing status. As the authors note, this number is significantly below the expected prevalence of hearing loss in this age group, suggesting multiple cases of hearing loss that were potentially missed by the primary care physicians and which may have contributed to the observed symptoms. Furthermore, the primary method of diagnosing dementia in this sample was score on the MMSE, along with self- or informant-report of cognitive changes (Jorgensen et al., 2014). As the MMSE, like other screening measures, is administered orally and contains multiple tests that depend on accurate hearing, the diagnosis of dementia in these individuals could be erroneous. Other factors, such as the level of noise in the testing environment, can also play a role: Administering the MMSE to normal hearing young

adults under varying levels of noise significantly influenced their scores on the test (Jorgensen et al., 2016). Dupuis and colleagues (2016) administered the MoCA to older adults with and without HL under quiet and noisy test environments. Older adults with HL had lower MoCA scores than those with normal hearing under quiet conditions. Testing in noise, however, resulted in lower scores for both groups, regardless of the level of HL. Considering the levels of noise observed in clinics and hospitals, these studies demonstrate the severe impact of simple audibility on cognitive test screening performance, independent of cognitive deficits. It is important to note that these scenarios are likely taking place with increased frequency. In Canada, over 70% of 60-to-75 year old adults with hearing loss were unaware that they had a hearing problem (Statistics Canada, 2015). For those that are aware of their hearing difficulties, the rates of hearing aid use are low, ranging from 14-23% (Chien & Lin, 2012; Kochkin 2000). Finally, at the time of this writing, the COVID-19 pandemic has forced many clinics and hospitals, particularly those treating older vulnerable populations, to turn to remote cognitive screening, which potentially exacerbates the already noted sensory limitations of these tests (see Phillips et al., 2020). To summarize, the great majority of OAs with potential hearing loss undergoing cognitive screening are: Not being asked about their hearing status, being tested under noisy conditions, and not using appropriate amplification. As such, a better understanding of the influence of HL on cognitive screening results is essential for increasing the accuracy of these tests and, by extension, the health care of affected individuals.

Previous research has examined the potential impact of hearing on MoCA performance. Glick and Sharma (2020) reported poorer MoCA scores in individuals with mild-moderate hearing loss relative to their normal hearing counterparts. Dupuis and colleagues (2015) also assessed MoCA performance in cognitively-healthy individuals with and without hearing loss.

They observed generally lower MoCA scores for those with pure-tone hearing loss. Furthermore, they found that the gap between hearing loss and normal hearing individuals persisted even when hearing-dependent subtests (namely delayed recall, digit span, attention to letters, and sentence repetition) were omitted from the MoCA scoring (Dupuis et al., 2015). Similarly, Saunders and colleagues (2018) also observed an association between MoCA scores and hearing, this time using a suprathreshold hearing instrument (QuickSIN), suggesting that this association is robust for both pure-tone and suprathreshold hearing. Pendlebury and colleagues (2013) tested the validity of administering the MoCA both face-to-face and over the telephone (T-MoCA) to a group of older adults recovering from stroke or transient ischemic attack. The researchers observed significantly lower scores using the T-MoCA on several subtests, including abstraction, verbal fluency, and sentence repetition, as well as overall lower accuracy at detecting MCI relative to the face-to-face MoCA (Pendlebury et al., 2013). Lin and colleagues (2017) tested a version of the MoCA for the hearing impaired (MoCA-HI) using a timed Microsoft Powerpoint presentation. Their findings suggested that individuals administered the MoCA-HI had better performance on the memory subtest than their verbally-administered counterparts. This demonstrates the difficulty of transferring verbal tests into multiple modalities as it can inherently change the nature of the test as well as the cognitive resources required to perform it (Lin et al., 2017). These findings suggest a role for factors such as test modality, sound quality, and the presence of audio-visual cues in cognitive screening. One factor seldom addressed when discussing auditory-cognitive associations in cognitive testing in general, and in cognitive screening specifically, is the influence of sex.

Sex-related differences

Sex and gender are two nuanced terms that have evolved and changed with the passage of time. For the purposes of this dissertation, sex is a biological construct differentiating the male

and female organisms, while gender is a social construct involving culturally-bound conventions among men and women and boys and girls (Krieger, 2003; Kronk & Dexheimer, 2020). Unfortunately, most studies addressing hearing and cognition do not disclose how sex and gender were assessed and in fact use the two terms interchangeably. In our discussion, I will refer to sex-related differences and in general focus on potential biological factors that may be contributing to auditory-cognitive associations. However, as the two are strongly intertwined, some gender-related differences will also be addressed, such as the association between hearing loss and social activity. For the sake of consistency, I will use the terms "men" and "women" even when discussing biological differences, in compliance with the latest American Psychological Association guidelines (American Psychological Association, 2020).

There are well-documented sex differences in the etiology and presentation of hearing loss (e.g., Ciletti & Flamme, 2008; Dubno et al., 2013). Women tend to have larger amplitudes of auditory brainstem response (ABR) than men (Liu et al., 2009; Wharton and Church, 1990), as well as larger transient-evoked otoacoustic emissions than men (Berninger, 2007). In addition, women commonly develop high frequency hearing loss later in life, around 50 years of age, in response to changes in hormonal function (Davis, 1995; Hederstierna et al., 2010). In contrast, men develop hearing loss gradually and sometimes as a consequence of environmental and gender-related factors such as occupational noise exposure (e.g., Helzner et al., 2005). Put differently, men are more likely to develop what is known as "sensory type" hearing loss, which is signified by outer hair cell damage due to noise, while women develop "metabolic type" hearing loss, which is signified by atrophy of the lateral wall of the cochlea and is related to cardio-vascular and other related factors, such as diabetes (Dubno et al., 2013). From these descriptions, we can also surmise that "sensory type" hearing loss is strongly influenced by

gender-related factors while “metabolic type” hearing loss is influenced by sex-related factors. Nevertheless, men in general tend to have worse hearing than women, even after correcting for such factors as age, occupation, and lifetime noise exposure, suggesting some biological influence in this sex-effect (Cruickhanks et al., 1998; Helzner et al., 2005). Overall, sex and gender differences in hearing are likely multifactorial, reflecting both environmental and biological factors.

Sex-differences are also evident in cognitive ability and the rates of the development of dementia. In healthy adults, men generally outperform women on visuospatial tests, while women outperform men on verbal memory tests (Vogel et al., 2003). This modality-specific difference is evident in other aspects of functioning as well. For example, longitudinal change in cortisol levels over a period of 4 years was associated with performance on measures of visual memory in men and verbal fluency in women (Beluche et al., 2010). Beyond healthy aging, women are more likely than men to develop Alzheimer’s disease, even after accounting for their longer lifespan (Vina & Lloret, 2010). This sexual dimorphism in disease rates may be associated with estrogen levels in the brain (Einstein, 1999). Furthermore, one of the greatest risk factors for the development of Alzheimer’s disease, the presence of the e4 allele of the apolipoprotein E gene (APOE-e4), seems to be a greater risk in women: Holland and colleagues (2013) observed that individuals with APOE-e4 had accelerated rates of brain atrophy relative to those without the allele, but that this was significantly more pronounced in women. Similarly, Mortensen & Hogh (2000) found an interaction between APOE status and cognition in women only, in which APOE-e4 carriers showed larger decline in scores on subtests from the Wechsler Adult Intelligence Scale (WAIS) relative to noncarriers. There was no relation between APOE status and cognition in men (Mortensen & Hogh, 2000).

Research on individuals with MCI has also revealed some sex-related differences: it was previously believed that MCI is more prevalent in men; however, a recent meta-analysis from Au and colleagues (2017) suggests that there are no sex differences in the prevalence of amnestic MCI, but that non-amnestic MCI is actually more prevalent in women. Sohn and colleagues (2018) showed that women with MCI display greater decline over time in cognitive scores compared to men. Sundermann and colleagues (2016) have shown that women with amnestic MCI outperform men on verbal memory tests even after accounting for hippocampal volume, leading the authors to speculate that women may have more cognitive reserve for verbal memory. Finally, sex differences are also present in several risk factors that are shared between dementia and hearing loss: metabolic factors, previously discussed in association with hearing loss, are also associated with the development of dementia. For example, Anstey and colleagues (2021) found that hypertension was associated with memory decline in women only while stroke was associated with memory decline in men only. Depression, discussed previously in the context of the social isolation hypothesis, is also associated with higher incident MCI and dementia (Goveas et al.,2011). Interestingly, the impact of depression may be more pronounced in women, as a study by Elbejjani and colleagues (2015) has shown that more depressive symptoms were associated with smaller hippocampal volumes in older women but not older men. Furthermore, the association between social isolation and hearing loss may be gender-dependent as well, with HL women between 60-69 years being more likely to have social isolation compared to NH women (Mick et al., 2014). No such association was observed in men. Overall, a wealth of literature points to sex-related differences in cognition, cognitive decline, and dementia.

Taken together, one would expect sex differences to emerge in auditory-cognitive interactions. Surprisingly, very few studies have examined these differences, with most researchers using sex as a control variable in their investigations. One reason for this discrepancy may be that Lindenberger and Baltes' (1994) seminal study on the association between aging, intelligence, and sensory functioning, did not observe any differences between men and women when their structural models included different sex groups. Since then, Helzner and colleagues (2005) examined sex and race differences in hearing loss and noted that, in a sample of 2052 healthy older adults, lower scores on a modified version of the Mini-Mental State Examination (MMSE) were associated with a higher risk of pure-tone hearing loss, and that this risk was significantly elevated in black women relative to other sexes/races. Eberhard and colleagues (2019) noted that women, but not men, showed an association between low-frequency pure-tone hearing loss and Mini-Mental State scores (N = 503, 63% women). In a large sample of 2167 women and 1664 men over the age of 65, Lyu and Kim (2018) measured the association between self-reported hearing loss and performance on the MMSE in Korean community-dwelling older adults. They observed that women, but not men, showed an association between self-reported hearing impairment and cognitive impairment, determined using age-, education-, and gender-adjusted normative values. Huang and colleagues (2019) examined pure-tone hearing loss and cognition in 655 older adults (51.71% women) as part of the National Health and Nutritional Examination Survey in the United States. A composite cognitive score was calculated based on three tests: the word learning and recall modules from the Consortium to Establish a Registry for Alzheimer's disease (CERAD), animal fluency test, and the Digit Symbol Substitution Test (Wechsler, 1997). They observed an association between the composite cognition score and hearing in men only (Huang et al., 2019). However, examination of individual test scores showed

that hearing in both genders was associated with the animal fluency test, while the other tests did not individually reach significance after controlling for potential covariates. Taken together, these findings suggest the existence of sex-related differences in auditory-cognitive interactions that require further investigation. Furthermore, all the studies discussed above used self-reported or pure-tone hearing as their hearing measure. Whether sex impacts the auditory-cognitive association between suprathreshold hearing and cognition remains unknown.

Current studies

In the current set of studies, I investigated how hearing loss influences scores on the MoCA and other neuropsychological measures, and whether these influences are impacted by sex. Our studies are unique in several aspects: 1) I will be able to compare how hearing impacts scores on the MoCA relative to other neuropsychological measures in the same sample, 2) I will examine differences in the auditory-cognitive relationship in both pure-tone and suprathreshold hearing measures, and 3) I will give special attention to addressing sex-related differences in these samples. I begin by addressing the psychometric properties of the MoCA and how hearing-dependent items contribute to these properties (Manuscript I). Following this, I directly examine the impact of pure-tone hearing loss on MoCA scores in healthy older adults (Manuscript II). Finally, I will examine how both pure-tone and suprathreshold hearing loss are associated with scores on the MoCA and other neuropsychological measures in those with MCI (Manuscript III). Generally, I predict that individuals with normal hearing will outperform their age-matched hearing loss counterparts on cognitive tasks. Furthermore, I expect to see sex-related differences in the expression of auditory-cognitive associations. These studies will further our knowledge of auditory-cognitive interactions at different stages of cognitive function in old age and will shed more light on the associated mechanisms involved.

Chapter 2

Manuscript I

The Montreal Cognitive Assessment (MoCA) after Omission of Hearing-dependent Subtests: Psychometrics and Clinical Recommendations

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Manuscript originally published in the Journal of the American Geriatrics Society (JAGS). I will refer to it as Al-Yawer et al., 2019 in subsequent manuscripts. Minor changes to grammar, spelling, formatting, and citation style were made to homogenize it with the rest of the dissertation.

Abstract

Background: Hearing loss is the third most common chronic health condition in older adults, yet it is often undiagnosed and/or untreated. Given the association between hearing loss and cognitive impairment, it is expected that many people undergoing cognitive screening may have hearing loss. The Montreal Cognitive Assessment scale (MoCA) is a brief screening test that assesses a wide range of cognitive functions sensitive to Alzheimer's disease and Mild Cognitive Impairment (MCI). Although MoCA items were carefully designed to be sensitive to deficits in MCI, they were not designed to take sensory declines into account. In the current investigation, we examined the MoCA's psychometric properties following omission of subtests primarily dependent on hearing status (memory, digit span, attention to letter, sentence repetition).

Design: Cross-sectional analytic (retrospective analysis).

Setting/Participants: We used the original MoCA validation study data[4]. Groups consisted of healthy controls (N=90), MCI (N=94), and mild Alzheimer's disease (N=93).

Measurements: We assessed sensitivity and specificity using absolute and proportional cut-off score adjustments. We developed receiver operating characteristics (ROC) curves to determine the best cut-off values for both MCI and AD patients using different combinations of auditory subtest omissions.

Results: Compared to the original MoCA (MCI sensitivity: 90%, specificity: 87%), MCI sensitivity was substantially reduced (absolute scoring: 43%, proportional scoring: 56%) when all auditory subtests were omitted, with the biggest contribution to the reduction coming from the delayed recall subtest. Excluding three subtests and maintaining delayed recall had no effect on

MCI sensitivity, but reduced specificity (sensitivity: 94%, specificity: 71% using proportional scoring). AD sensitivity, in contrast, was not strongly influenced by our manipulation and remained relatively high through all three subtest omission combinations.

Conclusion: The current study highlights the contribution that hearing-dependent subtests have on the sensitivity and specificity of the MoCA. Clinical recommendations related to these findings are discussed.

Introduction

Hearing loss (HL) is the third most common chronic health condition in older adults (OAs; Cruickshanks et al., 2010). Deficits in peripheral hearing are prevalent in almost one-third of adults 65 years of age and in over half of those 75 years of age (Mick et al., 2021; World Health Organization, 2018). HL is often undiagnosed and/or untreated. Importantly, the results of cognitive screening for an older adult with unidentified HL may not accurately reflect their functioning. The Montreal Cognitive Assessment scale (MoCA; Nasreddine et al., 2005) is a widely-used, brief cognitive screening tool that has high sensitivity for detecting mild cognitive impairment (MCI) and Alzheimer's disease (AD) in OAs. Here we demonstrate the potential effect of hearing-dependent subtests on the MoCA's sensitivity and specificity as a screening tool.

Hearing loss is independently associated with the development of dementia in OAs (Lin et al., 2011b; Livingston et al., 2017). Furthermore, when the quality of auditory test stimuli is reduced, performance on cognitive tests can be compromised (Jorgensen et al., 2016). Therefore, assessing cognitive functioning in OAs with hearing loss presents the challenge of dissociating scores that are low due to perceptual issues from those that are solely due to cognitive deficits. This dilemma can have significant consequences when cognition is screened in health care settings, which do not always have ideal testing conditions. Noise in the test environment can affect MoCA scores even for those with normal hearing (Dupuis et al., 2016). Thus, errors due to poor perception could affect an individual's score, potentially affecting diagnostic decisions reached based on that score.

Healthcare professionals cannot assume that older adults know that they have HL or how to accommodate for it. In Canada, over 70% of 60-75-year-old adults with HL are unaware of it

(Statistics Canada, 2015). Even for those who are aware of their difficulties, the rate of hearing aid use is low (23%; Chien & Lin, 2012). Thus, the majority of OAs with HL undergoing cognitive screening may be tested without adequately taking hearing loss into account.

Due to its brevity and the wide range of cognitive domains it covers (see Table 1), the MoCA is ideal for use in settings where a clinician needs to assess a patient's cognition quickly. Wittich and colleagues (2010) assessed how the psychometric properties of the MoCA could theoretically be affected in visually-impaired individuals by omitting visually-dependent subtests of the original MoCA validation sample. As MCI often involves declines in executive functions, the omission of visual items, which are often dependent on executive functions, resulted in reduced test sensitivity (Wittich et al., 2010). However, episodic memory, assessed using the delayed recall subtest, requires the perception, encoding, and recollection of spoken word stimuli, and thus depends on hearing. Dupuis and colleagues (2015) assessed performance on the MoCA in cognitively-healthy individuals with and without HL. They observed that omitting the delayed recall subtest contributed greatly to reducing the gap in scores between HL and normal hearing individuals. Nevertheless, they observed lower scores for the HL group, even when hearing-dependent subtests were omitted from scoring, suggesting that the observed deficits are not merely sensory artefacts. It is possible that deficits in a given sensory modality may influence an individual's score and give the impression of deficits in cognitive domains that are tested in that modality.

Previous studies have focused on the influence of sensory impairment on cognition in healthy OAs. We examined the potential contribution of hearing-dependent subtests to the sensitivity and specificity of the MoCA in a sample of OAs with MCI, AD, and controls for whom cognitive status had been independently verified without using the MoCA. We used the original MoCA

validation study data (Nasreddine et al., 2005) to recalculate MoCA scores with the omission of subtests that depend on hearing the test stimuli. We developed receiver operating characteristics (ROC) curves to determine the best cut-off values for each procedure to categorize patients as having MCI or AD.

Materials and Methods

Participants

The sample from the original MoCA validation study (54% women; Nasreddine et al., 2005) consisted of healthy controls (N=90; mean age 72.8 years), individuals with MCI (N=94; mean age 75.2 years), and with mild AD (N=93; mean age 76.7 years). MCI diagnosis was determined using previously established criteria (Petersen et al., 1999, 2001). The diagnosis of probable AD was made using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994), and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). Participants were not screened for hearing or vision loss at the time of testing.

Procedure

Table 1 lists all 12 MoCA subtests, and describes the primary modalities needed to perceive the stimuli and respond to the task. Beyond adequate perception of task instructions, the four subtests that depend on adequate perception of auditory stimuli are as follows: 1. Delayed recall: Participants repeat five words spoken by the tester in two learning trials and are later tasked to recall the words; 2. Digit span: The tester reads a series of single-digit numbers and participants are asked to repeat them in the same order (forward) and in reverse order (backwards); 3. Attention to letters: the tester reads a list of letters and participants are asked to tap when they

Table 1. Montreal Cognitive Assessment (MoCA) subtests and corresponding cognitive domains, sensory-motor domains activated, and test points.

MoCA Subtest	Cognitive Domain	Sensory / Motor Domain	Points awarded Original (/30)	Points awarded H1 (/20)	Points awarded H2 (/25)	Points awarded H3 (/25)
Trail making	**Visuospatial attention, task switching**	**Visual perception / Manual production**	1	1	1	1
Copy cube	**Visuoperceptual abilities**	**Visual perception / Manual production**	1	1	1	1
Clock drawing	**Semantic memory, visuospatial abilities, executive functioning**	**Recollection from semantic memory / Manual production**	3	3	3	3
Animal naming	**Confrontation naming, semantic memory**	**Visual perception / Oral production**	3	3	3	3
Delayed recall	**Episodic verbal learning and memory**	**Auditory perception / Oral production**	5	0	0	5
Digit span	**Attention, short-term memory, working memory**	**Auditory perception / Oral production**	2	0	2	0
Attention to letters	**Sustained attention**	**Auditory perception / Oral production**	1	0	1	0
Serial subtraction	**Attention, working memory, mental arithmetic**	**Not sensory dependent / Oral production**	3	3	3	3
Sentence repetition	**Attention, working memory, language (morphosyntax)**	**Auditory perception / Oral production**	2	0	2	0
Fluency	**Word generation, executive function**	**Not sensory dependent / Oral production**	1	1	1	1
Similarities	**Abstract reasoning**	**Not sensory dependent / Oral production**	2	2	2	2
Orientation	**Orientation to time and place**	**Not sensory dependent / Oral production**	6	6	6	6

hear the letter "*A"*; 4. Sentence repetition: The tester reads a pair of morphosyntactically complex sentences and participants are asked to repeat them verbatim.

We examined the psychometric properties of the MoCA using three combinations of auditory subtest omissions based on the procedures followed by Dupuis and colleagues (2015). The purpose of these procedures was to examine whether certain hearing-dependent subtests disproportionately influence the sensitivity and specificity of the MoCA. The three procedures were as follows: 1. MoCA-H1: All four auditory subtests were removed (10 points removed, total score /20); 2. MoCA-H2: Only the delayed recall subtest was removed (5 points removed, total score /25); 3. MoCA-H3: Digit span, attention to letters, and sentence repetition subtests were removed (5 points removed, total score /25).

The original MoCA recommended a cut-off score of 26/30 or above to indicate normal functioning, which corresponds to a proportional score of 0.866 (26/30). For all three subtest combinations, we established both absolute and proportional cut-off scores (following Wittich et al., 2010). For example, in MoCA-H1, 10 points were removed from the MoCA maximum score, such that the absolute cut-off changed to 16 (26-10), while the proportional cut-off is changed to 17 (0.866 x (30-10)). Additionally, we recalculated sensitivity, specificity, overall accuracy, and developed Receiver Operating Characteristics (ROC) curves for all groups, along with area under the curve (AUC) measurements to establish ideal cut-off scores.

Results

Absolute and proportional cut-off values for the three procedures are provided in Table 2. Overall, the three procedures showed a decrease in overall classification accuracy relative to the original MoCA scoring. Removing all four hearing-dependent subtests from the MoCA (MoCA-H1) resulted in a large decrease in MCI sensitivity which was more pronounced for the absolute

Table 2. Psychometric properties of the original MoCA and our three modified procedures (H1, H2, H3) with absolute and proportional scoring. Cut-off indicates the scores below which a participant would be deemed cognitively abnormal.

		Original MoCA	MoCA-H1		MoCA-H2		MoCA-H3	
			Absolute	Proportional	Absolute	Proportional	Absolute	Proportional
	Cut-off	26	16	17	21	22	21	22
MCI	Sensitivity (%)	90	43	56	53	63	87	94
	Accuracy (%)	86	70	74	73	76	84	83
AD	Sensitivity (%)	100	87	92	89	96	100	100
	Accuracy (%)	93	92	92	91	92	91	86
	Specificity (%)	87	97	92	93	89	81	71

MoCA-H1: Delayed recall, digit span, attention to letters, and sentence repetition subtests omitted from the total score; MoCA-H2: Delayed recall subtest removed; MoCA-H3: Digit span, attention to letters, and sentence repetition subtests removed.

cut-off score than the proportional score; sensitivity to AD remained high. MoCA-H2 omitted only the delayed recall subtest. Like MoCA-H1, this omission resulted in a decrease in the test's sensitivity to MCI, which was again more pronounced when using the absolute cut-off score; sensitivity to AD remained relatively high. MoCA-H3 omitted digit span, attention to letters, and sentence repetition. Using a proportional cut-off score resulted in a small increase in the test's sensitivity to MCI over the full MoCA at the cost of specificity (Table 2). Note that the overall test accuracy for MoCA-H3 remained lower than the original MoCA.

ROCs allowed us to determine sensitivity/specificity trade-offs at different cut-off values. For AD, the ROC curve rapidly plateaus (Figure 1), showing both high sensitivity and specificity. For MCI, the ROCs show less steep curves. This is particularly evident for MoCA-H1 and MoCA-H2 (Figure 1, panels C and E; AUC= 0.743 and 0.758, respectively), which both included the omission of the delayed recall subtest. MoCA-H3 (Figure 1 panel G), which did not omit delayed recall, had better sensitivity and specificity values at most cut-offs (AUC=0.824), but MoCA-H3 still had lower accuracy than the full MoCA (Figure 1, panel A; AUC=0.885). No significant differences were observed when data were stratified by sex.

Discussion

We assessed the psychometric properties of three procedures for scoring the MoCA omitting different hearing-dependent subtests. Omitting the delayed recall subtest, either by itself (MoCA-H2) or along with other hearing-dependent subtests (MoCA-H1), resulted in a significant loss of sensitivity to MCI. This is expected insofar as memory is the domain most implicated in MCI (Petersen et al., 2001) and is consistent with previous findings (Dupuis et al., 2015). We also observed decreases in specificity when the three other hearing-dependent subtests (digit span, attention to letters, and sentence repetition; MoCA-H3) were omitted. One of the MoCA's

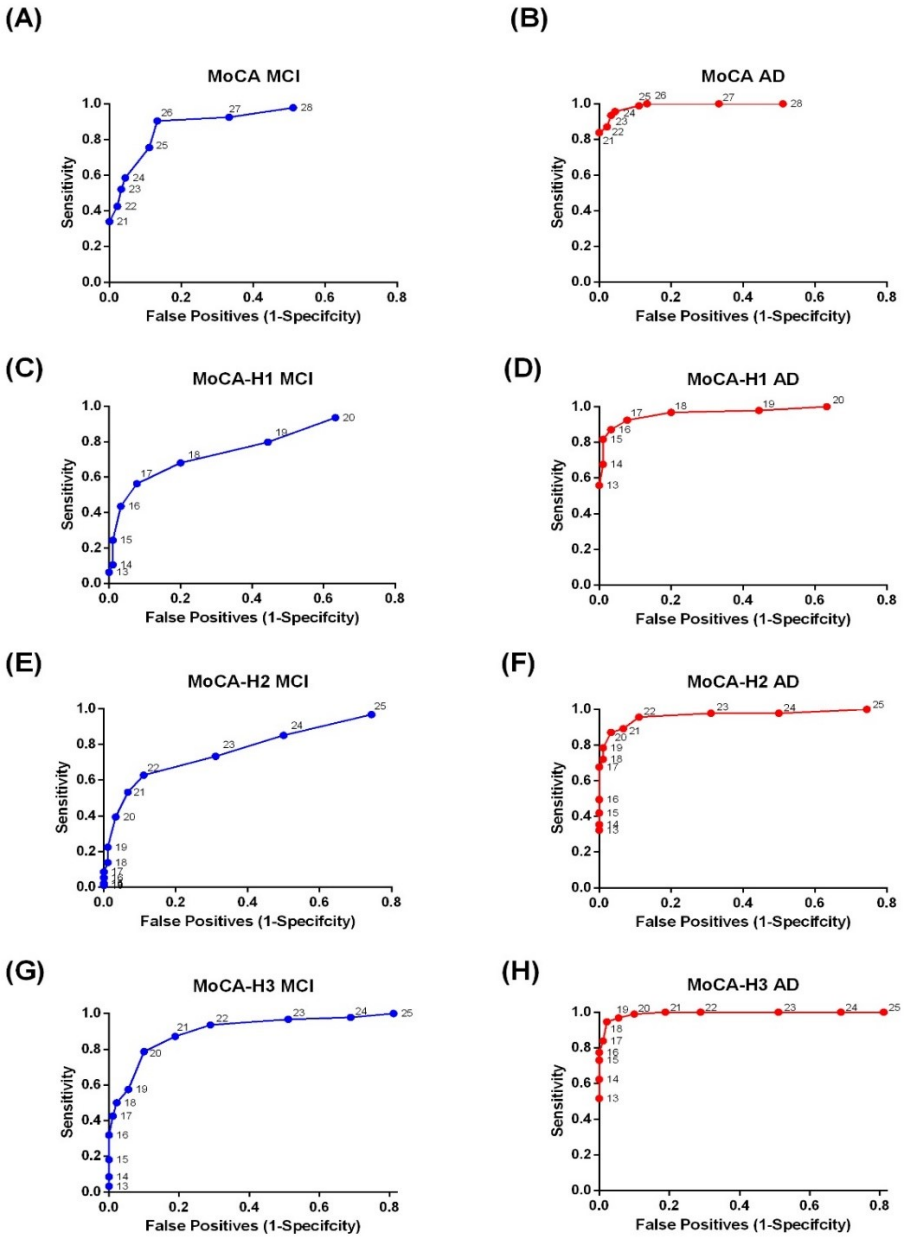

Figure 1. Receiver operating characteristics (ROC) curves showing the sensitivity and specificity for different cut-off scores on the original MoCA and our three modified procedures (H1, H2, H3). Values are presented for both mild cognitive impairment (MCI; left panels) and Alzheimer's disease (AD; right panels). Numbers on the curves represent different possible cut-off scores. The absolute and proportional cut-off scores we used to determine sensitivity and specificity comparisons in the present paper are presented in bold.

advantages as a screening tool is the breadth of cognitive domains it tests. In the interests of brevity, each domain is tested in a single sensory modality (e.g., episodic memory is dependent on learning auditorily presented items). The current study highlights the contribution that hearing-dependent subtests have on both the likelihood of cognitively impaired individuals being identified as such (sensitivity), and the cognitively healthy individuals being correctly identified as healthy (specificity).

These results for hearing largely parallel the findings for vision (Wittich et al., 2010) where the omission of visual subtests resulted in a reduction in sensitivity. We also similarly observed an advantage for using a proportional cut-off score compared to an absolute score. Nevertheless, the reduction in sensitivity, even with proportional scoring, was still meaningful. This demonstrates the potential consequences that hearing loss could have on an individual's apparent cognitive performance.

Limitations and future studies

Perceptual problems could result in reduced specificity because people who have HL and normal cognition could be misclassified as having cognitive impairment. Alternatively, clinicians may omit certain subtests to account for a person's sensory status, yet subtest omission can result in a misestimation of an individual's cognitive abilities and, in the case of the highly domain-specific subtests of the MoCA, significant deficits may be missed. Omitting subtests is a crude method to correct for the effects of sensory loss on cognitive testing. It does not reflect how a person with hearing loss would perform insofar as they may not be likely to score zero on every auditory subtest. The purpose of omitting subtests in this study was to examine the *potential* ramifications of testing individuals with untreated HL or older adults under noisy testing conditions (Dupuis et al., 2016). Importantly, we are not advocating item omission as an appropriate solution. Instead,

our procedures allowed us to observe the individual contribution of the hearing-dependent subtests to the MoCA's accuracy.

We have discussed our findings assuming a person has hearing loss as defined by pure-tone audiometric thresholds. However, it is important to note that age-related declines in suprathreshold auditory processing can occur even in those who would not be considered to have clinically significant threshold elevations. Declines in auditory processing may also affect performance on memory and attention tasks, such as those discussed in this investigation (Phillips, 2016; Pichora-Fuller et al., 2017).

The participants in this study had diagnoses based on thorough neuropsychological examinations, allowing us to examine the psychometric properties of the MoCA-H. However, similar to OAs seen in other memory clinics (Jorgensen et al., 2014), these participants were not assessed for sensory loss. Considering the high prevalence of hearing loss in OAs (Cruickshanks et al., 2010), it is likely that this sample included individuals with hearing difficulties. Future studies should compare MoCA scores to full neuropsychological batteries in individuals with different sensory abilities. Delayed recall tests, in particular, seem to contribute greatly to the variability in auditory-cognitive relationships (Dupuis et al., 2015). Research comparing test administration in different modalities (Jorgensen et al., 2014) or tests where auditory items have visual substitutions (Wong et al., 2018) is developing. What is needed are tests that can be administered either in the visual or auditory modality that have similar content validity and have been validated to have similar psychometric properties.

Clinical recommendations

Sensory loss is prevalent in the population, and yet only a small portion of older adults seen at memory clinics may be asked about hearing loss (Jorgensen et al., 2014). OAs who have not had a recent hearing test should be screened and/or referred to an audiologist. Technological advancements now permit relatively affordable and efficient hearing screening (Thompson et al., 2015). Health professionals administering cognitive screening tests should ensure that persons with hearing aids use them during testing. As individuals with HL can wait an average of 10 years before beginning hearing aid use (Davis et al., 2007), those who have HL but do not have a hearing aid may benefit from using generic amplifying devices (e.g., Pocket-talker). When testing individuals with HL, professionals should optimize the presentation of auditory test items by using clear speech spoken at a slow normal rate, reducing noise in the testing environment, and facing the person to enable speechreading (Carlos & Moye, 2014; Dupuis et al., 2016).

Conclusion

We demonstrated how the MoCA's sensitivity and specificity depend on subtests that rely on hearing test items. Clinicians need to be aware of their patients' sensory functioning and consider how these factors may affect performance on the test and influence clinical interpretations.

Chapter 3

Manuscript II

Sex-Related Differences in the Associations between MoCA Scores and Pure-Tone Measures of Hearing

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Manuscript accepted for publication in the American Journal of Audiology (AJA). I will refer to it as "Al-Yawer et al., in press" in the subsequent manuscript. Minor changes to grammar, spelling, formatting, and citation style were made to homogenize it with the rest of the dissertation.

Abstract

Purpose: Hearing loss (HL) is associated with cognitive performance in older adults, including performance on the Montreal Cognitive Assessment (MoCA), a brief cognitive screening test. Yet, despite well-established sex-related differences in both hearing and cognition, very few studies have tested whether there are sex-related differences in auditory-cognitive associations.

Methods: In the current cross-sectional retrospective analysis, we examined sex-related differences in hearing and cognition in 193 healthy older adults (M=69 years, 60% women). Hearing was measured using audiometry (pure-tone average (PTA) of thresholds at 500, 1000, 2000, and 4000 Hz in the worse ear). Cognition was assessed using the MoCA. Additionally, we calculated MoCA scores with hearing-dependent subtests excluded from scoring (MoCA-Modified).

Results: Men and women did not differ in age, education, or history of depression. Women had better hearing than men. Women with normal hearing were more likely to pass the MoCA compared to their counterparts with HL. In contrast, the likelihood of passing the MoCA did not depend on hearing status in men. Linear regression analysis showed an interaction between sex and PTA in the worse ear. PTAs were significantly correlated with both MoCA and MoCA-Modified scores in women, while this was not observed in the men.

Conclusions: This study is one of the first to demonstrate significant sex-related differences in auditory-cognitive associations even when hearing-related cognitive test items are omitted. Potential mechanisms underlying these women-specific effects are discussed.

Introduction

Hearing loss (HL) is one of the three most prevalent chronic health conditions in old age (Lin et al., 2011c). In 2016, the prevalence of HL was 28% in Canadian men aged 65-69 years, and 17% in women (Mick et al., 2021). An association between hearing loss and cognitive performance in older adults has been reported in cross-sectional (Golub et al., 2020; Harrison Bush et al., 2015; Lin et al., 2011a; Quaranta et al., 2014; Ray et al., 2018;) and longitudinal (Armstrong et al., 2020a; Lin et al., 2011a; Wen et al., 2016) studies. For example, Lin and colleagues (2011a) showed that pure-tone hearing levels were independently associated with cognitive function on tests of memory and executive functioning. Similar findings were obtained by Harrison Bush and colleagues (2015) using cognitive measures of memory, executive function, and processing speed. Notably in those studies, hearing accounted for a small but significant amount of variance in cognitive scores after accounting for confounders (0.4-2.2%, Harrison Bush et al., 2015; see Loughrey et al., 2018 for a recent review and meta-analysis). These associations have been shown with comprehensive neuropsychological testing and with screening measures used in primary care settings such as the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005; Dupuis et al., 2015; Saunders et al., 2018). Studies with the MoCA show that individuals with normal hearing outperform their HL counterparts, even when hearing-dependent items are not included in scoring (Dupuis et al., 2015) and that MoCA scores are correlated with the audiometric four-frequency pure-tone average (PTA; Saunders et al., 2018).

Mechanisms proposed to account for the auditory-cognitive association include: The common cause hypothesis, postulating a common factor acting on both auditory and cognitive declines that leads to the observed associations (Lindenberger & Baltes, 1994); the social isolation hypothesis, suggesting that isolation experienced by those with HL may moderate the

relationship with cognition through indirect pathways such as increase in depressive symptoms (Whitson et al., 2018); the information degradation hypothesis, suggesting that more cognitive resources are allocated to information processing when the quality of the sensory input is diminished (Schneider & Pichora-Fuller, 2000); and the sensory deprivation hypothesis, positing long-term effects of hearing loss on patterns of brain activation and cognition. These hypotheses are not mutually exclusive, since multiple mechanisms could underlie auditory-cognitive associations, with some pathways making a larger contribution depending on factors such as the individual's age, experiences, or sensory abilities (Pronk et al., 2019). For example, information degradation could be more significant in individuals with cognitive difficulties, such as those with mild cognitive impairment. In those individuals, fewer cognitive resources are available to be shared for both sensory and cognitive processing.

Sex is one factor that is seldom explored in studies of auditory-cognitive associations. There are well-established sex-related differences in performance on cognitive tests. In general, women tend to outperform men on tests of verbal memory, both in younger (Barret-Connor & Kritz-Silverstein, 1999; Kramer et al., 1988) and older (Aartsen et al., 2004) adults. In contrast, men tend to outperform women on tasks of visuospatial abilities (De Frias et al., 2006). This female verbal memory advantage has also been observed in individuals with mild cognitive impairment and Alzheimer's disease (Sundermann et al., 2016). Notably, there is not a difference in rates of decline on these measures; a metanalysis by Ferreira and colleagues (2014) showed no sex-related differences in the rate of cognitive decline in older adults between 60 and 80 years of age.

In men, pure-tone hearing loss tends to decline gradually over time starting in mid-life and often shows a "sensory" phenotype with damage to the outer hair cells (Dubno et al., 2013).

In contrast, women tend to experience an increased prevalence of hearing loss later, in the years following menopause, possibly owing to direct and indirect effects of reduced estrogen levels in the inner ear (Delhez et al., 2020; Hederstierna et al., 2010). As such, women often have a "metabolic" hearing loss phenotype with atrophy of the stria vascularis of the cochlea associated with metabolic disorders such as hypertension and diabetes. Lindenberger and Baltes (1994) tested for but did not observe sex-related differences in the association between sensory functioning, age, and intelligence. Subsequently, Helzner and colleagues (2005) observed that lower scores on a modified version of the Mini-Mental State Examination (MMSE; Folstein et al., 1975) were associated with a higher likelihood of HL in black women but not other sexes/races. However, it is unknown what factors and/or underlying mechanisms may have influenced black women' MMSE scores and their association with hearing loss. In another study, Lyu and Kim (2018) examined a sample of 3,831 community-dwelling older adults (56% women) and observed an association between self-reported hearing problems and performance on the MMSE in women only. Multiple studies have examined sex-related differences in performance on the MoCA, with the majority of studies reporting no significant differences between men and women (e.g., Aiello et al., 2021; Apolinario et al. 2018; Bruijnen et al., 2020). However, one study observed differences on individual subtests of the MoCA that are in line with sex-related differences that have been found on other cognitive tests (i.e., women outperform men on the verbal delayed recall subtest while men outperform women on the visuospatial subtests, Engedal et al., 2021). Nevertheless, to the best of our knowledge, no studies have examined how sex-related differences might influence auditory-cognitive associations on the MoCA.

In the current study, we explored the associations between hearing loss and scores on the MoCA in a sample of healthy older adults, stratified by sex. We hypothesized, based on previous research (Helzner et al., 2005; Lyu & Kim, 2018), that auditory-cognitive associations would differ between men and women. We predicted that poorer hearing would be associated with worse performance on the MoCA, and that women would show stronger associations between MoCA scores and pure-tone hearing compared to men.

Materials and Methods

Participants

Participants (N = 220) were recruited through an older adult participant pool at Concordia University and advertisements in a local paper. Participants were tested as part of a larger study on HL and balance (for descriptions of the sample see Bruce et al., 2017, 2019; Lai et al., 2017). Exclusion criteria were being under 60 years old or being unable to complete the cognitive measures. Older adults received an honorarium for participating. Demographic information (sex, history of major depression) was collected via self-report. The work has been approved by Concordia University's human ethics review committee. All participants provided written informed consent and were aware that their anonymized information would be used for research.

Hearing

All participants completed pure-tone audiometry to measure hearing detection thresholds. Audiometry was conducted using standard audiometric procedures with a calibrated audiometer and headphones (Maico MA 42) in a quiet room. The testers were all psychology students trained to carry out the standardized protocol for audiometric screening. Data from participants with an inter-aural difference >20 dB at two or more adjacent standard octave test frequencies were excluded from analyses (N = 16) because such inter-aural asymmetry indicated etiologies of hearing loss other than typical noise-induced or age-related hearing loss. Hearing loss was

defined as a pure-tone average (PTA) of thresholds at 500, 1000, 2000, and 4000 Hz >25 dB HL in the worse ear. The main analyses were conducted using the PTA for the worse ear as this more strongly represents lifelong damage to the cochlea; however, supplementary analyses were conducted using the PTA for the better ear.

Cognition

The MoCA was administered to all participants, including a 1-point correction to those with ≤ 12 years of education. The maximum MoCA score is 30, with a score of 26 or above being considered a passing score (Nasreddine et al., 2005). In addition to the total score, we calculated modified MoCA scores by omitting results for subtests in which stimuli were presented auditorily (Digit Span, Attention to Letters, Sentence Repetition, and Delayed Recall; MoCA-Modified; Dupuis et al., 2015; Al-Yawer et al., 2019). This change in scoring resulted in 10 points being deducted from the original MoCA scoring, yielding a maximum MoCA-Modified score of 20. To determine a cut-off point for MoCA-Modified, we used a proportional equivalent to the MoCA's 26/30 threshold for passing (86.66%), which would be 17/20 in the MoCA-Modified (.866 x 20 = 17.33). As such, a score of 17 or above was considered to be a passing score (see Wittich et al., 2010, Al-Yawer et al., 2019).

Statistical Analyses

In order to test our hypotheses, we first examined pass/fail rates on the MoCA and MoCA-Modified for those with/without HL using Chi-square tests. Second, we conducted a linear regression analysis using MoCA score as our dependent variable, with age, education, history of depression, sex, and PTA as independent variables. Additionally, an interaction term (Sex x PTA) was added in a second step to test the hypothesis of sex-related differences in associations between hearing and MoCA scores. No violations of normality were detected. Visual examination of scatterplots of standardised residuals versus predicted values revealed

some heteroscedasticity in the data. As such, a weighted least squares regression procedure was used, which met the assumption of homoscedasticity. Additionally, in separate analyses for men and women, we conducted Pearson partial correlations between scores on the MoCA and MoCA-Modified with PTA. All partial correlations were corrected for age, formal education, and history of depression, factors that have been associated with hearing, cognition, or both. Data were analyzed using SPSS V.23.0.

Results

Participants were excluded due to inter-aural differences greater than 20 dB at two or more adjacent standard octave frequencies (N = 16), missing data (N = 2), or being MoCA outliers (N=9), with outliers being defined as having a MoCA score +/- three standard deviations from the mean. The final sample consisted of 193 older adults, including 77 (40%) men and 116 (60%) women. Table 1 shows the demographic information for our sample stratified by sex (see Supplementary Table S1 for a breakdown by sex and hearing status). Men and women did not differ in age, education, or in the percentage reporting a history of major depression; however, women had better PTAs compared to men. Additionally, women had higher average MoCA scores than men, but there were no sex-differences in average MoCA-Modified scores (Table 1).

We compared MoCA pass/fail status to hearing pass/fail status (Figure 1) in men and women. In men, MoCA status did not depend on hearing status (Chi-square(1) = 1.579, p = .209). In women, those with normal hearing were more likely to pass the MoCA compared to their counterparts with HL (Chi-square(1) = 12.113, p = .001; Figure 1). Similarly, passing or failing the MoCA-Modified did not depend on hearing status in men (Chi-square(1) = .053, p = .817). In women, those with normal hearing were more likely to pass the MoCA-Modified compared to their counterparts with HL (Chi-square(1) = 13.341, $p < .001$).

Table 1. Demographic and cognitive variables for all participants (full sample) and stratified by sex. Findings are reported as mean (standard deviation). Results reported for depression status are from a chi-square analysis.

	All (N=193)	Men (N=77)	Women (N=116)	P	NP^2
Age (years)	68.82 (5.70)	68.91 (5.49)	68.77 (5.86)	.866	<.001
Range		(61 – 84)	(60 – 87)		
Education (years)	16.45 (3.06)	16.74 (3.12)	16.27 (3.01)	.322	.006
Range		(11 – 25)	(6 – 25)		
Depression (% yes)	10.7	10.1	11.1	.840	.015
PTA (dB HL) Worse Ear	26.95 (8.67)	30.01 (9.70)	24.91 (7.28)	<.001	.083
Range		(11.25 – 57.50)	(7.50 – 43.75)		
MoCA Score (Max=30)	26.98 (2.31)	26.30 (2.30)	27.44 (2.21)	.001	.059
Range		(18 – 30)	(20 – 30)		
MoCA-Modified Score (Max=20)	18.68 (1.50)	18.49 (1.52)	18.81 (1.47)	.150	.011
Range		(13 – 21)	(13 – 21)		

Note. PTA, Pure-tone average of 500, 1000, 2000, and 4000Hz in the worse ear; MoCA, Montreal Cognitive Assessment scale.

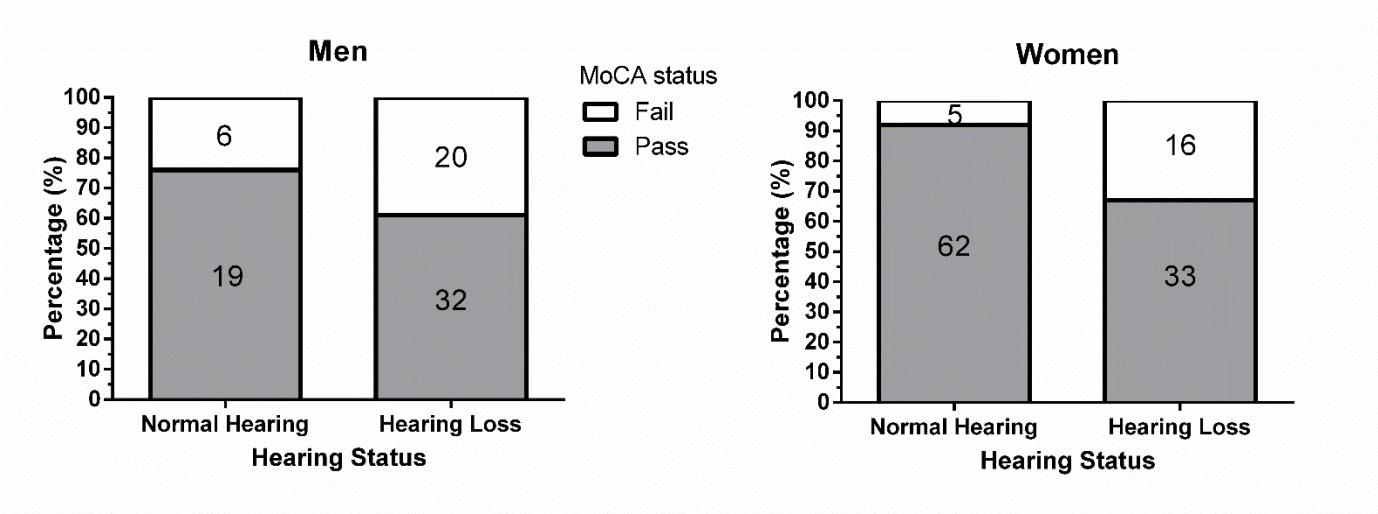

Figure 1. Percentage of participants passing/failing the MoCA (score < 26 constitutes failure) based on hearing status in men (N = 77; left panel) and women (N = 116; right panel). Values in bins represent the raw count.

Table 2 shows the linear regression model using MoCA score as the dependent variable, with age, education, history of depression, sex, and PTA as independent variables. Model 1 was significant ($R^2 = .141$, $p < .001$) and shows independent effects of Sex ($B = -.252$, $p = .001$) and PTA ($B = -.239$, $p = .004$) on MoCA score. In Model 2, the interaction term of Sex by PTA was added, which was significant ($B = .506$, $p = .040$) even accounting for covariates and for the independent effects of sex and PTA separately (full model $R^2 = .162$, $p < .001$; Table 2). A regression model examining hearing in the better ear showed a similar pattern, but did not reach significance (Supplementary Table S2).

Finally, to further understand the nature of the Sex by PTA interaction, we examined Pearson partial correlations of PTA with MoCA scores in men and women, controlling for participants' age, education, and depression status. The results showed that while men did not display any associations between PTAs and MoCA scores (PTA x MoCA $r = -.011$, $p = .929$; PTA x MoCA-Modified $r = -.059$, $p = .683$), women showed associations between PTA and MoCA scores ($r = -.302$, $p = .002$; Figure 2), and between PTA and MoCA-Modified scores ($r = -.247$, $p = .011$). The direction of these associations suggested that worse hearing (higher thresholds) was associated with worse MoCA scores.

Discussion

In the current investigation, we explored the relationship between PTA and MoCA scores in healthy older adults. Women with normal hearing were more likely to pass the MoCA relative to their counterparts who had HL; however, passing the MoCA did not depend on hearing status for men. Regression analysis revealed an interaction between sex and hearing, and Pearson partial correlations showed that MoCA scores were associated with PTA only in women.

Table 2. Regression Models for MoCA scores examining the predictive values of demographic variables, sex, and hearing in the worse ear (Model 1) and their interaction (Model 2).

MoCA Score	Model 1			Model 2		
	B	95% CI	t	B	95% CI	t
Age	.028	-.040 – .095	.805	.033	-.035 – .100	.954
Education	.049	-.063 – .160	.864	.050	-.060 – .160	.897
Depression Status	-.027	-1.090 – 1.037	-.049	.003	-1.050 – 1.057	.007
Sex	-1.159	-1.830 – -.489	-3.413*	-3.155	-5.168 – -1.142	-3.094*
PTA	-.067	-.111 – -.022	-2.926*	-.106	-.164 – -.048	-3.595*
Sex by PTA	-	-	-	.084	.004 – .165	2.073*
R^2 (Adjusted R^2)		.141* (.115)			.162* (.132)	
R^2 Change		-			.021*	

Note. PTA, pure-tone average of 500, 1000, 2000, 4000 Hz in the worse ear; MoCA, Montreal Cognitive Assessment; MoCA-Modified, MoCA Hearing. Model 1 (columns 2-4) included demographic factors and sex and PTA individually. Model 2 (columns 5-7) included all the aforementioned variables in addition to the interaction term between sex and PTA. Beta values represent unstandardized coefficients, while t statistic is the beta coefficient divided by its standard error. The change in R^2 represents the amount of variance that can be attributed to the interaction between sex and hearing after all other variables are considered.

*$p < .05$

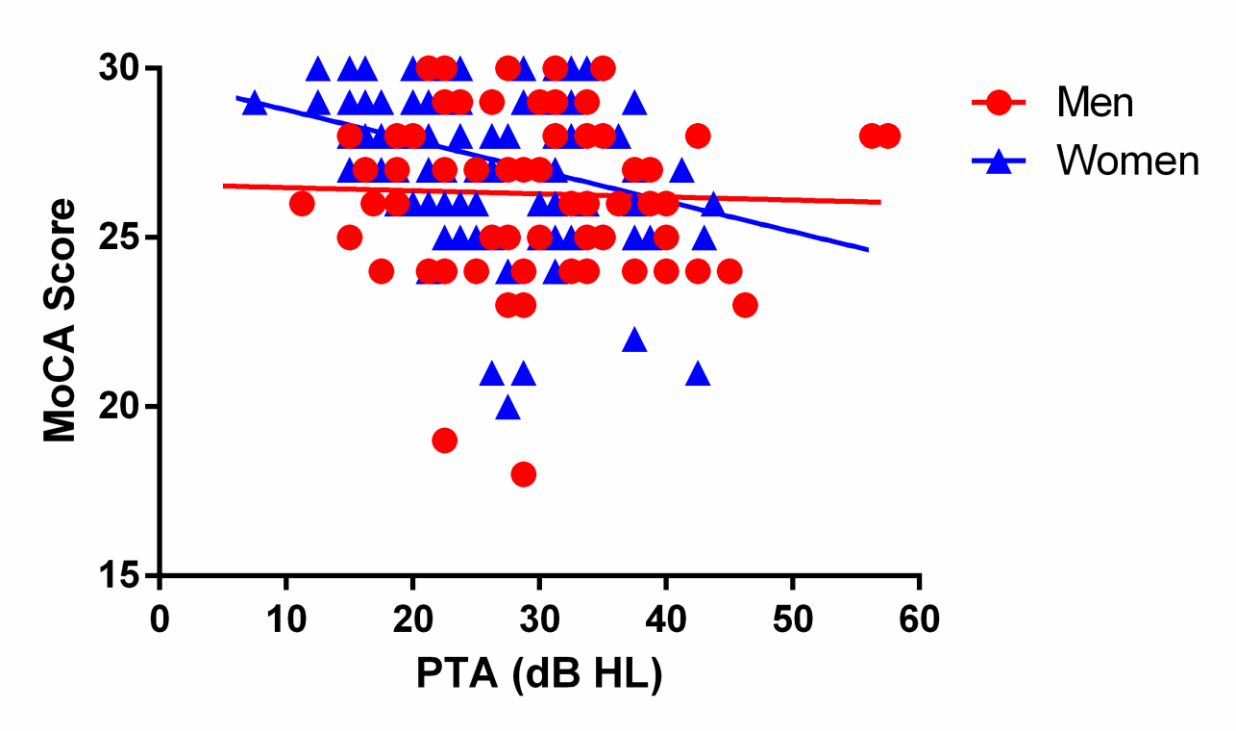

Figure 2. Scatterplot showing the association between MoCA scores and PTA thresholds in men (circles) and women (triangles). Hearing was determined using pure-tone average of thresholds at 500, 1000, 2000, and 4000 Hz in the worse ear. Men N = 77, women N = 116.

The association between PTAs and MoCA performance was evident only in the women. This finding held when examining the data categorically by comparing MoCA pass/fail status to hearing, and when examining the data continuously by looking at regression and correlational analyses. Importantly, this association was also observed when examining MoCA scores with hearing-dependent items omitted (MoCA-Modified). That this association was observed on MoCA-Modified scores indicates that these effects are not attributable to difficulty hearing auditory stimuli or instructions during testing, consistent with previous findings (Lin et al., 2011a; Phillips et al., Submitted). Instead, they appear to represent a more fundamental sex-related connection between declines in hearing and cognitive functioning.

In the current study, poorer hearing cannot explain why sex-related differences in the auditory-cognitive associations were only observed in women because they had better PTAs than men. Likewise, lower cognitive abilities are unlikely to explain the sex-related differences in auditory-cognitive associations because the women in our sample had higher mean MoCA scores than the men. In contrast to our current findings, most previous studies showed no sex-related differences in MoCA scores (e.g., Aiello et al., 2021; Apolinario et al. 2018). However, we note that mean MoCA-Modified scores in our study did not differ between the sexes. This finding is in line with other studies showing better performance by women on the delayed recall subtest, which is not included in the MoCA-Modified (Engedal et al., 2021).

There is some evidence from prior studies to suggest that sensory-cognitive interactions show sex-related differences: Helzner and colleagues (2005) observed a higher likelihood of hearing loss only in black women with lower MMSE scores, yet it was unclear why this effect was not observed in other sexes/races, particularly white women**.** The sample in the current study was over 75% white (data not shown), and thus race-specific analyses are untenable. Lyu and

Kim (2018) observed an association between self-reported hearing problems and performance on the MMSE in women alone.

Our findings are unlikely to reflect the influence of perceptual conditions during testing (information degradation hypothesis), as the effects in women were observed even on MoCA test items that are not hearing-dependent (MoCA-Modified). Moreover, if sensory deprivation played a role then the auditory-cognitive associations should have been greater for men than women as men had worse hearing. It is possible that auditory-cognitive associations depend on the phenotype and specific sub-type of age-related HL. Men are more likely to develop the "sensory" phenotype, with damage to outer hair cells of the cochlea due to occupational noise, while women are more likely to develop the "metabolic" phenotype, with deterioration of the stria vascularis in the cochlea from conditions such as cardiovascular disease or diabetes (Dubno et al., 2013). A common cause of auditory-cognitive associations could be implicated for the metabolic sub-type of age-related hearing loss insofar as the risk of cognitive decline may also be increased by conditions such as cardiovascular disease or diabetes.

Finally, hormonal influences on hearing and cognition may also play a role. Estrogen receptors in the inner ear are thought to play a positive role in sensory processing (Hederstierna et al., 2010). Lower estradiol levels in post-menopausal women have been associated with worse performance on cognitive tasks (Ryan et al., 2012) and post-menopausal changes in hormone levels have been associated with a higher risk of Alzheimer's disease in women (Mosconi et al., 2017). Therefore, it is possible that lower estrogen levels following menopause mediate the association between hearing and cognition in women, especially those who have the metabolic subtype of age-related HL. Further studies addressing these possibilities are required.

Limitations

We observed significant associations between hearing and cognition in women over and above the effects of age, education, and depression. However, the sample was recruited for a study assessing balance and physical ability, and a subset of the sample had to be medically cleared for physical exercise, thus biasing the selection of participants towards physically healthy individuals, and so may not be representative of the population. Furthermore, we had limited information regarding the onset, duration, and etiology of hearing loss in our sample. Finally, we used the worse rather than the better ear in our main analyses. The difference between the two ears was statistically significant but small given that it falls within the +/- 5 dB range of clinical test error (mean PTA worse ear = 26.95 dB, mean PTA better ear = 22.04 dB, t = 11.943, $p <$ .001). An additional regression model examining hearing in the better ear showed a similar pattern to the pattern found using data for the worse ear, but it did not reach significance for the interaction term (Supplementary Table S2). It may be that the worse ear is more representative of long-term damage to the cochlea and thus more likely to show an association with cognition.

Conclusion

Our study is one of the first to focus on and show sex-specific differences in auditory-cognitive associations. We demonstrated associations between PTA as a hearing measure and MoCA score only in women, even when hearing-dependent items were not included in scoring. If these preliminary findings of stronger auditory-cognitive coupling in women than men are replicated, then sex- and possibly gender-related factors will need to be considered in future studies addressing the mechanisms of auditory-cognitive interactions. The current results highlight the complex relationship between sex, hearing, and cognitive screening scores, and underscore the need for further investigation of sex- and gender-related differences in auditory-cognitive associations.

Supplementary Table S1. Demographic and cognitive variables for those with normal hearing and hearing loss (based on the cut-off of a 25 dB HL pure-tone average of thresholds at 500, 1000, 2000, and 4000 Hz in the worse ear). Men normal hearing N = 25, hearing loss N = 52; women normal hearing N = 67, hearing loss N = 49. Findings are reported as mean (SD). Significant differences between participants with normal hearing and hearing loss are noted as *p < .05.

		Normal Hearing	Hearing Loss	*P*	*Effect Size*
Age (years)	**Men**	65.80 (4.54)	70.40 (5.31)	<.001*	.16
	Women	66.31 (4.13)	72.12 (6.23)	<.001*	.21
Education (years)	**Men**	16.90 (2.61)	16.67 (3.33)	.787	.001
	Women	16.56 (2.37)	15.87 (3.72)	.270	.002
Depression (% yes)	**Men**	10.0	10.2	.980	.003
	Women	10.8	11.6	.889	.013
MoCA Score (Max=30)	**Men**	26.56 (2.35)	26.17 (2.29)	.493	.006
	Women	28.00 (1.64)	26.67 (2.63)	.003*	.07
MoCA-Modified Score (Max=20)	**Men**	18.68 (1.65)	18.40 (1.46)	.459	.007
	Women	19.13 (.95)	18.37 (1.90)	.012*	.05

Note. PTA, pure-tone average of 500, 1000, 2000, 4000 Hz in the worse ear; MoCA, Montreal Cognitive Assessment; MoCA-Modified, MoCA Hearing. Results for self-reported depression status are from a chi-square analysis and effect sizes reported are Cramer's V. Due to violation of the homogeneity of variance assumption, Welch's ANOVA procedure was used and ω^2 effect sizes are reported for the following variables: Male age, female age, education, MoCA, and MoCA-Modified scores. For all other variables, a univariate ANOVA was used and effect sizes reported are η_p^2.

Supplementary Table S2. Regression Models for MoCA scores examining the interaction between sex and hearing in the better ear (based on pure-tone average of thresholds at 500, 1000, 2000, and 4000 Hz in the better ear). *p < .05.

MoCA Score	Model 1			Model 2		
	B	95% CI	t	B	95% CI	t
Age	-.007	-.074 - .060	-.202	-.003	-.067 - .060	-.100
Education	.041	-.070 - .152	.732	.035	-.076 - .142	.624
Depression Status	.138	-.948 – 1.225	.251	.139	-.948 – 1.200	.254
Sex	-1.026	-1.729 - -.324	-2.884*	-2.864	-5.013 - -.718	-2.508*
PTA Better ear	-.044	-.098 - .011	-1.582	-.085	-.153 - -.016	-2.313*
Sex by PTA	-	-	-	.082	-.009 - .174	1.693
R^2 (Adjusted R^2)		.082* (.055)			.097* (.065)	
R^2 Change					.015	

Note. PTA, pure-tone average of 500, 1000, 2000, 4000 Hz in the better ear; MoCA, Montreal Cognitive Assessment; MoCA-Modified, MoCA Hearing. Model 1 (columns 2-4) included demographic factors and sex and PTA individually. Model 2 (columns 5-7) included all the aforementioned variables in addition to the interaction term between sex and PTA. Beta values represent unstandardized coefficients, while t statistic is the beta coefficient divided by its standard error. The change in R^2 represents the amount of variance that can be contributed to the interaction between sex and hearing after all other variables are considered.

Chapter 4

Manuscript III

Sex-specific interactions between hearing and memory in older adults with Mild Cognitive Impairment: Findings from the COMPASS-ND study

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Manuscript submitted to Ear and Hearing. Minor changes to grammar, spelling, formatting, and citation style were made to homogenize it with the rest of the dissertation.

Abstract

Objectives: Hearing loss in older adults is associated with performance on cognitive tasks and the risk of developing dementia. However, very few studies have investigated sex-related effects on these associations. A previous study of cognitively healthy older adults showed an association between hearing and cognition in women only. In the present study, we examined the effects of sex and hearing on cognition in individuals with mild cognitive impairment (MCI). We predicted that women with hearing loss would be more likely to show poorer performance on the cognitive measures compared to women with normal hearing, while cognitive performance in men would not depend on hearing. We further predicted that these auditory-cognitive associations would not depend on test modality, and would thus be observed in women for both auditory and visual tests.

Design: Participants were 101 older adults with amnestic MCI (M=71 years, 45% women) in the Canadian Consortium on Neurodegeneration in Aging (CCNA) COMPASS-ND study. Performance on the Montreal Cognitive Assessment (MoCA), Rey Auditory Verbal Learning (RAVLT), and Brief Visuospatial memory test – revised (BVMT-R) was analyzed to investigate sex-related differences and/or hearing-related differences. Participants were categorized as having normal hearing or hearing loss using two different measures: pure-tone hearing screening results (normal based on a pure-tone threshold $\leq$ 25 dB HL at 2000 Hz in the worse ear) and speech-in-noise speech reception thresholds (SRTs; normal < -10 dB SNR on the Canadian Digit Triplet Test; CDTT).

Results: Men and women did not differ in age, years of education, or other relevant covariates. Yet, women with better hearing on either pure-tone or speech-in-noise measures outperformed their worse hearing counterparts on the MoCA total score. Additionally, women with better

hearing were more likely to recall several words on the MoCA delayed recall trial relative to those with worse hearing. Women with normal hearing showed significant correlations between CDTT SRTs and both MoCA and RAVLT scores, while no correlations were observed in men. In contrast, men but not women showed an effect of hearing group on BVMT-R test status.

Conclusions: There were sex-specific differences in auditory-cognitive associations in individuals with MCI. These associations were mostly observed in women and on auditory tests. Potential mechanisms and implications are discussed.

Introduction

It is estimated that about one-third of older adults over 65 years of age and one-half of older adults over 75 years of age have impaired hearing thresholds (Mick et al., 2021; World Health Organization, 2021). Hearing loss (HL) has been associated with cognitive decline and with the development of dementia in healthy older adults (e.g., Lin et al., 2011a, 2011b; Loughrey et al., 2018). Individuals with mild cognitive impairment (MCI) also display this association (e.g., Quaranta et al., 2014). Previous findings from Al-Yawer and colleagues (in press) have shown sex-related differences in auditory-cognitive associations in healthy older adults, suggesting that women show associations between hearing and cognitive measures, while men do not. In the current study, we examined the associations between hearing and cognitive measures in a sample of individuals with MCI, focusing on potential sex-related differences.

A growing body of literature has shown hearing loss to be associated with adverse physical and psychological health outcomes, such as hypertension (Gates et al., 1993), diabetes (Austin et al., 2009), social isolation (Mick et al., 2014), depression (Acar et al., 2011), and decline in functional activities of daily living (Dalton et al., 2003). HL has also been associated with an increased risk of incident dementia (e.g., Deal et al., 2017; Lin et al., 2011b; Quaranta et al., 2014) and lower scores on cognitive tests in healthy older adults (e.g., Armstrong et al., 2020a; Dupuis et al., 2015). These associations have been observed for both pure-tone average (PTA) detection thresholds and suprathreshold hearing measures such as dichotic sentence identification and dichotic digits tests (for review see Loughrey et al., 2018; Gates et al., 2010). Indeed, eliminating hearing loss in middle- and older-age can potentially reduce the risk of dementia by up to 8% (Livingston et al., 2017, 2020). A better understanding of the potential mechanisms underlying auditory-cognitive associations is needed.

Several mechanisms have been proposed to account for auditory-cognitive associations, starting with work based on the Berlin Aging Study (Baltes & Lindernberger, 1997; Lindenberger & Baltes, 1994). Since then, these hypotheses have been discussed, reviewed, and refined (e.g., Dennis & Cabeza, 2008; Pronk et al., 2019; Schneider & Pichora-Fuller, 2000; Wingfield et al., 2005). Briefly, the common cause hypothesis proposes that a third factor acts independently on both hearing and cognition (e.g., vascular or neural factors). The information degradation hypothesis proposes that hearing difficulty incurs short-term effects insofar as more cognitive resources are required for information processing when the quality of the sensory input is diminished. The sensory deprivation hypothesis proposes that, over time, hearing loss affects cognition because there are changes in auditory brain regions or cognitive reserve corresponding to structural changes in the brain caused by decreased neural activity in these regions. Finally, the social isolation hypothesis suggests that, because hearing loss is associated with increased loneliness and social isolation, these negatively affect an individual's cognitive abilities. Note that these hypotheses are not mutually exclusive. For example, hearing loss could have immediate effects on the perception of auditory test items (as in the information degradation hypothesis), while long-term hearing loss could have negative consequences on brain structures which would then affect cognition (as in the sensory deprivation hypothesis).

MCI is considered a risk state for the development of dementia and Alzheimer's disease (Peterson, 2011). MCI is defined by an objective decline in one or more cognitive domains, usually involving episodic memory, but with no associated decline in functional activities. The presence of HL in MCI has been associated with higher levels of some disease biomarkers (e.g., cerebrospinal fluid measures of Tau), as well as faster accumulation rates of said biomarkers longitudinally (Xu et al., 2019), suggesting that HL may be associated with neuropathological

decline. Declines in pure-tone detection thresholds and suprathreshold auditory processing are more prevalent in individuals with MCI relative to those with normal cognition (Häggström et al., 2018; Idrizbegovic et al., 2011; Quaranta et al., 2014; but see Giroud et al., 2021). Performance on hearing measures has also been associated with neuropsychological test scores (e.g., Gates et al., 2010). Studying auditory-cognitive associations in individuals with MCI, who are at higher risk for transitioning into dementia, may help elucidate how having HL affects the cognitive deficits observed in this condition.

Sex-related differences in hearing and dementia

There are well-documented sex-related differences in the etiology and presentation of hearing loss (e.g., Dubno et al., 2013). In addition to lifelong differences in the auditory brainstem response and transient-evoked otoacoustic emissions (Berninger 2007; Liu et al., 2017), women commonly develop high-frequency hearing loss later in life, around 50 years of age, compared to men, in whom adult-onset HL can be detected as early as 30 years of age (Davis, 1995). Furthermore, men generally tend to have worse high-frequency hearing than women, even after correcting for such factors as age, occupation, and lifetime noise exposure (Cruickshanks et al., 1998; Helzner et al., 2005). Hearing loss in women may be influenced by hormonal fluctuations associated with menopause, although the exact nature of the association remains unknown (Da Silza Souza et al., 2017; Hederstierna et al., 2010). Research into the effects of hormone replacement therapy (HRT) on hearing may shed some light on this relationship. Curhan and colleagues (2017) showed that postmenopausal women who underwent HRT were more likely to have hearing loss compared to those who did not undergo HRT. While this relationship may vary based on the type and duration of HRT (e.g., Armstrong et al., 2020b), these findings suggest a protective role for sex hormones, most probably estrogen/estradiol, in

the development of hearing loss in women. Overall, sex likely plays a role in the development of hearing loss in some etiologies (Reavis et al., submitted).

Sex-related differences are evident in the onset and progress of cognitive impairment and dementia. For example, the incidence of Alzheimer's disease is higher in women, even after accounting for their longer lifespan (Vina & Lloret, 2010). This has been suggested to be a consequence of reduced estrogenic protection against amyloid-B toxicity. It was previously believed that MCI is more prevalent in men (Petersen et al., 2010); however, a recent meta-analysis (Au et al., 2017) found no sex-related differences in the prevalence of amnestic MCI, but that non-amnestic MCI is more prevalent in women. Sohn and colleagues (2018) showed that women with MCI displayed greater decline over time in cognitive scores compared to men. In cognitively healthy older adults, differences have also been observed with regards to specific cognitive domains; men generally outperform women on visuospatial tests, while women tend to outperform men on auditory verbal memory tests (Vogel et al., 2003). Sundermann and colleagues (2016) have shown that women with amnestic MCI outperform men on verbal memory tests, even after accounting for hippocampal volume, leading to the suggestion that women may have more cognitive reserve for auditory verbal memory than men.

In light of the literature on sex-related differences in both hearing impairment and cognitive impairment, one could expect sex-related differences to emerge in auditory-cognitive associations. Surprisingly, very few studies have examined such differences, with most research using sex as a control variable in analyses (e.g., Deal et al., 2017; Harrison-Bush et al., 2015; Lin et al., 2011a). One notable exception is Lindenberger and Baltes' original study (1994) in which sensory functioning mediated the association between age and intelligence in cognitively normal older adults. This structural model remained significant when accounting for sex and did not

differ between men and women. Another study by Phillips and colleagues (Submitted) similarly observed an association between hearing and cognition but no interaction with sex in a national Canadian sample. In contrast, Helzner and colleagues (2005) examined sex-related and race-related differences in hearing loss and noted that lower scores on a modified version of the Mini-Mental State Examination (MMSE, Folstein et al., 1975) were associated with a higher risk of pure-tone hearing loss, and that this risk was significantly elevated in black women relative to individuals of other sexes/races. Eberhard and colleagues (2019) noted that women, but not men, showed an association between low-frequency pure-tone hearing loss and MMSE scores. Moreover, Lyu and Kim (2018) observed an association between self-reported hearing loss and performance on the MMSE, but only in women. Recent research from Al-Yawer and colleagues (in press) has shown a negative association in cognitively normal older women between scores on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) scale and audiometric hearing loss, even when hearing-dependent items were not included when scoring the MoCA (MoCA-Modified; Al-Yawer et al., 2019). An effect that was not observed in men. We note one other study (Huang et al., 2019) in which the opposite pattern was observed, with composite cognitive scores being associated with hearing in men only and not in women. Nevertheless, the aforementioned findings suggest the existence of sex-related differences in auditory-cognitive associations that warrant further investigation.

In the current study, we used data from the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study of the Canadian Consortium on Neurodegeneration in Aging (CCNA, Chertkow et al., 2019) to examine possible sex-related differences in auditory-cognitive associations in individuals with amnestic MCI. As memory is the domain most involved in amnestic MCI, we focus on a screening measure of general

cognition that has a strong memory component (MoCA) and more specialized episodic learning and memory measures in both the auditory verbal (Rey Auditory Verbal Learning Test, RAVLT; Schmidt, 1996) and visuo-spatial (Brief Visuospatial Memory Test-Revised, BVMT-R; Benedict, 1997) domains. We included tests in both sensory modalities because finding differences in visual tests of memory as a function of hearing status would support the common cause and deprivation mechanisms and suggest that differences in cognition are not based solely on difficulties perceiving hearing test stimuli. In contrast, the information degradation hypothesis would not predict changes in results on visual tests because of hearing difficulties. We compared total scores on these three cognitive measures and item-specific recall on the MoCA for men and women with normal hearing or hearing loss, as defined either by pure-tone screening thresholds or by speech recognition thresholds (SRTs) in noise on the Canadian Digit Triplet Test (CDTT; Ellaham et al., 2016; Giguère et al., 2020; Pereira et al., 2021). We predicted, based on previous findings (Al-Yawer et al., in press), that women with hearing loss would be more likely to show poorer performance on the cognitive measures compared to women with normal hearing, while cognitive performance in men would not depend on hearing. We further predicted that these auditory-cognitive associations would not depend on test modality, and would thus be observed in women for both auditory verbal (MoCA, RAVLT) and visual (BVMT-R) tests.

Materials and Methods

Participants

Individuals in this study were recruited as part of the COMPASS-ND study in CCNA (Chertkow et al., 2019). Participants were recruited at over 20 sites throughout Canada. General inclusion criteria for COMPASS-ND include: age less than 85 years, subjective or objective cognitive complains, and sufficient proficiency in either English or French. Exclusion criteria

include: the presence of other significant brain disease (e.g., multiple sclerosis, Huntington's disease), ongoing alcohol or drug abuse, lack of a study partner, and a total MoCA score < 13/30. Written informed consent was obtained from all participants. The COMPASS-ND study was approved by the Jewish General Hospital Research Ethics Board.

To establish a diagnosis of MCI, the following criteria were used: participants had to be over 60 years old, with cognitive complaints reported by the participant or their informant. Furthermore, participants had to have a global Clinical Dementia Rating (CDR; Morris, 1993) ≤ 0.5, and a score ≥ 15 on the Lawton-Brody instrumental activities of daily living (IADL) scale (Lawton & Brody, 1969; Graf, 2008). Finally, participants had to demonstrate impairment in one or more cognitive domains greater than what would be expected for the participant's age and education. Operationally, this meant a score below education-adjusted Alzheimer's Disease Neuroimaging Initiative (ADNI) cut-offs on the WMS-R Logical Memory II subtest (Petersen et al., 2010; Wechsler, 1987), a Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989) word-list score below 6, a MoCA score between 13-24/30 (inclusive), or a global CDR score > 0. The final sample consisted of 101 individuals who met these criteria for MCI (COMPASS-ND data release version 03.2020).

Procedure

We report data from the screening, clinical workup, and neuropsychological testing visits of the COMPASS-ND study. Data were stored and accessed from the Longitudinal Online Research and Imaging System (LORIS) database (Das et al., 2011).

Demographics

As part of the screening and clinical workup visits, demographic information was collected. Note that biological sex was assessed using the question: "What is your sex?" We will refer to our participants as men and women but note that we did not ask any questions referring to gender. In the current investigation, we include the participants' self-reported age, sex, years of education, history of hypertension, hyperlipidemia, cardiovascular health (presence of angina, atrial fibrillation, or heart attack), peripheral vascular disease, smoking, and type I or II diabetes. These risk factors have been previously associated with risk of hearing loss (e.g., Helzner et al., 2005). Vision was assessed using two measures: the Minnesota Reading Acuity chart (MNREAD) reading acuity measure (Mansfield et al., 1994) for which participants read 19 sentences of varying print sizes at a distance of 40 cm from the participant, and the Mars Letter Contrast Sensitivity measure (Arditi, 2005; Dougherty et al., 2005), for which participants try to identify 48 letters of varying contrasts presented at a distance of 40 cm from the participant.

We report the participants' scores on the Geriatric Depression Scale (GDS; Yesavage et al., 1983) because depression has been associated with both hearing loss and cognitive decline (see Rutherford et al., 2018 for review). To assess the level of social activity of our participants (as in the social isolation hypothesis), the responses to the following question were noted: "Taking only your current situation into consideration, how would you rate your participation/involvement in social activities?" with the three possible answers being "High", "Normal", and "Low."[1]

Hearing

Pure-tone Screening

[1] This question was part of a larger questionnaire on social network size. The results from the other questions are shown in Supplementary Digital Content 1 table, and do not indicate any sex-related differences in social variables in this sample at the time of testing.

Ability to detect pure-tones presented over earphones was assessed using a GSI 18 portable audiometer in a quiet room. A 2000 Hz tone was presented at 40 dB HL as an initial check of the participant's ability to detect sound. If the participant detected the tone, then tones at 1000, 2000, and 4000 Hz were presented at an intensity of 25 dB HL, with tones administered to the right and left ears separately and with two trials at each frequency in each ear. The better trial in each ear was used to categorize hearing (see below). If the participants failed the initial 2000 Hz check at 40 dB HL and they did not have their own hearing aid, they were provided with a pocket-talker (POCKETTALKER Ultra, Williams Sound) during clinical and neuropsychological testing (N=2).

For the purposes of data analysis, participants were initially assigned to one of six hearing categories based on their ability to detect 2000 Hz: 1) Normal Hearing, participants were able to detect the 2000 Hz tone at 25 dB HL in both ears. 2) Mild 1, participants detected the 2000 Hz tone at 25 dB HL in the better ear and at 40 dB HL in the worse ear. 3) Mild 2, participants detected the tone at 40 dB HL in both ears. 4) Moderate 1, participants detected the tone at 25 dB HL in the better ear, but failed to detect it at 40 dB HL in the worse ear. 5) Moderate 2, participants detected the tone at 40 dB HL in the better ear, but failed to detect it at 40 dB HL in the worse ear. 6) Moderate 3, participants failed to detect the tone at 40 dB HL in either ear[2]. Figure 1 shows the distribution of these categories in men and women.

Due to the small number of participants in some of the hearing categories (Figure 1), we dichotomized the hearing variable based on pure-tone screening. The normal hearing (NH_{PT}) group included participants who were able to detect the 2000 Hz pure tone at 25 dB HL in the

[2] We validated this screening protocol in an independent sample of older adults (N=242, age=70.67, 69.4% women) with full audiograms at 1000, 2000, and 4000 Hz. The 6 hearing categories here were strongly correlated with pure-tone averages in both the better ($r = .84$, $p < .001$) and worse ($r = .85$, $p < .001$) ears (see Giroud et al. 2021 for details).

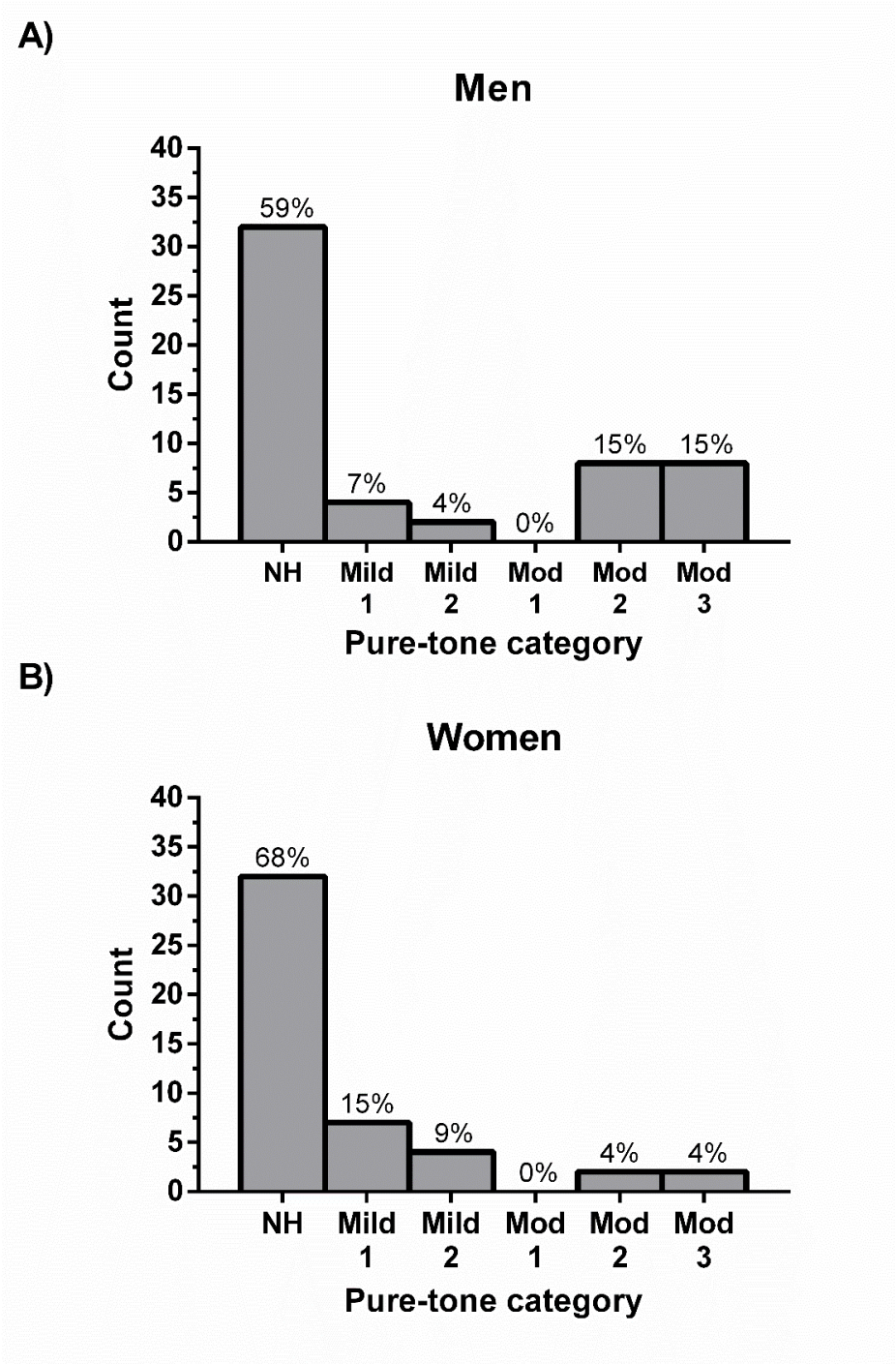

Figure 1. Histogram representing the number of participants in each of the six pure-tone hearing categories in A, men (N=56) and B, women (N=45). Percentages represent the percentage of participants that fall into a given category. See text for category descriptions. NH, normal hearing; Mod, Moderate hearing loss.

worse ear (equivalent to category 1, above). The hearing loss (HL_{PT}) group included participants who were not able to detect the 2000 Hz pure tone at 25 dB HL in their worse ear (equivalent to categories 2-6, above). This resulted in 64 individuals (63.4%; 32 men and 32 women) being categorized as having normal hearing, and 37 (36.6%; 22 men and 15 women) being categorized as having hearing loss.

Canadian Digit Triplet Test (CDTT)

The CDTT (Ellaham et al., 2016; Giguère et al., 2020) was administered to assess participants' suprathreshold hearing abilities (speech reception thresholds (SRT) in noise). The test was administered in a quiet office using a Dell laptop, a pair of headphones (DD45), and a response keypad. On each of 24 trials, the participant heard a set of three digits presented in a speech-shaped background noise. The participant was instructed to enter the digits heard on each trial using a keypad arranged as on a touch-tone phone keypad. The level of the noise presented on each trial was adjusted using an automated adaptive procedure. The dependent measure was the participant's SRT, which corresponds to the signal-to-noise ratio (SNR) at which the digit triplets are correctly recognized 50% of the time. The standard deviation (SD) of the responses for a participant and the number of reversals made as the noise level was adjusted over the 24 trials were used to identify erratic runs. Over the 24 trials, if a participant had a mean SRT > 4 or a SD > 3 dB SNR then their CDTT data were excluded from analysis (N=3).

For our analyses, we used a value of SRT = -10.00 dB SNR as the threshold for categorizing our CDTT scores, with scores < -10.00 being considered normal hearing (NH_{SRT}), and scores ≥ -10.00 being considered hearing loss (HL_{SRT}). This value was chosen based on the results of a validation study conducted in older adults with normal audiograms; specifically,

SRTs lower than the mean SRT plus 2 SD (-11.5 + (2*0.7) dB SNR) were considered to be normal (Pereira et al., 2021).

Cognition

Participants in the COMPASS-ND study are administered a battery of cognitive tests as part of the neuropsychological testing session (see Chertkow et al., 2019 for a full test list). As memory is the domain most affected in amnestic MCI, we focused on measures of general cognition with a strong memory component (MoCA) and more specialized episodic learning and memory measures in both the verbal (RAVLT) and visual (BVMT-R) domains.

MoCA

The MoCA was administered to all participants during the screening visit and the results on the MoCA contributed to the study diagnosis of MCI (see above). A 1-point correction was added to the score of those who had 12 or less years of education (Nasreddine et al., 2005). The MoCA is scored out of 30, with a score of 26 or above needed to pass. In addition, we examined MoCA-Modified scores (Dupuis et al., 2015; Al-Yawer et al., 2019) by excluding any hearing-dependent items (digit span, attention to letters, sentence repetition, delayed recall), reducing the total possible score to 20 on the MoCA-Modified instead of the MoCA's 30. On the MoCA-Modified, a score of 17 or above is considered an optimal cut-off for passing (Al-Yawer et al., 2019).

We conducted additional analyses of the delayed recall subtest of the MoCA. For this subtest, participants repeat five words read by the tester in two learning trials and they are asked to recall the words five minutes later. If a word was correctly repeated on both learning trials, but was not accurately recalled later, then this would suggest problems with retrieval, despite the

word having been correctly repeated during the learning trials. For our analyses, we first examined the percentage of participants who correctly repeated a word on both learning trials. Second, among those who correctly repeated a given word on the learning trials, we examined differences in the percentages of individuals who recalled that word after the five-minute delay. We compared results based on sex and hearing group membership.

Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT is an auditory test of learning and memory (Schmidt, 1996). The examiner reads a list of 15 words to the participant five times and the participant is asked to repeat the words in the list after each of the five readings. After all five test repetitions of the list have been administered, the participant is read and asked to recall a distractor list. Then, the participant is asked to recall the original list. After a 20-minute delay (in which other non-verbal cognitive tests are administered), the participant is asked to recall the original list once again. Here we report the total number of words correctly recalled over the 5 trials (RAVLT Total), and the number of words recalled after the 20-minute delay (RAVLT Delayed). To dichotomize RAVLT scores, we converted both values into Z-scores using age-corrected norms (Schmidt, 1996) and specified that a Z-score of -1.5 or above was considered to be a passing score.

Brief Visuospatial Memory Test-Revised (BVMT-R)

The BVMT-R is a visual test of learning and memory (Benedict, 1997). The participant is shown six figures on a single sheet of paper for 10 seconds, after which the paper is removed and the participant asked to draw the figures from memory. This same page is shown to the participant again two more times, for a total of 3 trials. After a 20-minute delay (in which other non-visual cognitive tests are administered) the participant is asked to draw the figures again

from memory. Scoring is based on the accuracy with which the shape of the figure is recalled and its correct location on the page. Here we report the total figure score over the 3 trials (BVMT-R Total), and figure recall after a 20-minute delay (BVMT-R Delayed). To dichotomize BVMT-R total and delayed scores, we converted the scores into Z-scores using age-corrected norms (Benedict, 1997), with a Z-score of -1.5 or higher considered to be a passing score.

Statistical Analyses

We examined our data in three separate ways. First, we conducted Chi-square tests to examine the differences in the proportion of individuals who passed or failed a cognitive test depending on their hearing group membership (NH vs. HL). Second, we conducted separate univariate 2 x 2 (sex by hearing category) ANCOVAs with continuous scores on our cognitive measures as the outcome variables, controlling for age and years of formal education. To test the *a priori* hypotheses that the auditory-cognitive association would differ by sex, we conducted planned comparisons (simple effects) of the cognitive measures to compare the NH versus HL groups within each sex. Bonferroni corrections were applied where necessary. Third, we examined Pearson partial correlations between the cognitive measures and the CDTT SRTs, controlling for age, years of formal education, and pure-tone hearing category. We conducted one additional analysis with the MoCA, in which we used Chi-square tests to analyze the proportion of participants who correctly recalled individual words on the MoCA delayed recall subtest based on only the words that were correct on both learning trials (as described above). Data were analyzed using SPSS V.23.0 and R Statistics version 3.6.2.

Results

Demographics

Table 1 shows the demographic and health information of our final sample, which included 54 men and 47 women (total N=101). Men and women did not significantly differ in age, education, depression scores, or the presence of hypertension, hyperlipidemia, diabetes, cardiovascular issues (angina, atrial fibrillation, or heart attacks), peripheral vascular disease, or smoking. Men had significantly better reading acuity than women (Table 1), though both were in the normal vision range. No differences were observed in self-reported social activity. There were no differences in the percentages of men and women categorized as having pure-tone HL (men HL_{PT} = 40.7%, women HL_{PT} = 31.9%; Chi-square(1) =.843, p = .358), nor was there a difference between men and women in the percentage using a hearing aid or a Pocketalker during cognitive testing (Table 1). Additionally, there were no differences in the percentages of men and women categorized as having SRT HL (men HL_{SRT} = 52.1%, women HL_{SRT} = 42.9%; Chi-square(1) = .764, p = .382). When we compared the two hearing measures to assess concordance between NH and HL distinctions, 46.7% of individuals were categorized as both NH_{PT} and NH_{SRT}, 32.2% were categorized as both HL_{PT} and HL_{SRT}, 15.6% were categorized as NH_{PT} and HL_{SRT}, while only 5.6% were categorized as HL_{PT} and NH_{SRT}.

Results within sexes were examined. As seen in Table 2, men in the NH_{PT} group were significantly younger than men in the HL_{PT} group (mean difference = 4.72 years; Table 2), but they did not differ in any other variables (all p's > .1). Similarly, women in the NH_{PT} group were significantly younger than women in the HL_{PT} group (mean difference = 4.64 years)[3], but they did not differ in any other variables (all p's > .1; Table 2). As seen in Table 3, similar findings

[3] We controlled for age (or used age-corrected normative data) in all of our analyses. Nevertheless, in order to ensure that age was not a major confounder, we re-ran our analyses using age-balanced group samples (excluding 8 participants at the extremes of our age range) and found no changes in the general pattern of results for any of the three cognitive measures (MoCA, RAVLT, BVMT-R).

Table 1. Demographic variables and differences between men and women in the sample. Bolded values are significant ($p < .05$).

	Overall (n=101)	Men (n=54)	Women (n=47)	F/X^2	P	Np^2/Cramer's V
Age (years)	71.19 (6.40)	71.77 (6.79)	70.51 (5.91)	.976	.326	.010
Education (years)	15.62 (4.07)	15.39 (4.25)	15.89 (3.88)	.384	.537	.004
Hearing Aid use (%)	14.9	20.4	8.5	2.795	.095	.166
Pocket Talker use (%)	2.0	1.9	2.1	.010	.921	.010
MNREAD (logMAR)	.14 (.16)	.10 (.15)	.18 (.16)	6.315	**.014**	**.061**
Mars Contrast Sensitivity (logCS)	1.69 (.15)	1.70 (.15)	1.69 (.15)	.028	.868	.001
Hypertension (%)	31	29.6	32.6	.103	.748	.032
Diabetes Type I or II (%)	14.3	15.1	13.3	.062	.804	.025
Smoking (%)	3.2	0.0	6.7	1.102	.294	.189
Angina (%)	5.0	7.4	2.2	1.432	.231	.120
Atrial Fibrillation (%)	6.0	9.3	2.2	2.211	.137	.149
Heart Attack (%)	7.1	7.7	6.5	.050	.822	.023
Peripheral Vascular Disease (%)	3.0	1.9	4.3	.508	.476	-.072
Hyperlipidemia (%)	45	46.3	43.5	.080	.778	.028
Social Activities (% Low)	39.6	40.7	38.1	4.363	.113	.213
Geriatric Depression Scores	6.95 (5.02)	6.78 (5.39)	7.15 (4.60)	.136	.713	.001

Continuous variables are tested with univariate ANOVAs and provide the F-value, P-value, and partial Eta squared (Np^2). Categorical variables are tested with Chi-square tests and provide the X^2-value, p-value, and Cramer's V.

Table 2. Demographic variables for men and women in the pure-tone NH and HL groups (based on 25 dB HL cut-off for 2000 Hz in worse ear). Men normal hearing n = 32; hearing loss n = 22; women normal hearing n = 32, hearing loss n = 15. Bolded values are significant (p < .05).

		NH_{PT}	HL_{PT}	*P*	ηp^2/Cramer's V
Age (years)	**Men**	69.96(5.84)	74.41(7.34)	**.016**	**.106**
	Women	69.03(5.27)	73.67(6.14)	**.011**	**.137**
Education (years)	**Men**	16.31(3.58)	15.50(5.17)	.875	<.001
	Women	16.52(4.03)	14.57(3.28)	.109	.056
MNREAD (logMAR)	**Men**	.08 (.14)	.14 (.17)	.167	.037
	Women	.18 (.18)	.20 (.18)	.758	.002
Mars Contrast Sensitivity (logCS)	**Men**	1.71 (.15)	1.67 (.14)	.406	.014
	Women	1.70 (.14)	1.66 (.18)	.377	.018
Hypertension (%)	**Men**	25	36.4	.369	.122
	Women	25	50	.096	.245
Diabetes *(%)*	**Men**	18.8	9.5	.359	.126
	Women	9.4	23.1	.220	.183
Smoking (%)	**Men**	0	0	-	**-**
	Women	10	0	.464	.189
Angina (%)	**Men**	9.4	4.5	.506	.091
	Women	0.0	7.1	.126	.225
Atrial Fibrillation (%)	**Men**	9.4	9.1	.972	.005
	Women	3.1	0.0	.504	.099
Heart Attack (%)	**Men**	6.5	9.5	.683	.057
	Women	3.1	14.3	.158	.208
Peripheral Vascular Disease (%)	**Men**	0.0	4.5	.231	.165
	Women	6.3	0.0	.339	.141
Hyperlipidemia (%)	**Men**	46.9	45.5	.918	.014
	Women	43.8	42.9	.955	.008
Social Activities (% Low)	**Men**	31.3	54.5	.230	.233
	Women	35.5	45.5	.603	.155
Geriatric Depression Score	**Men**	6.66 (5.68)	6.95 (5.07)	.844	.001
	Women	6.66 (4.87)	8.20 (3.91)	.289	.025

Continuous variables are tested with univariate ANOVAs and provide the p-value, and partial Eta squared (Np^2) for NH_{PT} vs. HL_{PT} comparisons. Categorical variables are tested with Chi-square tests and provide the p-value and Cramer's V.

were observed when groups were compared based on CDTT SRT hearing category, with the exception of reading acuity in men, which was better in NH_{SRT} men relative to HL_{SRT} men, but with both groups being within the normal acuity range (Table 3). Because the within-sex hearing subgroups differed in age, we used age as a covariate in all subsequent analyses.

Comparing Hearing Group Membership to Cognitive Test Pass/Fail Status

MoCA

Using a MoCA score of 26/30 or more as a passing score, and considering men and women separately, we compared the number of participants passing/failing the MoCA who were in the NH or HL groups (based on pure-tone and SRT criteria). As seen in Figure 2, there were no differences in the percentages of men passing or failing the MoCA based on either hearing group determined by pure-tone (Chi-square(1) = .002, p = .965) or by CDTT SRT (Chi-square(1) = .034, p = .853) criteria (Figure 2, left panels). In women, however, those in the HL_{PT} (Chi-square(1) = 7.353, p = .007) or HL_{SRT} group (Chi-square(1) = 4.978, p = .026) were less likely to pass the MoCA than those in the corresponding NH_{PT} and NH_{SRT} groups (Figure 2, top and bottom right panels, respectively).

We conducted further analysis of those who did or did not pass the MoCA excluding hearing-dependent items from scoring (MoCA-Modified), with a score of ≥ 17/20 considered to be a passing score (see Al-Yawer et al., 2019). Similar to the total MoCA score analysis, there were no differences in the percentages of men passing or failing the MoCA-Modified based on hearing group determined either by pure-tone (Chi-square(1) = .198, p = .657) or CDTT SRT (Chi-square(1) = .250, p = .617) criteria. In contrast to the findings when the total MoCA score was examined for women, there were no differences in the percentage of women passing or

Table 3. Demographic variables for men and women in the speech-in-noise NH and HL groups (based on -10 dB SNR SRT cut-off on the CDTT). Men normal hearing n = 23; hearing loss n = 24; women normal hearing n = 24, hearing loss n = 18. Bolded values are significant (p < .05).

		NH_{SRT}	HL_{SRT}	*P*	ηp^2/Cramer's V
Age (years)	**Men**	69.79(6.06)	74.29(7.13)	**.023**	**.107**
	Women	68.18(5.28)	74.11(5.21)	**.001**	**.247**
Education (years)	**Men**	14.76(3.59)	15.94(4.70)	.337	.020
	Women	16.58(4.38)	15.25(3.26)	.285	.029
MNREAD (logMAR)	**Men**	.04 (.14)	.17 (.15)	**.003**	**.174**
	Women	.17 (.20)	.20 (.12)	.543	.009
Mars Contrast Sensitivity (logCS)	**Men**	1.72 (.16)	1.65 (.14)	.132	.050
	Women	1.73 (.14)	1.64 (.17)	.084	.073
Hypertension (%)	**Men**	17.4	36.0	.147	.209
	Women	33.3	38.9	.710	.057
Diabetes *(%)*	**Men**	18.2	12.0	.553	.087
	Women	12.5	18.8	.588	.086
Smoking (%)	**Men**	0	0	-	**-**
	Women	11.1	0	.488	.192
Angina (%)	**Men**	13.0	4.0	.257	.163
	Women	0	5.6	.243	.180
Atrial Fibrillation (%)	**Men**	4.3	8.0	.602	.075
	Women	0	0	-	-
Heart Attack (%)	**Men**	13.6	4.0	.237	.172
	Women	4.2	5.6	.834	.032
Peripheral Vascular Disease (%)	**Men**	0	4.0	.343	.138
	Women	4.2	5.6	.834	.032
Hyperlipidemia (%)	**Men**	43.5	48.0	.753	.045
	Women	41.7	38.9	.856	.028
Social Activities (% Low)	**Men**	30.4	48.0	.230	.213
	Women	43.5	33.3	.342	.238
Geriatric Depression Score	**Men**	6.43 (6.23)	7.32 (5.18)	.594	.006
	Women	6.63 (4.64)	7.22 (4.52)	.679	.004

Continuous variables are tested with univariate ANOVAs and provide the p-value, and partial Eta squared (Np^2) for NH_{SRT} vs. HL_{SRT} comparisons. Categorical variables are tested with Chi-square tests and provide the p-value, and Cramer's V.

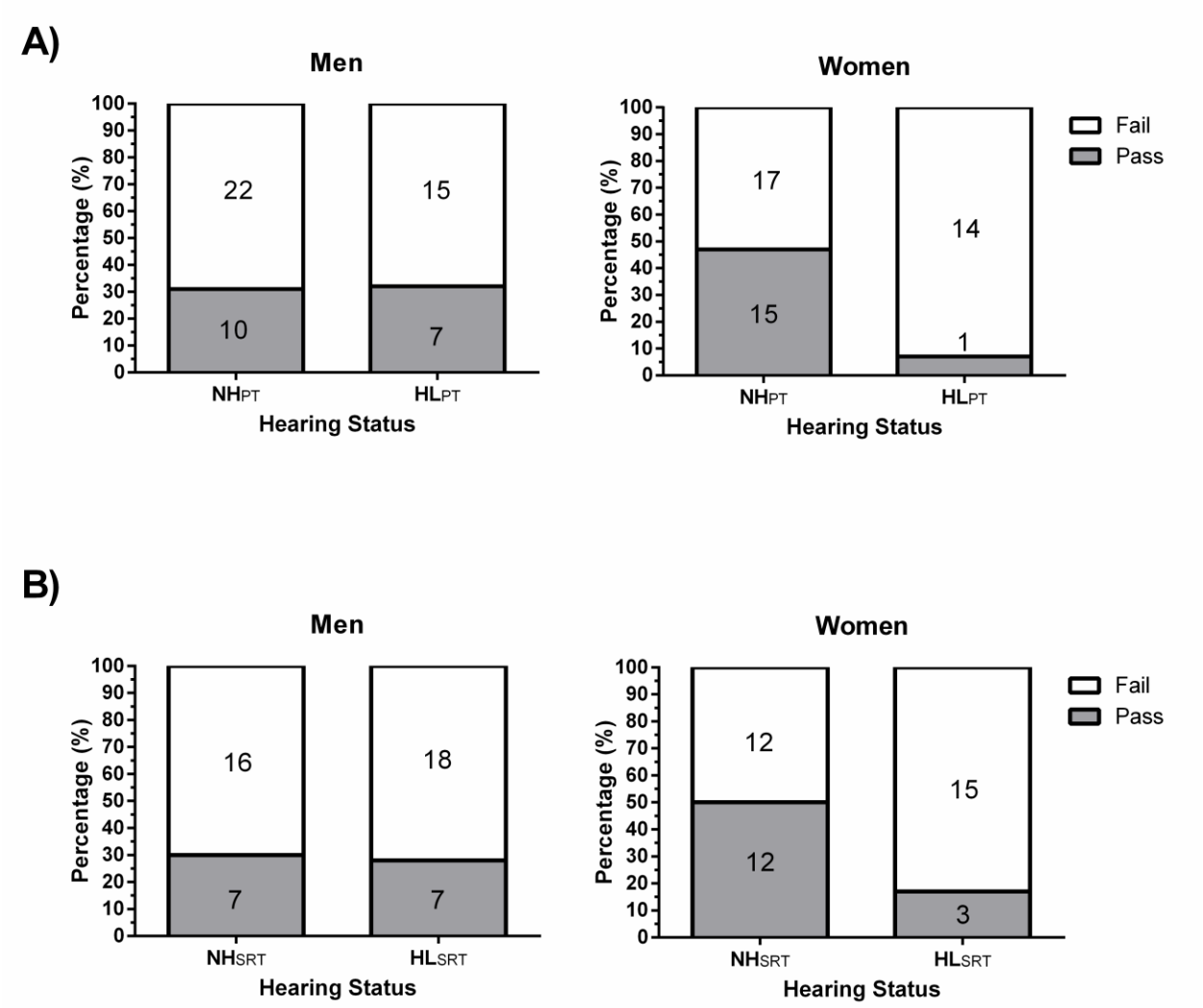

Figure 2. Diagram representing the percentage of participants passing/failing the MoCA based on hearing status in men (N=56) and women (N=45). A, pure-tone screening category in men (left) and women (right); B, Canadian Digit Triplet Test (CDTT) category in men (left) and women (right). Numbers in bins represent the number of participants that fall in a given category.

failing the MoCA-Modified based on hearing group based on pure-tone (Chi-square(1) = 1.099, p = .295) and CDTT SRT criteria (Chi-square(1) = 1.643, p = .200).

RAVLT

As seen in Table 4, for the within-sex analyses, we examined the proportion of individuals categorized as "passing" or "failing" the RAVLT using a threshold of Z = -1.5 to determine if there were differences between hearing groups. There was no difference between the proportion passing or failing the RAVLT total score for the hearing groups determined based on the pure-tone (Men: Chi-square(1) = .586, p = .444; women: Chi-square(1) = 1.176, p = .278) or CDTT SRT criteria (Men: Chi-square(1) = .259, p = .611; women: Chi-square(1) = .700, p = .403).

Similarly, we observed no difference in the proportion passing or failing the RAVLT delayed recall trial for hearing groups defined either by pure-tone (Men: Chi-square(1) = .043, p = .836; women: Chi-square(1) = .354, p = .552) or SRT criteria (Men: Chi-square(1) = 1.545, p = .214; women: Chi-square(1) = 1.123, p = .289).

BVMT-R

As with the RAVLT, we compared the proportion of individuals in each hearing group who were categorized as "passing" or "failing" the BVMT-R using a threshold of Z = -1.5 (Table 4). For men, there was no difference in the proportions of those passing or failing the BVMT-R total score depending on pure-tone hearing group (Chi-square(1) = .673, p = .412). However, there was a significant difference between the proportion of men in the two CDTT SRT hearing groups who passed or failed the BVMT-R (Chi-square(1) = 5.880, p = .015), such that men in the

Table 4. Percentages of men and women classified as "Failed" on the MoCA, RAVLT, and BVMT-R within hearing groups. Failure on the MoCA was indicated by a score < 26. Failure on the RAVLT and BVMT-R was indicated by Z-scores < -1.5 based on published norms. Bolded values are significantly different between NH and HL individuals based on a Chi-square analysis ($p < .05$).

		Pure-tone		Canadian Digit Triplet Test	
		NH_{PT}	**HL_{PT}**	**NH_{SRT}**	**HL_{SRT}**
MoCA	**Men**	68.8	68.2	69.6	72.0
	Women	**53.1**	**93.3**	**50.0**	**83.3**
RAVLT Total	**Men**	21.9	13.6	21.7	16.0
	Women	18.8	6.7	20.8	11.1
RAVLT Delayed	**Men**	43.8	40.9	30.4	48.0
	Women	25.0	33.3	25.0	38.9
BVMT-R Total	**Men**	34.4	45.5	**21.7**	**56.0**
	Women	28.1	46.7	25.0	44.4
BVMT-R Delayed	**Men**	28.1	31.8	**13.0**	**40.0**
	Women	28.1	40.0	29.2	38.9

RAVLT, Rey Auditory Verbal Learning Test; BVMT-R, Brief Visuospatial memory test-revised; CDTT, Canadian Digit Triplet Test; NH, normal hearing; HL, hearing loss

NH_{SRT} group more frequently had a "passing" rather than a "failing" score on the BVMT-R total score. For women, there were no differences in the associations between BVMT-R total and hearing groups based on pure-tone (Chi-square(1) = 1.564, p = .211) or CDTT SRT (Chi-square(1) = 1.750, p = .186) criteria.

On the delayed recall trial, there was no difference in the proportion of men categorized as "passing" or "failing" the BVMT-R delayed recall trial based on pure-tone hearing (Chi-square(1) = .085, p = .770); however, there was a significant difference between the proportion of men in the two CDTT SRT hearing groups who passed or failed the BVMT-R delayed recall trial (Chi-square(1) = 4.408, p = .036), such that men in the NH_{SRT} group were more likely to be classified as having a "passing" rather than "failing" score on the delayed recall trial (Table 4). In women, there were no differences in the proportions passing or failing the BVMT-R delayed recall trial based on either pure-tone hearing groups (Chi-square(1) = .663, p = .416) or CDTT SRT hearing groups (Chi-square(1) = .437, p = .508).

Comparing Mean Differences on Cognitive Test Scores Based on Sex and Hearing

Table 5 shows the mean cognitive scores for men and women for those with and without hearing loss as defined by both pure-tone hearing and the CDTT SRT. In the following sections, we report analyses on these cognitive measures using a two-way ANCOVA with sex and hearing group (either pure-tone or CDTT SRT) as between-subject factors. All analyses controlled for age and years of education.

MoCA

Pure-tone Hearing Groups. There was no main effect of sex (F(1, 95) = .431, p = .513, Np^2 = .005) or hearing group (F(1, 95) = 2.676, p = .105, Np^2 = .027) on total MoCA scores

Table 5. Means and standard deviations for the cognitive measures for men and women. Pure-tone hearing loss was based on a threshold greater than 25 dB HL at 2000 Hz in the worse ear. CDTT hearing loss was based on SRT values at and above -10 dB SNR.

		Pure-tone		Canadian Digit Triplet Test	
		NH_{PT}	HL_{PT}	NH_{SRT}	HL_{SRT}
MoCA	**Men**	24.06 (2.59)	24.05 (3.50)	24.13 (2.72)	23.60 (2.87)
	Women	24.59 (3.07)	22.67 (2.50)	24.83 (2.78)	23.06 (3.06)
RAVLT Total	**Men**	37.59 (10.70)	37.27 (9.23)	39.48 (9.99)	35.72 (9.19)
	Women	41.50 (9.98)	38.73 (8.85)	42.50 (10.50)	37.72 (9.19)
RAVLT Delayed	**Men**	5.09 (3.47)	5.32 (3.77)	5.52 (3.07)	4.84 (3.72)
	Women	7.63 (3.74)	5.87 (3.83)	7.79 (3.80)	6.11 (4.09)
BVMT-R Total	**Men**	14.88 (6.93)	14.36 (7.99)	16.17 (6.35)	13.44 (8.25)
	Women	17.38 (7.53)	14.53 (8.20)	19.04 (8.05)	14.06 (7.35)
BVMT-R Delayed	**Men**	6.13 (3.19)	6.23 (3.50)	7.04 (2.85)	5.68 (3.65)
	Women	6.88 (3.16)	5.40 (3.56)	7.21 (3.23)	5.67 (3.51)

NH, Normal hearing; HL, Hearing loss; MoCA, Montreal Cognitive Assessment scale; RAVLT, Rey Auditory Verbal Learning Test; BVMT-R, Brief Visuospatial memory test-revised.

(Interaction $F(1, 95) = 1.826$, $p = .180$, $Np^2 = .019$). However, the planned comparison showed that women in the NH_{PT} group significantly outperformed women in the HL_{PT} group ($F(1, 95) = 3.975$, $p = .049$, $Np^2 = .040$), but this pattern was not observed in men ($F(1, 95) = .080$, $p = .778$, $Np^2 = .001$).

CDTT SRT Hearing Groups. There was a main effect of hearing group ($F(1, 84) = 6.783$, $p = .011$, $Np^2 = .075$), showing that individuals with NH_{SRT} had better MoCA scores. The main effect of sex ($F(1, 84) = .014$, $p = .905$, $Np^2 = .001$) was not significant (Interaction $F(1, 84) = .660$, $p = .419$, $Np^2 = .008$). However, planned comparisons showed that women with NH_{SRT} outperformed women with HL_{SRT} ($F(1, 84) = 5.549$, $p = .021$, $Np^2 = .062$). As was the case when PTA was used to categorize HL, this effect was not observed in men ($F(1, 84) = 2.026$, $p = .158$, $Np^2 = .024$; Table 5).

RAVLT

Pure-tone Hearing Groups. There was no main effect of sex ($F(1, 95) = 1.324$, $p = .253$, $Np^2 = .014$), or hearing group ($F(1, 95) = .095$, $p = .759$, $Np^2 = .001$) on total RAVLT scores (Interaction $F(1, 95) = .107$, $p = .745$, $Np^2 = .001$). Planned comparisons did not reach significance (Table 5). For the delayed recall on the RAVLT, the effect of sex approached significance ($F(1, 95) = 3.537$, $p = .063$, $Np^2 = .036$), suggesting that women outperformed men, while pure-tone hearing status ($F(1, 95) = .037$, $p = .848$, $Np^2 = <.001$) did not have a significant effect (Interaction $F(1, 95) = 1.417$, $p = .237$, $Np^2 = .015$). The planned comparisons were not significant.

CDTT SRT Hearing Groups. Using hearing group based on CDTT SRT as a factor and RAVLT total score as an outcome, the ANCOVA revealed non-significant effects for sex ($F(1,$

84) = .931, p = .337, Np^2 = .011) and hearing group (F(1, 84) = 1.728, p = .192, Np^2 = .020) on RAVLT scores (Interaction F(1, 84) = .044, p = .835, Np^2 = .001). Planned comparisons did not reach significance. An ANCOVA examining the effects on RAVLT delayed recall on sex and hearing group based on CDTT SRT revealed a significant effect of sex (F(1, 84) = 4.435, p = .038, Np^2 = .050), indicating better performance in women over men, but not for hearing group (F(1, 84) = .707, p = .403, Np^2 = .008; Interaction F(1, 84) = .172, p = .679, Np^2 = .002). The planned comparisons were not significant.

BVMT-R

Pure-tone Hearing Groups. There was no significant effect of sex (F(1, 95) = .471, p = .494, Np^2 = .005), or pure-tone hearing group (F(1, 95) = .009, p = .926, Np^2 = <.001) on total BVMT-R recall score (Interaction F(1, 95) = .396, p = .531, Np^2 = .004). Planned comparisons did not reach significance. Likewise, there were no significant effects on BVMT-R delayed recall accuracy of sex (F(1, 95) = .037, p = .848, Np^2 < .001), or hearing group (F(1, 95) = .053, p = .818, Np^2 = .001; Interaction F(1, 95) = 1.089, p = .299, Np^2 = .011). Planned comparisons did not reach significance.

CDTT SRT Hearing Groups. There were no significant effects of sex (F(1, 84) = .790, p = .377, Np^2 = .009), or CDTT SRT hearing group (F(1, 84) = 2.367, p = .128, Np^2 = .027) on total BVMT-R score (Interaction F(1, 84) = .188, p = .666, Np^2 = .002. Planned comparisons did not reach significance. Similarly, there were no significant effects on the delayed recall in the BVMT-R of sex (F(1, 84) = .003, p = .959, Np^2 < .001), or CDTT SRT hearing group (F(1, 84) = 2.011, p = .160, Np^2 = .023; Interaction F(1, 84) = .011, p = .918, Np^2 = .001). Again, planned comparisons did not reach significance.

Associations Between Hearing and Cognition

We examined partial correlations between the CDTT SRTs and cognitive variables, controlling for age, education, and pure-tone hearing category (correlations were not assessed for the pure-tone measure as it was not a continuous variable, see methods section). CDTT SRTs were not associated with any of the cognitive variables for men or women (Table 6). Visual inspection of the scatterplots showed a linear relationship in women who performed below (better than) the CDTT threshold of -10 dB SNR. As such, when the sample was split based on this threshold, we observed significant associations between CDTT SRT and cognitive variables in the NH_{SRT} female group only. Specifically, as seen in Table 6, a negative association was observed between CDTT SRT and MoCA scores (r = -.510, p = .018), and between CDTT SRT and RAVLT total scores (r = -.622, p = .003; Figure 3). No associations were observed in HL_{SRT} women, or in NH_{SRT} and HL_{SRT} men (Table 6).

Hearing Group and Individual MoCA Word Recall

In an additional analysis, we examined the five-word delayed recall trial of the MoCA by comparing hearing groups in terms of the percentage of individuals who correctly recalled each word given that the participant had repeated it correctly in the two learning trials (as seen in Dupuis et al., 2015).

Pure-tone Hearing Groups

As seen in Table 7, the percentages who correctly repeated the words on the learning trials did not differ between the NH_{PT} and HL_{PT} groups for either men or women. When examining the percentages of men who were able to recall the words at a delay, given that they correctly repeated the words during the learning trials, there were no differences between hearing groups in recall accuracy for any of the five words (all p > .1; Figure 4). In women, however,

Table 6. Pearson partial correlations between CDTT SRTs in dB SNR and performance on cognitive measures. Correlations are presented for men and women in the NH_{SRT} and HL_{SRT} groups (based on -10 dB SNR SRT cut-off on the CDTT). All correlations are corrected for age, education, and pure-tone hearing category. Results reported as r(p).

	Men			Women		
	Total (n=47)	**NH_{SRT} (n=23)**	**HL_{SRT} (n=24)**	**Total (n=42)**	**NH_{SRT} (n=24)**	**HL_{SRT} (n=18)**
MoCA	-.152 (.319)	.016 (.948)	-.030 (.894)	-.241 (.139)	**-.510 (.018)**	-.005 (.987)
MoCA-Modified	-.168 (.270)	.253 (.282)	-.178 (.428)	-.201 (.221)	-.344 (.126)	-.071 (.801)
RAVLT Total Score	-.255 (.091)	.064 (.788)	-.189 (.399)	-.196 (.232)	**-.622 (.003)**	.195 (.486)
RAVLT Delayed Score	-.106 (.489)	.237 (.315)	-.075 (.740)	-.063 (.703)	-.346 (.125)	.132 (.640)
BVMT-R Total Score	-.226 (.136)	.250 (.289)	-.325 (.140)	-.236 (.148)	-.333 (.140)	-.026 (.926)
BVMT-R Delayed Score	-.234 (.123)	.211 (.372)	-.227 (.310)	-.081 (.624)	-.259 (.257)	.084 (.767)

NH, Normal hearing; HL, Hearing loss; MoCA, Montreal Cognitive Assessment scale; RAVLT, Rey Auditory Verbal Learning Test; BVMT-R, Brief Visuospatial memory test-revised

Table 7. Word learning and word recall percentage correct scores in men and women for words on the MoCA delayed recall item. Successful learning was defined as correct recall of a given word on both learning trials of the MoCA. Successful recall was defined as correct recall of a given word on the delayed recall subtest of the MoCA for participants with successful learning. Bolded values are significant ($p < .05$) on a Chi-square test comparing the proportion of individuals with correct recall by hearing category.

		Men					Women				
		Face	**Velvet**	**Church**	**Daisy**	**Red**	**Face**	**Velvet**	**Church**	**Daisy**	**Red**
% Learning	**NH_{PT}**	96.9	93.8	87.5	84.4	87.5	96.8	90.3	74.2	83.9	93.5
	HL_{PT}	90.9	90.9	72.7	86.4	90.9	93.3	73.3	93.3	80.0	100.0
	NH_{SRT}	100.0	95.7	82.6	91.3	95.7	95.7	**95.7**	78.3	78.3	91.3
	HL_{SRT}	92.0	100.0	76.0	88.0	88.0	94.4	**66.7**	77.8	83.3	100.0
% Recall	**NH_{PT}**	48.4	50.0	35.7	33.3	46.4	50.0	64.3	**65.2**	**53.8**	62.1
	HL_{PT}	50.0	45.0	56.3	26.3	50.0	28.6	36.4	**28.6**	**8.3**	53.3
	NH_{SRT}	52.2	50.0	31.6	33.3	50.0	**59.1**	63.6	61.1	50.0	61.9
	HL_{SRT}	43.5	40.0	47.4	27.3	40.9	**23.5**	50.0	42.9	33.3	55.6

NH, normal hearing; HL, hearing loss; % Learning, percentage of participants (within sex and within hearing group) who correctly repeated the word in both of the MoCA's learning trials; % Recall, percentage of the participants who correctly repeated the word and successfully recalled it during the delayed recall trial.

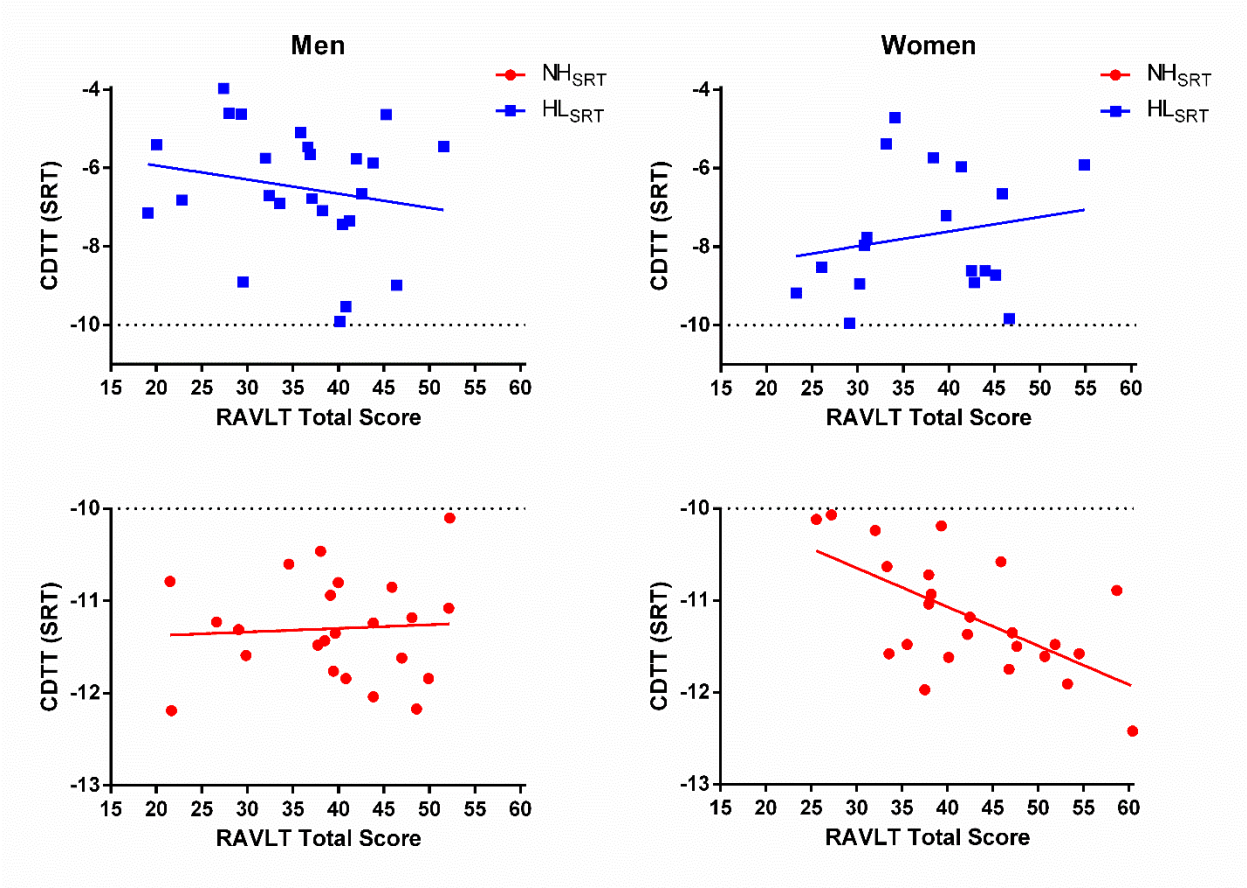

Figure 3. Scatterplots showing the partial correlations between RAVLT total scores and CDTT SRTs in men (left) and women (right). Circles represent individuals with CDTT SRTs below the -10 dB SNR threshold (normal hearing, NH_{SRT}). Squares represent individuals with CDTT SRTs at and above the -10 dB SNR threshold (hearing loss, HL_{SRT}).

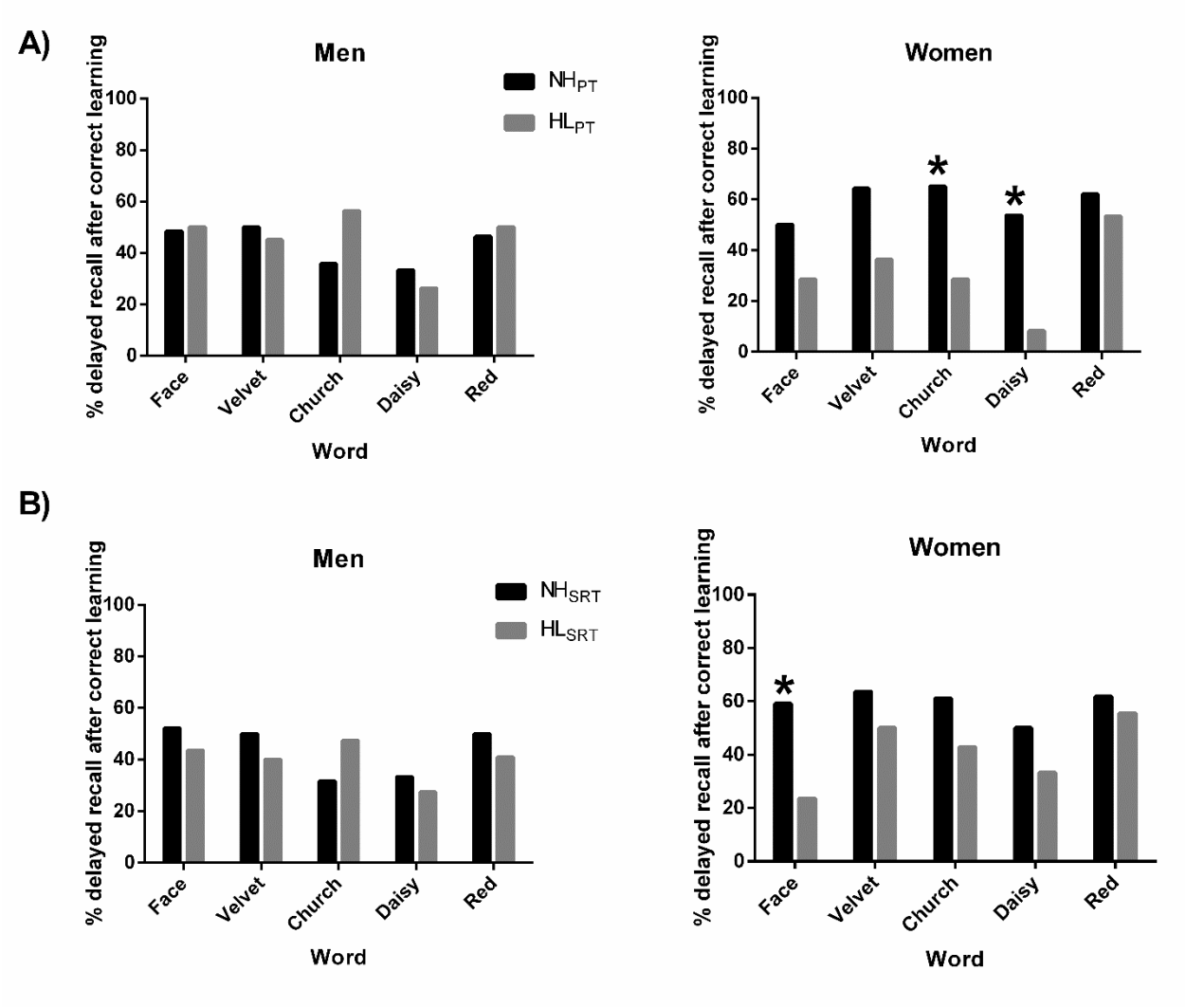

Figure 4. Figure showing the percentage of participants who correctly recalled a word during the delayed recall trial of the MoCA for participants who correctly encoded the word during the two learning trials. A, percentage correct delayed recall in men (left) and women (right) based on pure-tone (PT) hearing category; B, percentage correct delayed recall in men (left) and women (right) based on Canadian Digit Triplet Test (CDTT) SRT category. * $p < .05$ between the normal hearing (NH) and hearing loss (HL) groups based on Chi-square tests.

memory for the word “church”, which is in the middle section of the list, differed significantly between hearing group, indicating that NH_{PT} women had better recall than those in the HL_{PT} group (Chi-square(1) = 4.678, p = .031). Similarly, NH_{PT} women had better recall than those in the HL_{PT} group for the word “daisy”, which is the fourth word of the list (Chi-square(1) = 7.118, p = .008; Figure 4).

CDTT SRT Hearing Groups

There was no difference in the proportion of men who correctly repeated the words on the learning trials based on CDTT SRT hearing groups. Further, there was no difference in the proportion of men who correctly recalled words at a delay given correct recall on the learning trials (all $p > .1$). In women, we observed a difference in the proportion of individuals learning the word “velvet,” which is the second of the list, showing that NH_{SRT} women were more likely to learn the word relative to HL_{SRT} individuals (Chi-square(1) = 5.992, p = .014; Table 7). No other differences in learning were observed. In recall, HL_{SRT} women were less likely to recall the word “face”, which is the first word on the list, relative to NH_{SRT} women (Chi-square(1) = 4.932, p = .026; Figure 4). No other findings reached significance (all $p > .1$; Table 7).

Discussion

In the current investigation, we examined sex-related differences in the connections between hearing and cognitive performance in individuals with MCI. Our main finding was a sex-specific effect of hearing group (whether classified by pure-tone or CDTT SRT) on total MoCA scores whereby significant differences between NH and HL individuals were observed in women only, as well as differences in passing or failing the MoCA based on hearing status. For two episodic memory measures, the auditory RAVLT and the visual BVMT-R, there were also sex-specific effects, although the effects of sex on these two cognitive tests were reversed.

Specifically, in women, CDTT SRT was significantly correlated with performance on the MoCA and RAVLT, but only in women with better hearing. In contrast, passing or failing the BVMT-R depended on the hearing category defined by the CDTT SRT, but only in men. These results lend partial support to previous findings of sex-specific differences in auditory-cognitive connections in women (Al-Yawer et al., in press; Eberhard et al., 2019; Helzner et al., 2005; Lyu & Kim, 2018) and extends them to a population of individuals with MCI.

We used two hearing measures in this study: pure-tone and CDTT speech reception thresholds. While the two measures yielded similar classifications, they were not identical, with more individuals being identified as having normal hearing using pure-tone compared to CDTT SRTs, justifying thorough examination of both measures. It is important to note that there were no overall differences in the proportions of men and women in the NH and HL groups as determined either by pure-tone or CDTT SRT results. Therefore, these sex-related differences in the association between cognitive scores and hearing cannot be attributed to simply a difference between the number of men and women in the NH and HL groups. Furthermore, we observed no differences between men and women in age, education, depression scores, hypertension, hyperlipidemia, diabetes, cardiovascular health, or smoking, thereby eliminating differences in those characteristics as explanatory factors. Men had better reading acuity than women; however, while this was statistically significant, both groups had clinically normal vision, and thus this difference would not have been expected to have a functionally significant effect on our cognitive tests, which do not require reading.

The MoCA

Passing the MoCA depended on hearing group in women only, with women in the HL group being more likely to fail the MoCA than to pass it. This finding was further corroborated

by analysis of the continuous MoCA scores, such that women with HL (whether defined by PT or SRT) had lower scores than their NH counterparts. Additionally, an analysis of results on the delayed recall items showed similar sex-specific effects such that women in the NH group were more likely than those in the HL group to correctly recall several of the MoCA's words, despite there being no differences in learning between the NH and HL groups. Since these differences were found in women who had successfully repeated the words during the learning trials, it is unlikely that the finding can be attributed to faulty perception earlier in the test insofar as words were not misheard. Nevertheless, even if the words were perceived successfully in both hearing groups, it remains possible that individuals with hearing loss required more resources to achieve similar perception, leading to worse recall. McCoy and colleagues (2005) have shown that individuals with hearing loss had worse recall of the first and second words of a three-word list despite no differences in recall of the third word between hearing loss and normal hearing individuals. In our study, a similar observation of differences in recall of the first four MoCA words but never in the last word, "red." Our findings are also partially in line with previous studies in which men and women with HL were less likely to recall MoCA words compared to counterparts with NH (Dupuis et al., 2015; Lim & Loo, 2018). In contrast to our findings with the full MoCA, when the MoCA was scored excluding the hearing-dependent items (MoCA-Modified), the results were non-significant, showing no differences between NH and HL groups based on test status. From our previous discussion, we know that there were no differences in the percentage of individuals learning the MoCA delayed recall words between the hearing groups, but that this learning may have nevertheless been more effortful for individuals with HL. Subsequently, the lack of differences between hearing groups when hearing-dependent items are excluded may reflect the effortfulness involved with hearing. However, it is also possible that the

smaller range of scores allowed on the MoCA-Modified (0-20) was inadequate to display the effects that were seen with the full MoCA. Previous findings from our group have shown that the MoCA-Modified is psychometrically less accurate than the full MoCA, particularly its accuracy at detecting MCI (Al-Yawer et al., 2019). Further research with the MoCA-Modified in individuals with MCI and hearing loss is required.

RAVLT and BVMT-R

Results on the RAVLT and BVMT-R also showed specific sex-related effects, though they were less frequent than the MoCA findings. We predicted that women with normal hearing would outperform their counterparts with hearing loss on these two tests. Surprisingly, results on the RAVLT did not show this difference when the cognitive results were examined categorically (pass/fail status on the RAVLT for the NH group vs. the HL group) or continuously (RAVLT scores for the NH group vs. the HL group). We observed a significant correlation between RAVLT total scores and CDTT SRT, but only in women in the NH_{SRT} group. No such correlations with RAVLT scores were observed in men. Associations between measures of auditory memory and hearing have been observed previously (e.g., Harrison-Bush et al., 2015; Lin et al., 2011a). In contrast to the pattern of results observed for women, we observed one finding only in men which was that those in the NH_{SRT} group were more likely to be categorized as "passing" on both the total score and delayed recall trials of the BVMT-R relative to their HL_{SRT} counterparts. Only one other study to date (Huang et al., 2019) observed connections between hearing and cognitive performance in men only. A closer examination of that study's test-by-test analysis indicates that their effect was mainly driven by performance on the Digit Symbol Substitution Test (Wechsler, 1997), a visuospatial test of processing speed, sustained attention, and working memory. It is interesting that the male-only significant effects in our

study and the study of Huang and colleagues (2019) were evident on tests in which stimuli were presented visually. Men did have better reading acuity than women in our study, and men in NH_{SRT} group had better visual acuity than men in the HL_{SRT} group. However, no differences were observed in visual contrast sensitivity and the differences seen in visual acuity are unlikely to influence performance. Men tend to outperform women on visuospatial tests in studies with younger adults (Vogel et al., 2003), however studies with older adults generally do not show a male visuospatial advantage (e.g., Aartsen et al., 2004; Barret-Connor & Kritz-Silverstein, 1999). In our study, we also did not observe a difference in raw BVMT-R scores (Table 5). Overall, women in our study showed specific associations between hearing and MoCA and RAVLT scores, while men showed an association between hearing and test status on the BVMT-R. Further research into these test-specific and possibly modality-specific sex-related differences is required.

Both pure-tone (e.g., Lin et al., 2011a) and speech-in-noise test results (e.g., Gates et al., 2010) have been associated with cognitive performance. Insofar as performance on speech-in-noise tests involve the functioning of the auditory cortex and other brain regions, difficulties on these tests may signal cortical deterioration, including in areas involved in cognition (Rudner et al., 2019). In our study, we observed significant correlations in women only, namely between CDTT SRT and the MoCA and RAVLT total scores within the NH_{SRT} group. These correlations were significant even controlling for age, education, and pure-tone hearing category. This finding is partially in line with studies showing that higher order auditory functioning was strongly associated with cognitive function (e.g., Humes et al., 2013), and with studies showing this association after controlling for pure-tone thresholds (e.g., Gates et al., 2010). The correlations in this study between MoCA and RAVLT scores with CDTT SRTs were only

observed in women, and only in the NH_{SRT} group and not the HL_{SRT} group. It is unclear why we observed these effects in the NH_{SRT} group only. We know of one other study (Golub et al., 2020) in which auditory-cognitive associations in individuals with normal hearing were equivalent to, or stronger than, those with hearing loss. Golub and colleagues (2020) found that those with normal hearing, but not with hearing loss, showed significant negative associations between hearing and cognitive scores on the Spanish-English Verbal Learning Test, an episodic memory measure that is structurally similar to the RAVLT. The authors speculated that one explanation for this finding is a lack of sensitivity of their hearing measure (pure-tone audiometry) to hearing loss. However, we observed a similar association in our study using CDTT, a speech-in-noise measure which more closely resembles real-life conditions of social interactions in noisy environments. Further research into this finding is required.

Sex-related Differences and Potential Mechanisms

The observed pattern of results on the MoCA and RAVLT indicate that hearing loss can have a significant effect on cognitive performance in women, whereas these auditory-cognitive associations were only observed in men when cognition was measured as passing/failing the visually presented BVMT-R test. We observed no sex-related differences in age, education, depression, hypertension, hyperlipidemia, diabetes, cardiovascular health, nor smoking, making these factors unlikely explanations for our findings. Within-sex analyses also indicated no significant differences between the NH and HL groups for any of these factors, with the exception of the HL group being older than the NH group for both sexes such that age was unlikely to be driving sex-specific findings. Furthermore, we used age as a covariate in our ANCOVAs and the analyses involving cognitive test status (pass/fail) were based on age-corrected normative data, again eliminating age as a likely contributor to our results.

What could account for these sex-specific findings? Sex-related differences in auditory processing have been documented. For example, auditory brainstem responses (ABR) have shorter latencies and larger amplitudes in women than men (Liu et al., 2017; Wharton and Church, 1990); women have larger transient-evoked otoacoustic emissions than men (Berninger, 2007); and women develop hearing loss later than men (Dubno et al., 2013; but see Homans et al., 2017 for evidence of only minimal sex-related differences in audiometric thresholds). Furthermore, Liu and colleagues (2017) showed that ABR latencies were correlated positively with testosterone levels and negatively with estradiol levels, suggesting a role for sex hormones in auditory processing. While we did not examine the ABR in the current study, we did observe sex-related differences in the effect of hearing on cognitive measures, raising the possibility of the involvement of sex hormones in higher-order auditory-cognitive links.

Returning to the previously discussed potential mechanisms of auditory-cognitive associations, our findings are not completely consistent with the information degradation hypothesis insofar as we observed auditory-cognitive connections in tests that rely heavily on both the auditory (MoCA, RAVLT) and visual (BVMT-R) modalities. However, the effects observed on the BVMT-R were limited and only observed in men. This may reflect a sex-related modality effect, in which men are more likely to show auditory-cognitive associations on visuo-spatial tests. Furthermore, correlations between hearing variables and the MoCA-Modified, which excludes hearing-dependent subtests from scoring of the MoCA, did not reach significance. Previous findings in cognitively healthy older adults observed significant correlations between the MoCA-Modified and pure-tone hearing (Al-Yawer et al., in press). Reconciling these two findings, information-degradation may be a more important factor in individuals with MCI who already have limited cognitive resources. In the context of the social

isolation hypothesis, there were no significant differences in level of social engagement between women and men in either the NH or HL groups. However, we note that participation in the COMPASS-ND study required a study partner, which may have biased our sampling to individuals not suffering from significant isolation (Palmer et al., 2016). Furthermore, we measured social activity based on the response to a single question. More studies looking at social variables in greater detail are required, though recent efforts suggest that social variables only weakly influence the auditory-cognitive association, if at all (Hämäläinen et al., 2020). In the context of the sensory deprivation hypothesis, it is possible that hearing loss differentially affects brain function and structure in men and women. However, longitudinal research is needed to assert this hypothesis.

It has been previously proposed (Al-Yawer et al., in press) that post-menopausal changes in estrogen levels may act as a common cause in cognitively healthy older women by independently affecting both hearing and cognition. While the evidence in this study is cross-sectional, we observed specific auditory-cognitive connections in women, this time in a sample of individuals with MCI. Post-menopausal reduction in estrogen, the sex hormone suggested to play a protective role in the inner ear, has downstream negative effects on women' hearing and likely contributes to the development of their hearing loss (Hederstierna et al., 2010; Reavis et al., Submitted; Stenberg et al., 2001). Given the association of menopause with cognitive decline and the development of dementia in women (Mosconi et al., 2017), reductions in estrogen may act as a common cause for auditory-cognitive associations in women. Our findings suggest that the mechanisms involved in these associations may carry different contributions in men and women. Our results add to an emerging literature on sex-related differences in auditory-cognitive

interactions (Al-Yawer et al., in press; Eberhard et al., 2019; Helzner et al., 2005; Lyu & Kim, 2018).

Limitations

In the current study, we observed sex-related differences in auditory-cognitive connections between men and women with MCI while controlling for age and years of formal education. We examined a multitude of other variables (e.g., cardiovascular risk factors) and showed largely no differences based on sex or hearing status. However, we note that these factors were not included directly in our analyses and thus may show an effect in a larger sample study with more statistical power. Additional information about other factors that have been demonstrated to have sex-related associations with dementia (e.g., APOE-e4 genetic status), would further help elucidate these findings (Farrer et al., 1997). It is important to recognize that in addition to sex-related factors (e.g., genetic and hormonal differences between males and women), gender-factors (e.g., gendered behaviors and experiences) may have also played a role in the observed findings. Gender-related factors (e,g., work noise exposure) are known to influence hearing loss (Helzner et al., 2005; Palmer et al., 2016). Thus, while the current study addressed sex-related differences in auditory-cognitive associations, it is likely that gender also played a role in the observed associations, as sex and gender are strongly intertwined (Reavis et al., submitted).

We used hearing group (NH_{PT} vs. HL_{PT}) as a factor in our study because pure-tone detection thresholds were not measured. Using our hearing screening protocol, hearing was assessed on a pass/fail basis because the six "hearing categories" based on the detection of 2000 Hz tones presented at 40 and 25 dB HL in each ear were not all sufficiently populated to be suitable for analyses. Yet despite the limited data provided by our pure-tone hearing screening measurement,

we still observed effects of hearing group on the MoCA, lending support to the strength of these effects. Another limitation of our hearing data is that we did not have access to information regarding the duration or specific etiology of hearing loss, which can vary between sexes (Dubno et al., 2013). For the RAVLT and BVMT-R pass/fail categorization, we used age-corrected normative data, but we note that these data were not sex-corrected and therefore may be skewed in favor of one sex over the other. We focused on memory as a cognitive measure because of the strong role of memory in amnestic MCI; however, further investigation is required into other cognitive domains.

Conclusion

In the current study of older adults with amnestic MCI, we observed sex-specific effects of hearing on cognitive performance measured with the MoCA and the RAVLT in women, and the BVMT-R in men. We additionally observed some effects of hearing on delayed word recall on the MoCA in women, even after accounting for correct recall of the to-be-remembered words during learning trials. Our findings, while preliminary, extend previous studies in older adults with normal cognition and suggest that there are also sex-related differences in auditory-cognitive connections in older adults who have MCI. These findings highlight the importance of regular audiological assessments for older adults, even those in the early stages of cognitive decline. Future studies should examine sex-related differences in auditory-cognitive associations, and whether these differences extend to other areas, such as the impact of auditory rehabilitation on cognitive performance.

Supplementary Table 1. Differences between men and women in social variables included in the social network size questionnaire. Questions are from the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) protocol (Chertkow et al., 2019).

Item	Options	X^2	*p*	Explanation
"During your lifetime, can you estimate the number of friends that you have had?"	-Fewer than normal -Normal amount -More than normal	6.941	.031	Women more likely to report "more than normal" number of friends than men
"Taking your whole lifetime into consideration, how would you rate your participation or involvement in social activities (including going out with friends, membership in associations, volunteer work, etc.)?"	-Low -Normal -High	7.192	.027	Women more likely to report "high" lifetime social participation than men
"Taking only your current situation into consideration, how would you rate your participation/involvement in social activities?"	-Low -Normal -High	4.363	.113	-
"How many people do you know well enough to go visit their home?"	-None -1 to 2 -3 to 4 -5 or more	1.391	.499	-
"In the past week, how many times did you talk to someone—friends, relatives, or others—on the telephone (either you called them or they called you)?	-None -Once -Twice -3 to 4 -Once or more a day	7.511	.111	-
"In the past week, how many times did you spend time with someone who does not live with you, for instance you went to see them or they came to visit you, or you went out to do things together?"	-None -Once -Twice -3 to 4 -Once or more a day	2.043	.728	-

CHAPTER 5

GENERAL DISCUSSION

The overarching goal of this dissertation was to explore auditory-cognitive associations in older adults and potential sex-related differences in these association. The three main thread lines that make up this work are as follows: 1) explore auditory-cognitive associations in a cognitive screening measure (the MoCA), and how that compares to other neuropsychological measures; 2) examine differences in the auditory-cognitive association in pure-tone hearing compared to speech-in-noise, or suprathreshold, hearing; 3) address sex-related differences in how this relationship is expressed. In the following discussion, I will summarize our main findings from the three studies, address the aforementioned themes individually, followed by a synthesis of our findings and a discussion of the implications of the work in the context of potential auditory-cognitive mechanisms.

Summary of Presented Studies

In Study I, I examined the psychometric properties of the MoCA with and without hearing-dependent items. This was modeled after previous findings with the MoCA and vision-dependent items (Wittich et al., 2010). I found that, as expected, scoring the MoCA without hearing-dependent items resulted in a significant decrease in its sensitivity and overall accuracy at detecting both MCI and AD. Furthermore, I found that this effect was largely driven by the delayed recall subtest of the MoCA. This subtest, which involves recalling a list of five words presented orally earlier in the test, is dependent on good audition and is also the only subtest on the MoCA that directly assesses episodic memory, the domain most impacted in amnestic MCI. When only the other hearing-dependent items were omitted from scoring, while keeping delayed recall, the test's specificity significantly declined. This carries implications for using the MoCA in the assessment of older adults with hearing loss.

In Study II, I directly examined the association between hearing and cognition in a sample of community-dwelling older adults. Significant sex-related differences were observed with associations between pure-tone hearing in the worse ear and MoCA scores being evident only in women. This was observed both continuously and categorically. Additionally, when hearing-dependent items were excluded from MoCA scoring (MoCA-Modified), the associations remained significant in the worse ear. This study was one of the first to demonstrate sex-related differences in the auditory-cognitive associations. The implication of these findings suggested that auditory-cognitive associations may preclude different mechanisms in men and women. These findings helped motivate our third and final manuscript.

In Study III, I used data from the Canadian Consortium on Neurodegeneration in Aging (CCNA) to examine the associations between hearing (both pure-tone and speech-in-noise) and cognition in a sample of individuals with MCI. In this sample, I focused on measures of episodic memory (RAVLT and BVMT-R) in addition to the MoCA and MoCA-Modified. I directly compared a number of demographic and health variables between men and women, allowing me to rule them out as explanatory variables for the observed findings. As in Study II, I observed several women-only associations, including a relationship between passing/failing the MoCA and hearing status in women alone, as well as better recall of some MoCA delayed recall words in women with normal hearing relative to those with hearing loss. Further, I found correlations between speech-in-noise thresholds with scores on the MoCA and the RAVLT only in women with normal hearing. Finally, I observed one finding that was unique to the men in the sample, in which normal hearing men were more likely to pass the BVMT-R than their hearing loss counterparts. The results from this study partially corroborated some of our preliminary findings

in Study II in a sample of individuals with amnestic MCI, and added new findings with other measures of hearing and cognition.

The MoCA and Other Neuropsychological Measures

The MoCA plays a unique role in this dissertation for several reasons: 1) It is the only cognitive measure that is common to all three studies; 2) being a screening measure, it is shorter and covers more cognitive domains than more specialized neuropsychological measures. This also means that it is more commonly used in primary care settings to screen for cognitive impairment; 3) I was able to directly examine the contributions of hearing-dependent items on auditory-cognitive associations using the MoCA-Modified (referred to as MoCA-H1 in Manuscript I). In Study I, I showed that hearing-dependent items, especially the delayed recall subtest, were greatly influential in the MoCA's sensitivity to MCI. However, in healthy older adults (Study II), the association between MoCA and hearing was evident even when hearing-dependent items were not included in scoring (MoCA-Modified), at least in women. On the other hand, in women with MCI (Study III), associations between hearing and cognition were only observed in the full MoCA but not in the MoCA-Modified. Taking all our studies into account, perceptual factors have the *potential* to influence MoCA scores (as seen in Study I), and our findings in those with MCI support this as they show that correlations between the MoCA and our hearing measure were only significant for the full MoCA and not the MoCA-Modified. On the other hand, the findings from Study II in healthy older adults suggest that hearing loss has a genuine effect on cognition that extends beyond perceptual limitations. The discrepancy between Studies II and III could be attributed to the different populations, with those with MCI being more likely to be influenced by perceptual factors due to their limited cognitive resources. Further discussion of the potential underlying mechanisms follows in the implications section.

Another potential reason for the discrepancy is the different hearing measures used, discussed in the following section.

One goal of the dissertation was to assess auditory-cognitive associations on the MoCA and compare them to other neuropsychological measures, those being the RAVLT and the BVMT-R (Manuscript III). Interestingly, we did not observe many effects on these two neuropsychological measures relative to our findings with the MoCA. I did not observe any differences in scores on the RAVLT between individuals with normal hearing and those with hearing loss in our sample with MCI, contrary to previous studies with healthy older adults (Guglielmi et al., 2020; Wu & Chiu, 2016). I did observe some associations between the CDTT and RAVLT scores, but those were only observed in women with normal hearing. For the BVMT-R, only one previous study, conducted with cognitively healthy older adults, has examined differences in auditory-cognitive associations on the BVMT-R (Wong et al., 2018), and were unable to find any differences between hearing groups on that measure. In line with Wong and colleagues (2018), I also did not observe significant differences between normal hearing and hearing loss groups on the BVMT-R. However, when examining BVMT-R scores categorically, I found that normal hearing men were more likely to "pass" the BVMT-R relative to those with hearing loss. Overall, the associations between MoCA and hearing seemed to be the most robust in individuals with MCI, possibly pointing to the MoCA's brevity making it more susceptible to interference by auditory and perceptual factors. An examination of these associations based on the hearing measures used follows.

Pure-tone Versus Suprathreshold Hearing

In the current set of studies, I looked at hearing using two different types of measures. Pure-tone hearing (pure-tone average, PTA, in Study II, and pure-tone screening in Study III), which

is commonly used in audiology clinics, was used to assess the audibility of sound, sometimes referred to as peripheral hearing. I also examined suprathreshold hearing using a measure of speech comprehension and understanding in noise, that being the Canadian Digit Triplet Test (CDTT; Study III). In the next section, I will examine our findings in the context of pure-tone versus suprathreshold hearing.

The Canadian Digit Triplet Test requires listening to three digits under noisy conditions and then inputting them into a designated keypad (Ellaham et al., 2016). Thus, the CDTT requires three items to be repeated per trial and has a limited set of potential lexical items (1-9). The majority of our findings in Study III were observed in relation to the CDTT, with few exceptions. Certainly, this discrepancy can partially be attributed to the way pure-tone hearing was measured in that study (see Manuscript III limitations section). While many studies have observed associations between PTA and cognition (e.g., Lin et al., 2011a), several studies have failed to observe associations between pure-tone hearing and cognitive function (e.g., Hong et al., 2016; Wong et al., 2018). Furthermore, other studies have suggested that cognition was only associated with suprathreshold hearing measures, but not pure-tone hearing (Häggström et al., 2018; Idrizbegovic et al., 2011). Gates and colleagues (2010) showed that executive functioning accounted for a significant amount of variance (5-21%) in suprathreshold hearing measures even after accounting for pure-tone hearing. Notably, this finding was true for both cognitively normal individuals and those with mild cognitive impairment, though the effects were more pronounced in those with MCI (Gates et al., 2010). All these studies suggest that the association between suprathreshold hearing and cognition may be more reliable than that between pure-tone hearing and cognition. Performance on suprathreshold hearing measures reflects function of the auditory cortex and other associated areas, and impairments on these measures may signal cortical

deteriorations in the brain, not just in the auditory cortex but in various areas involved in cognitive functioning as well (Rudner et al., 2019). Older adults can frequently have normal pure-tone detection thresholds, suggesting intact cochlear hair cells' function, but impaired suprathreshold hearing in noise. In other words, even though speech may remain largely audible, they have difficulties with speech comprehension and understanding, especially under noisy conditions (Pichora-Fuller et al., 2017; Vermiglio et al., 2012). Our current findings are in line with this, suggesting that suprathreshold measures of hearing may be more strongly associated with cognition than pure-tone thresholds, specifically in individuals who are already at a cognitive disadvantage (MCI). Future studies using multiple suprathreshold measures along with PTA and comparing their associations with multiple neuropsychological measures are required.

Sex-related Differences

A unique finding in this dissertation was the emergence of sex-related differences in auditory-cognitive associations over two studies and several different measures. In Study I, I observed that there were no significant sex-differences in the psychometric properties of the MoCA with or without hearing-dependent items. In contrast, I observed several unique sex-related effects in auditory-cognitive associations in the women of Studies II and III. This suggests that the sex-related differences observed in Studies II and III are unlikely to be reflecting differences in the psychometric properties of the MoCA or MoCA-Modified between men and women. Yet I observed some unique auditory-cognitive associations in women only. In general, in terms of both cognition and hearing, women in both studies performed equivalent to, or better than, the men. While it is tempting to explain these sex-related differences as a consequence of better cognitive performance in women, this is inconsistent with the findings in Study III, in which the sample consisted of individuals with MCI, and the women in that sample performed worse on the MoCA than the healthy men in Study II (Study III women average

MoCA score = 23.63; Study II men average MoCA score = 26.32). In other words, if better cognitive performance was more likely to be associated with hearing, then we would not have expected to see any associations in the individuals with MCI, which was not the case. This is also inconsistent with findings from other studies in which individuals with significant cognitive decline showed an association with hearing (e.g., Gates et al., 2010). In terms of hearing, I note that women had better hearing than men in Study II, while in Study III both men and women had similar rates of pure-tone hearing loss (41% and 32%, respectively). Again, this cannot explain the current findings as I observed sex-related differences in both studies.

In order to further elucidate these findings, I attempted to find other explanatory variables for the differences between men and women. In Study II I observed no differences in age, educational attainment, nor depression status between men and women. Further, in Study III I observed no differences in social activities, depression scores, hypertension, hyperlipidemia, cardiovascular health, vascular disease, diabetes, and smoking between men and women in that sample. This in itself is somewhat unusual, as there are well-documented sex-differences in depression (Seedat et al., 2009), hypertension (Ramirez & Sullivan, 2018), and diabetes (Mauvis-Jarvis, 2015), to name a few. I note that our studies are not epidemiological in nature and therefore the sample selection may have been influenced by multiple factors, such as socioeconomic status, general health (in Study II), hearing loss severity, and the availability of informants (in Study III). Nevertheless, I maintain that, despite not being commonly explored, previous studies have observed unique sex-related differences in auditory-cognitive associations (Eberhard et al., 2019; Helzner et al., 2005; Huang et al., 2019). Helzner and colleagues (2005) reported that scores on the Mini-Mental State Examination were associated with hearing in black women alone, but not in black men, white men, nor white women. Eberhard and colleagues

(2019) observed an association between MMSE scores and low frequency hearing loss in women alone. In both studies, unique associations with cognition were observed in women only. Similarly, Studies II and III of this dissertation, which included individuals from two different samples and at different levels of cognitive functioning (healthy and MCI), also show some unique associations in women. While the evidence is currently sparse, I believe that sex-related differences in auditory-cognitive associations are important and should be explored further. In the following section, I put together all of our findings and discuss possible interpretations in the context of auditory-cognitive mechanisms.

Implications For Auditory-Cognitive Associations

I have discussed our findings in the context of our cognitive measures, our hearing measures, and sex-related differences. In this section, I discuss all our findings from an intersectional perspective, focusing on the potential mechanisms underlying auditory-cognitive associations.

In the information degradation hypothesis, poor sensory function requires increased resources be dedicated to information processing and thus has an immediate impact on the availability of cognitive resources for other cognitive functions (e.g., Schneider & Pichora-Fuller, 2000; Wingfield et al., 2005). As such, if information degradation was the underlying mechanism, then individuals with hearing loss would be at a disadvantage on tests that rely on good audition, while their performance on visual tests should be normal or close to normal. In our studies, I examined this hypothesis in two ways: First, by comparing scores on the MoCA to the MoCA-Modified, and second, by comparing auditory-cognitive associations on verbal relative to visual tests. Interestingly, with regards to the MoCA and MoCA-Modified, our findings varied between the two studies. In Study II, women-only effects were observed on both the MoCA and MoCA-Modified, while in Study III these effects were only observed on the

MoCA but not the MoCA-Modified. As alluded to previously, this may reflect the different populations involved in the studies. In healthy older adults (as in Study II), the availability of cognitive resources may be such that they can compensate for perceptual difficulties (e.g., hearing loss) without sacrificing too many of the resources needed for cognitive processing. Thus, in this population, auditory-cognitive associations are seen on both the MoCA and MoCA-Modified and likely reflect a genuine effect of hearing loss on cognition. This finding is even more meaningful considering the large effect the hearing-dependent subtests on the MoCA have on the psychometric properties of the test, as demonstrated in Study I. In individuals with MCI (as in Study III), the limited availability of cognitive resources would make them more susceptible to perceptual factors, resulting in auditory-cognitive associations between MoCA scores and hearing, but not the MoCA-Modified, as it excludes hearing-dependent items. This is further supported by the lack of observed associations between the BVMT-R, a visual measure, and hearing, at least in women. On the RAVLT, associations with hearing were only observed in MCI women with normal suprathreshold hearing while those with hearing loss did not show any associations. As discussed in Manuscript III, this finding is similar to other reports (Golub et al., 2020) in which associations between hearing and cognitive performance on a verbal memory measure were only observed in those with normal hearing. In their cross-sectional study, Golub and colleagues (2020) examined data from two epidemiological studies encompassing 6451 cognitively healthy individuals over the age of 50 (mean age 59.4 years, younger than the 71.19 years mean in Study III). They observed the expected association between peripheral hearing and cognitive performance on several measures, including the digit symbol substitution test, and the Spanish-English Verbal Learning Test (SEVLT), a measure that is structurally analogous to the RAVLT. Interestingly, when separated by hearing status, those with normal hearing showed

significant associations with cognitive scores, while those with hearing loss did not, controlling for confounders such as age, education, and cardiovascular disease. It is difficult to say whether our findings in Study III and Golub and colleagues' (2020) findings are representative of the same underlying mechanism due to the different hearing (PTA versus CDTT) and cognitive (SEVLT versus RAVLT) measures used, but both seem to point to an association between hearing and cognition that extends beyond the binary of normal hearing/hearing loss. Overall, the findings in this dissertation support the notion that information degradation likely plays a role in auditory-cognitive associations, but is likely to be more impactful in those with more cognitive decline, such as those with MCI. Other mechanisms likely play a larger role in our observed findings.

The sensory deprivation hypothesis proposes a long-term effect of sensory loss on cognition through deterioration in the function and structure of impacted brain regions. The studies in this dissertation were cross-sectional and therefore unable to adequately investigate this hypothesis. Nevertheless, some cautious deductions follow. One aspect of this dissertation that may be interpreted in a sensory deprivation context was the relationship between pure-tone and suprathreshold hearing, discussed previously. Both pure-tone and suprathreshold hearing have been associated with brain volume in older adults (e.g., Giroud et al., 2021; Uchida et al., 2018; Wong et al., 2010). However, older adults can have difficulties understanding speech in noise while having normal pure-tone hearing (Vermiglio et al., 2012). In line with this finding, I observed in Study III that our participants were categorized as having normal pure-tone hearing but speech-in-noise hearing loss about 15% of the time, while the opposite was less common and only occurred for about 5% of the participants (similar findings were observed for men and women separately). Further, previous studies observed associations between suprathreshold

hearing measures and cognition even after controlling for pure tone hearing (Gates et al., 2010). This is partially supported in Study III, in which I observed associations between the CDTT SRTs with MoCA and RAVLT scores after controlling for pure-tone hearing, though this was only observed in normal hearing women. As such, associations between suprathreshold hearing with cognition may reflect changes in brain morphology in the auditory cortex and beyond that are a result of long-term hearing impairment (e.g., Giroud et al., 2021), consistent with the sensory deprivation hypothesis. However, note that this is speculative as longitudinal studies exploring the relationship between hearing, cognition, and brain morphology are required. In the context of our sex-related findings, the differences in morphology, trajectory, and presentation of hearing loss between men and women would indeed suggest that they would display different auditory-cognitive relationships. However, since men tend to develop hearing loss earlier than women (Davis, 1995), sensory deprivation would be expected to have a more significant impact on their brains and eventually on their cognition. This is not in line with the auditory-cognitive associations being more frequently seen in women in our studies. Further studies can explore longitudinal factors associated with hearing loss in men and women (e.g., years with hearing loss) and their relationship with cognition.

The social isolation hypothesis proposes that hearing loss results in social isolation and loneliness, which in turn have an adverse effect on cognition. The sensory deprivation and social isolation hypotheses are sometimes combined as both involve long-term sequalae of hearing loss, sometimes referred to together as the cascade hypothesis (e.g., Uchida et al., 2018). As with the sensory deprivation hypothesis, longitudinal studies that examine the change in social activities over time following hearing loss are better suited to address this hypothesis. Nevertheless, I did examine this hypothesis in our studies in a limited capacity. In Study II, I controlled for the

presence of depression in our participants, and found associations between pure-tone hearing and MoCA scores in women. I also note no significant differences in the proportion of individuals reporting depression between men and women, making it an unlikely explanatory variable for our sex-related differences. In Study III, our results showed no differences between men and women in social activity, nor any differences between those with normal hearing and hearing loss within each sex on that measure. While these findings are in no way conclusive (see limitations section), the observed pattern suggests that social factors likely only have a limited, if any, contribution to our auditory-cognitive findings, in line with recent findings from the Canadian Longitudinal Study of Aging (Hämäläinen et al., 2020).

Finally, the common cause hypothesis proposes that a third variable acts on both cognition and hearing independently. Some of the proposed common causes include oxidative stress, genetics, and vascular factors. In the context of our studies, I observed unique sex-related differences in that the majority of our findings were observed with women, but not men. This led us to speculate on the role that estrogen, the main female sex hormone, might play in this relationship, and whether it could be a common cause. Several pieces of evidence lend themselves to this interpretation: Firstly, hearing loss in women tends to coincide with the time of menopause, possibly owing to declines in estrogen levels in the inner ear, which normally plays a protective role in the female cochlea (Davis, 1995; He & Ren, 2018; Hederstierna et al., 2010; Nolan et al., 2013). Secondly, other lines of evidence have suggested that hormone replacement therapy, a procedure that restores estrogen levels in post-menopausal women, is itself associated with the risk of hearing loss, though the exact nature of the association remains under debate (Curhan et al., 2017). Thirdly, estrogen depletion and menopause are associated with metabolic disorders such as diabetes, which themselves have also been associated with

hearing loss (Stachowiak et al., 2015). This is in line with Dubno's (2013) view of "metabolic" hearing phenotypes being more common in women than men. The final piece of evidence connecting estrogen and auditory-cognitive associations is that Alzheimer's disease, which is more common in women, has also been associated with hormonal changes in estrogen distribution in the brain following menopause (e.g., Mosconi et al., 2017; See Scheyer et al., 2018 for review). The previous points lend support to the hypothesis that post-menopausal changes in estrogen levels in women are related to the auditory-cognitive association. In line with this view, I observed, in both Studies II and III, unique auditory-cognitive associations in women only, despite no significant differences in demographic variables between the sexes. One exception being the unique men-only associations observed on the BVMT-R, discussed previously. This is of course only speculative as I did not directly measure hormonal levels in study participants. Future studies dedicated to examining this relationship on a hormonal level are required.

Put together, the findings from this dissertation lend some partial support to both the information degradation and the common cause hypotheses. As noted by Pronk and colleagues (2019) and others, auditory-cognitive mechanisms are not mutually exclusive and likely carry different contributions depending on the context. For example, information degradation could be playing a bigger role in auditory-cognitive associations in individuals with MCI. However, this hypothesis cannot account for all of our effects, as I observed associations even when hearing-dependent items were not included in MoCA scoring (in Study II). Our women-specific results are more interpretable in a common cause outlook, suggesting that multiple mechanisms may be at play in this relationship. Our studies were only able to examine the sensory deprivation and social isolation hypotheses in a limited capacity, and as such further dedicated studies are

required. Clearly, the relationships between hearing and cognition are complex and require an intersectional, multifactorial approach.

Limitations

The individual limitations of the studies in this work are noted in their respective manuscripts. Across Manuscripts, comparisons between Studies II and III may be difficult due to the use of different PTA frequencies. Pure-tone average in Study II was based on thresholds collected at 500, 1000, 2000, and 4000 Hz, while in Study III pure-tone hearing was only examined at 2000 Hz. As hearing loss in older adults often manifests in the higher frequencies (Cruickshanks et al., 1998), then this frequency may not cover the deficits in our Study III sample, which may explain some of the discrepancies between the two studies. Nevertheless, as noted in Study III, our hearing screening categories showed strong correlations with normal four-frequency pure-tone average in an independent sample. Another factor that limits comparison was selection bias in the two studies. As noted previously, the participants in Study II were recruited as part of a larger study on health and balance, biasing selection towards individuals who were physically healthy. On the other hand, CCNA participants in Study III were also recruited based on physical health (cognitive health notwithstanding) as well as availability of study partners. These biases not only limit comparability between studies, but also the generalizability of our findings. As noted earlier, we did not observe sex-differences in several demographic factors in Study III, such as presence of hypertension and diabetes, which is not in line with findings from epidemiological studies (e.g., Ramirez & Sullivan, 2018; Mauvis-Jarvis, 2015). Therefore, the current findings likely reflect associations in individuals at the higher end of functional ability, including in individuals with MCI. This limits the generalizability of the results and suggest that future studies with less limited inclusion criteria are required.

Our studies had overall small sample sizes, particularly in our analyses which necessitated splitting the sample by sex. This limited our ability to fully investigate the contribution of several risk factors of cognition and hearing, and reduced the power of our analyses overall, especially in Study III. For example, in said study, 50% of women with pure-tone hearing loss had hypertension, compared to only 25% of those with normal pure-tone hearing, but this difference did not reach statistical significance. A larger sample size might have helped further elucidate both the sex- and hearing-differences in our participants.

As stated previously, social isolation had been proposed as a potential mechanism underlying auditory-cognitive associations. While we did measure social activity in Study III, it was only examined in a superficial way that does not convey the underlying complexity of the construct. Other preliminary analyses that we carried out with social variables in Study III did not show any meaningful social differences between hearing groups (data not shown). Current research in this area individually examines a multitude of psychosocial factors such as types of social activities, frequency of activities, social network size, loneliness and desire for more social participation, to name a few (e.g., Hämäläinen et al., 2020). Promising results have also been observed from the development of a specialized questionnaire on the social impact of hearing loss, the Social and Emotional Impact of Hearing Impairment (SEI-HI) questionnaire (Littlejohn et al., 2020). Future research focusing on social factors and their relationships with audition and cognition is required.

I observed unique auditory-cognitive association in women in two different populations over two studies (Manuscripts II and III). These findings were observed after accounting for demographic factors such as age, education, depression, and others. However, one important factor that was not addressed due to low numbers was race. Previous studies have consistently demonstrated a lower risk of hearing loss in black older adults (e.g., Agrawal et al., 2008;

Helzner et al., 2005). Dementia prevalence rates also vary widely between races, even after accounting for disparities in educational achievement and socioeconomic factors (for review see Mehta & Yeo, 2017). A study by Brenowitz and colleagues (2019), which included a substantial number of black participants (630 individuals, 35% of full sample), observed no differences between black and white individuals in the association between sensory loss (including hearing loss) and risk of dementia. Finally, the study by Helzner and colleagues (2005), one of the few to observe unique sex-related differences in auditory-cognitive associations, found these associations in black women only, but not in white women nor in men of either race. I note that other demographic factors in that study, such as lower household income, were also associated with hearing loss in black women alone and not any other sex/race (Helzner et al., 2005). As such, future investigations into the role of race and related demographic factors in auditory-cognitive associations are needed.

Future Directions

No discussion of auditory-cognitive associations would be complete without mention of hearing aid or cochlear implant use and their implications. Proper auditory rehabilitation for older adults would be expected to reduce the cognitive load and improve speech recognition and understanding. As such, in the context of previously discussed mechanisms, one would expect that auditory rehabilitation would benefit cognition if the information degradation or the social isolation hypotheses were correct, as hearing aids would reduce cognitive load and help encourage older adults to increase their socialization. If long-term hearing aid use caused cortical changes in the brain, then that may benefit cognition in the context of the sensory deprivation hypothesis as well. In the current set of studies, hearing aid use was either not assessed (Study I) or not common enough to be assessed (Studies II and III). Nevertheless, I believe this is an important area to examine as the current literature presents many interesting questions in this

regard. Findings with the MoCA and auditory rehabilitation have been mixed. For example, Castiglione and colleagues (2016) observed that cochlear implant users showed a significant improvement in MoCA scores 1 year after implantation. In the same study, long-term hearing aid users outperformed their untreated counterparts on the MoCA and were comparable to healthy (non-hearing impaired) controls. Promising findings from Glick and Sharma (2020) suggest that long-term use of well-fitted hearing aids (6 months) was associated with significant cortical reorganization in the brains of individuals with hearing loss that more closely resembles the brains of those with normal hearing. This was additionally associated with improved scores on the MoCA in those that used hearing aids relative to their prior scores. Conversely, Saunders and colleagues (2018) noted that while normal hearing older adults outperformed their hearing loss counterparts on the MoCA, there were no advantages to those with hearing loss that used amplification. In fact, hearing aid users performed more poorly than unaided hearing loss individuals (Saunders et al., 2018). However, note that this study involved a small sample size and was cross-sectional in nature. A longitudinal study from the US-based Health and Retirement Study (HRS) found that the slope of decline in episodic memory scores was slower after hearing aid use (Maharani et al., 2018a). Interestingly, Maharani and colleagues (2018b) noted no sex-differences in the rates of cognitive decline after hearing aid use, despite women having higher memory scores than men. More longitudinal studies looking at change in MoCA scores over time after auditory rehabilitation are required.

Finally, the current set of studies focused on hearing and its potential relationship with cognition in older adults. However, it must be noted that other senses, such as vision, have also shown some associations with cognition. Visual acuity has been associated with cognitive decline in older adults (Anstey et al., 2002; Lin et al., 2004). In addition to pure visual acuity,

other visual variables such as contrast sensitivity (Cronin-Golomb et al., 2007), depth perception (Mendez et al., 1996), and visual impairments such as glaucoma (Bayer et al., 2002), cataracts (Goldstein et al., 2003), and macular degeneration (Pham et al., 2006) have also been associated with cognitive decline and/or the development of dementia. Findings from our group using CCNA participants have shown an association between visual performance (reading acuity and contrast sensitivity) and grey matter volume in several brain areas related to visual processing in individuals with or at risk for Alzheimer's disease (Rehan et al., 2021). Furthermore, some research has suggested that dual-sensory (vision and audition) impairments show stronger associations with cognitive decline than a single sensory impairment (Brenowitz et al., 2019; Maharani et al., 2018b), consistent with the common cause hypothesis. Brenowitz and colleagues (2019) recently demonstrated that dual-sensory impaired individuals were at higher risk for the development of dementia over a period of 10 years compared to single-sensory or non-sensory impaired individuals. Maharani and colleagues (2018b) combined data from three longitudinal studies of aging and observed that those with dual-sensory impairments showed greater declines in episodic memory scores than those with no sensory impairments, and that the strength of this association was stronger in dual-sensory impaired individuals relative to single-sensory impaired individuals. I noted that men in Study III showed worse reading acuity than women, and further the men with hearing loss, as defined by our speech-in-noise measure, had worse reading acuity than men with normal hearing. It would be interesting to see if our sex-related findings can be replicated when examining visuo-cognitive associations and whether individuals with combined visual- and hearing-impairments show worse cognitive performance.

Clinical Implications

As discussed in the general introduction of this dissertation, early detection of Alzheimer's disease is essential in managing the great financial and psychological burdens of the

disease (Prince et al., 2015). The increasing recognition of hearing loss as a modifiable risk factor for AD (Livingston et al., 2017, 2020) has led to renewed interest in better understanding auditory-cognitive associations and their underlying mechanisms. Our findings lend support to previous research, emphasizing the increased need for concurrent sensory and cognitive assessments. This is doubly true when conducting cognitive screening, as observed in our findings with the auditory-cognitive associations in the MoCA. Associations between cognitive scores and hearing were more frequently observed in the MoCA relative to the two other neuropsychological measures used in Study III. While this is preliminary, from a clinical standpoint the current findings allude to a stronger effect of hearing on cognitive screening measures, which as previously noted are shorter and cover multiple cognitive domains, making them more susceptible to sensory interference. Greater attention to sensory deficits needs to be given when conducting cognitive screening with older adults, in line with current recommendations (Ismail et al., 2020).

Our findings were mostly relegated to the women in our sample. As discussed in the introduction, I referred to sex-related differences in this dissertation, but the observed findings likely represent a combination of both sex- and gender-related factors. For example, we noted that men are more likely to develop the "sensory" phenotype of hearing loss, marked by outer hair cell damage due to noise exposure (Dubno et al., 2013), which is often gender-related (i.e., men being more likely to work in noisy jobs such as construction work). In our studies, we compared differences in sex-related factors, such as cardiovascular risk, and in gender-related factors, such as social activity and depression. Thus, while we refer to our findings as "sex-related," it is likely that both sex and gender factors played a role in the observed results. Considering that female sex is a risk factor for the development of dementia (Vina & Lloret,

2010), and hearing loss is impacted by multiple sex- and gender-related factors, then OA women with cognitive complaints should undergo audiological testing in addition to cognitive testing, using both pure-tone and suprathreshold hearing measures.

Conclusions

In conclusion, the results of my work contribute to the body of literature suggesting that hearing loss is associated with cognitive ability in older adults. Furthermore, I report unique sex-related differences in the auditory-cognitive association that were observed over two different studies and populations. In Study I, I demonstrated the large role that hearing-dependent items play in the psychometric properties of the MoCA, particularly the delayed recall subtest. In Study II, I showed that healthy older women displayed unique associations between pure-tone hearing and cognitive test scores, including the MoCA and MoCA-Modified. In Study III, I demonstrated that this unique sex-related association was observable in a sample of individuals with MCI, and partially extended to verbal tests of episodic memory (the RAVLT). My results support the hypothesis that auditory-cognitive associations reflect genuine effects of hearing loss on cognition, especially in cognitively healthy older adults, but that information degradation likely plays a role in associations in older adults with MCI. Findings from the current studies suggest a role for sex-related factors in auditory-cognitive associations while highlighting the importance of considering these factors in clinical settings.

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