# INVESTIGATING THE RELATIONSHIP BETWEEN COGNITIVE CONTROL AND SPEECH-IN-NOISE RECOGNITION IN TINNITUS FROM PERCEPTUAL, NEUROANATOMICAL, AND ELECTROPHYSIOLOGICAL ASPECTS

BY

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DISSERTATION

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# ABSTRACT

**Purpose:** Individuals with tinnitus commonly report difficulties understanding speech in adverse listening environments. Although such speech-in-noise (SiN) difficulties are believed to relate to deficits in cognitive control, there is as yet no evidence to underpin this assumption. The aim of this dissertation was to investigate the relationship between cognitive control and SiN recognition in individuals with tinnitus and normal hearing sensitivity.

**Method:** Three studies linking behavioral to brain imaging measures were conducted. In the first study, the effect of tinnitus pitch on the recognition of consonants in noise at various frequency ranges was examined to better understand if the tinnitus percept impacts SiN recognition. Using voxel-based morphometry, the second study investigated the relationship between SiN performance and gray matter volume in auditory and cognitive processing regions in individuals with tinnitus. Lastly, using electroencephalogram to record brain activity during Go/Nogo tasks, the third study examined whether event-related potentials related to cognitive control are associated with SiN performance in individuals with tinnitus.

**Results and Discussion:** Overall, the findings of the three studies suggest that 1) perceiving tinnitus at a given frequency does not interfere with speech recognition at the same frequency, suggesting that the effect of tinnitus on SiN recognition may involve higher-level cognitive processes rather than being solely mediated by perceptual abilities; 2) individuals with tinnitus and normal hearing showed comparable SiN recognition and neuropsychological performance relative to hearing-matched controls, however, they still demonstrated neuroanatomical changes and neural alterations pertaining to cognitive control; and 3) individuals with tinnitus may use different cognitive control strategies relative to hearing-matched controls to maintain their performance of daily tasks.

**Conclusions:** The findings confirmed that incorporating multimodal approaches to examine the relationship between cognitive control and SiN recognition can be beneficial to detect neuroanatomical or neural alterations before any overt changes in behavioral performance. Further, the results will serve as the baseline for future endeavors to explicitly investigate the effect of tinnitus and hearing loss on cognitive control abilities and SiN recognition, which can be invaluable in advancing tinnitus consultation and intervention.

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# ABBREVIATIONS

| | |
|---|---|
| ACC | anterior cingulate cortex |
| BAI | Beck Anxiety Inventory |
| BDI | Beck Depression Inventory |
| BOLD | blood-oxygen-level-dependent |
| CON_HL | controls with hearing loss and no tinnitus (Study 1) |
| CON_NH | controls with normal hearing and no tinnitus (Study 1) |
| CTR | control group (Studies 2 and 3) |
| DPOAE | distortion product otoacoustic emission |
| EEG | electroencephalogram |
| EHFPTA | extended high-frequency pure-tone average from 9 to 14 kHz (Study 2) or to 16 kHz (Study 3) |
| ELU | Ease of Language Understanding |
| ERP | event-related potential |
| fMRI | functional magnetic resonance imaging |
| FWE | family-wise error |
| GLM | general linear model |
| GM | gray matter |
| HFPTA | high-frequency pure-tone average of 1, 2, and 4 kHz |
| IFG | inferior frontal gyrus |
| LDL | loudness discomfort level |
| MFG | middle frontal gyrus |
| MNI | Montreal Neurological Institute |
| MoCA | Montreal Cognitive Assessment |
| MRI | magnetic resonance imaging |
| MTG | middle temporal gyrus |

| | |
|---|---|
| ObA | object-animal task |
| PTA | pure-tone average of 0.5, 1, and 2 kHz |
| QuickSIN | Quick Speech-in-Noise test |
| ROI | region-of-interest |
| RT | reaction time |
| SFG | superior frontal gyrus |
| SI | Stroop interference |
| SiC | single-car task |
| SiN | speech-in-noise |
| SNR | signal-to-noise ratio |
| SSQ12 | The 12-item Speech, Spatial and Qualities of Hearing scale |
| STG | superior temporal gyrus |
| TEA | Test of Everyday Attention |
| TIN | tinnitus group (Studies 2 and 3) |
| TIN_HL | tinnitus patients with hearing loss (Study 1) |
| TIN_NH | tinnitus patients with normal hearing (Study 1) |
| TIV | total intracranial volume |
| TFI | Tinnitus Functional Index |
| TMT | Trail Making Test |
| VBM | voxel-based morphometry |
| vmPFC | ventromedial prefrontal cortex |
| WIN | Words-in-Noise test |
| WRS | word recognition score |

# CHAPTER 1: INTRODUCTION

## 1.1 General Introduction

Tinnitus is a subjective perception of sound when there is no external sound source (Moller, 2007, 2016). The prevalence of tinnitus ranges between 11.9 and 30.3% of the adult population in various studies in individuals who reported having experienced tinnitus for more than five minutes (McCormack et al., 2016). Although tinnitus usually co-occurs with hearing loss (Lockwood et al., 2002), it has been reported that 7.4 to 8% of the tinnitus population had normal hearing sensitivity (Barnea et al., 1990; Davis & Rafaie, 2000; Sanchez et al., 2005).

In individuals with tinnitus, around 80% of them naturally habituate to their tinnitus and do not require medical attention; however, for the remaining 20%, the habituation to tinnitus does not occur, making it clinically significant (Henry, 2016; Henry et al., 2003, 2009). Some common tinnitus-related problems include reduced quality of life, inability to concentrate, sleep difficulties, negative effect on hearing, participation restrictions due to deficits in receiving spoken messages, and reduced sound intensity or quality due to tinnitus (Erlandsson & Hallberg, 2000; Hall et al., 2018; Henry et al., 2005; Manchaiah et al., 2018; Tyler & Baker, 1983; Watts et al., 2018). It is also common for individuals with tinnitus to have impaired psychological health due to comorbid anxiety and depression (Bhatt et al., 2016; Trevis et al., 2018). The effect of tinnitus on each individual can be multifaceted, which has led to the development of several questionnaires attempting to quantify patients' complaints in a variety of domains (Haider et al., 2016), for example, the sleep and concentration domains in the Tinnitus Primary Function Questionnaire (Tyler et al., 2014). However, these domains are mainly evaluated using established, closed-question formats, which might not truly encompass all related aspects of complaints in each individual with tinnitus (Hall et al., 2018). For example, difficulties performing a speech-in-noise test do not necessarily correspond to the subscales in the quality of life or hearing domains in established tinnitus questionnaires.

### 1.2 Speech-in-Noise Recognition in Tinnitus

Speech comprehension difficulties are frequently reported in individuals with tinnitus regardless of their hearing sensitivity (Tyler & Baker, 1983), especially in adverse listening environments (Vielsmeier et al., 2016). Many recent speech-in-noise (SiN) studies focused on individuals with normal hearing sensitivity (clinically defined as less than or equal to 25 dB HL from 0.25 to 8 kHz) or near-normal hearing thresholds to eliminate the effect of hearing loss on SiN performance (Gilles et al., 2016; Hennig et al., 2011; Huang et al., 2007; Jain & Sahoo, 2014; Moon et al., 2015; Ryu et al., 2012; Valderrama et al., 2018). These studies suggest that individuals with tinnitus have poorer SiN recognition compared with hearing-matched controls, regardless of the heterogeneity of the tinnitus population or the complexity of the SiN tasks. Although behavioral and neuroanatomical evidence has indicated that the effect of “hidden hearing loss” at the extended high-frequency range (usually from 9 to 16 kHz) should not be overlooked in individuals with tinnitus exhibiting normal hearing in the conventional frequency range (Brannstrom & Waechter, 2018; Melcher et al., 2013; Schaette & McAlpine, 2011), the manner in which the “hidden hearing loss” affects SiN recognition is still unknown.

How an individual processes the stimulus in an acoustic challenge relies on the abilities of the listener, the quality of sound, and the acoustic environment (Koeritzer et al., 2018; Peelle, 2018). Further, within-individual factors such as the listener’s peripheral hearing acuity, central auditory processing, and cognitive functions are believed to affect SiN recognition (Akeroyd, 2008; CHABA, 1988; George et al., 2007; Humes et al., 2006). While SiN difficulties in listeners with hearing impairment can be explained by reduced peripheral hearing acuity, a growing body of evidence suggests that such difficulties are also present in those with relatively intact peripheral hearing, indicating that other factors may need to be considered while explaining SiN difficulties in those individuals (Dryden et al., 2017). Regardless of hearing sensitivity, when speech stimuli or the background maskers become sufficiently complex, a listener's cognitive control abilities can come into play to overcome the increased difficulties of the speech task (Ben-David et al., 2012; Heinrich et al., 2015; Rajan & Cainer, 2008; Schoof & Rosen, 2014).

Previous SiN studies postulated that speech comprehension difficulties in tinnitus involve a "central contribution" (Ivansic et al., 2017). In line with the previous assumption, the results of our recent study (Tai & Husain, 2018) showed a significant between-ear difference (right-ear advantage or left-ear disadvantage) of SiN recognition in a tinnitus group with normal and symmetrical hearing, the difference in between-ear SiN performance is believed to be modifiable by cognitive functions such as attention or working memory (Hiscock & Kinsbourne, 2011), leading to a conceivable involvement of cognitive control on SiN recognition in tinnitus. There might also be an as yet unknown neuroanatomical reason for the between-ear difference (Jerger et al., 1994; Wong et al., 2010). We explored this to some extent in Chapter 3, although we focused on only one aspect of neuroanatomy, that of gray matter volume.

## 1.3 Cognitive Control in Tinnitus

### *An Overview of Cognitive Control*

Cognitive control, commonly known as executive functions in the field of cognitive psychology, refers to a variety of top-down processes that human beings use to complete their daily tasks (Diamond, 2013). The three core processes of cognitive control include 1) inhibitory control (inhibition), which involves the suppression of automatic and prepotent responses, 2) working memory (updating), which involves the ability to hold and update information in mind for mental tasks, and 3) cognitive flexibility (shifting), which involves one's ability to shift back and forth between tasks (Diamond, 2013; Diamond & Ling, 2016; Miyake et al., 2000). These processes cannot be easily dissociated but rather work together, for example, working memory supports inhibitory control by holding a goal in mind, so one knows what stimuli are irrelevant and should be inhibited (Diamond, 2013). The core function of inhibitory control can be sub-categorized into response inhibition and interference inhibition (also known as executive attention or selective attention) depending on the object being inhibited: the former requires the suppression of behavioral response, and the latter involves restraining an automatic response to task-irrelevant stimuli (Diamond, 2013; Friedman & Miyake, 2004). Both response and interference inhibition involve maintaining a task goal in mind and therefore are highly relevant to each other (Friedman & Miyake, 2004).

### *Reduced Cognitive Control Abilities in Tinnitus*

**Evidence from Behavior Measures.** Behavioral or cognitive tasks are often used to assess different aspects of cognitive control in terms of response inhibition (e.g., Go/Nogo or the Stop-Signal task, which will be described in more detail in Chapter 4) or interference inhibition (e.g., Stroop task, Trail-Making Test, or dual-task paradigm). Tinnitus studies using the Go/Nogo task or the Stop-Signal task demonstrate consistent findings that individuals with tinnitus have impaired response inhibition, manifested by increased response times and error (Araneda, De Volder, Deggouj, & Renier, 2015; Krick et al., 2017; Trevis et al., 2016). Additionally, studies focused on interference inhibition using the Trail Making Test (TMT) (Gabr et al., 2011; Jozefowicz-Korczynska et al., 2005; Pajor et al., 2013) or a dual-task paradigm (Degeest et al., 2017; Hallam et al., 2004; Rossiter et al., 2006; Stevens et al., 2007) confirmed deficits in attention and cognitive processing in individuals with tinnitus, such deficits have also been found in young adults with tinnitus and normal hearing sensitivity (Degeest et al., 2017; Gabr et al., 2011). However, studies using the Stroop task demonstrated mixed findings: a classical Stroop effect, manifested by increased reaction times and decreased response accuracy in incongruent trials, were not consistently found in individuals with tinnitus (Andersson et al., 2000, 2005; Araneda, De Volder, Deggouj, Philippot, et al., 2015; Jackson et al., 2014; Stevens et al., 2007; Waechter & Brännström, 2015).

Instead of examining individual functions of the attentional system, Heeren et al. (2014) used the Attention Network Test (Fan et al., 2002) to assess how the three attentional functions—alerting, orienting, and executive (Petersen & Posner, 2012; Posner & Petersen, 1990)—interact. They found that individuals with tinnitus showed a specific deficit in the top-down executive control of attention while the alerting and orienting functions of attention were preserved. In line with their findings, recent reviews on cognitive control in tinnitus provide an overarching conclusion: tinnitus impacts top-down control of executive attention or inhibitory control instead of causing a general cognitive decline (Clarke et al., 2020; Mohamad et al., 2016; Tegg-Quinn et al., 2016; Trevis et al., 2018). Notably, deficits in cognitive control are believed to be related to tinnitus generation and maintenance (Araneda, De Volder, Deggouj, Philippot, et al., 2015; Araneda, De Volder, Deggouj, & Renier, 2015; Hallam et al., 2004; Trevis et al., 2016).

**Evidence from Objective Measures.** In addition to behavioral measures, objective measures such as event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI) have been invaluable in understanding cognitive processing associated with specific sensory or cognitive events. It is speculated that individuals with tinnitus pay more attention to their tinnitus than to the task stimuli due to the negative emotional connection related to tinnitus

(Jastreboff, 1990). Such an assumption has been corroborated by a reduced amplitude of the N1 component (which reflects auditory bottom-up selective attention) in the attended condition of behavioral tasks in the tinnitus group relative to the control group (Delb et al., 2008; Hong et al., 2016; Jacobson & McCaslin, 2003). Moreover, reduced amplitudes or prolonged latencies of the P3a or P3b components (both reflect attentional control) have also been found in individuals with tinnitus, indicating a failure to shift their attention from salient stimuli (e.g., tinnitus) to task stimuli (Attias et al., 1996; Gabr et al., 2011; Hong et al., 2016; Mannarelli et al., 2017). Overall, findings in ERP studies demonstrate altered cognitive processing in individuals with tinnitus, manifested by changes in attention-related ERP components (N1, P3a, or P3b).

Likewise, fMRI findings also suggest differences in cognitive processing between individuals with and without tinnitus (Amaral & Langers, 2015; Araneda et al., 2018; Husain et al., 2015). Task-based fMRI is advantageous in that the observed changes in blood-oxygen-level-dependent (BOLD) response of specific brain regions can reflect cognitive processing that is not detectable through behavioral measures. For example, significantly different BOLD responses of the attention and short-term memory networks were found in individuals with tinnitus relative to controls without the presence of significant between-group differences in short-term memory or one-back tasks (Amaral & Langers, 2015; Husain et al., 2015). Irrespective of task difficulty, a general trend was found in task-based fMRI studies: in comparison to individuals without tinnitus, those with tinnitus showed higher BOLD responses during a task in regions related to cognitive control (e.g., Araneda et al., 2018). Increased brain activity in regions related to cognitive control may imply that individuals with tinnitus recruit the top-down cognitive functions relatively more to retain comparable behavioral performance to those without tinnitus.

### 1.4 Effect of Cognitive Control on Speech-in-Noise Recognition

One goal of the new interdisciplinary field, cognitive hearing science, is to understand how cognitive processes affect speech comprehension in adverse listening conditions (Arlinger et al., 2009). Although it has been shown that cognitive functions are important for SiN recognition (Akeroyd, 2008; Dryden et al., 2017; Mattys et al., 2012), the association among various cognitive functions and SiN performance remains to be determined. The working memory model of Ease of Language Understanding (ELU) proposed by Ronnberg (2003) states that in suboptimal conditions such as hearing impairment or adverse listening environments, the working memory system will reduce the effect of the mismatch between perceived speech and stored phonological representations in long-term memory (Ronnberg, 2003; Ronnberg et al., 2008, 2009, 2013). In individuals with hearing impairment, measures of working memory, especially the reading span task, may provide the most significant association between cognitive ability and SiN recognition (Akeroyd, 2008). However, in individuals with normal hearing sensitivity, the relationship between SiN performance and working memory capacity has been found to be non-significant (Cahana-Amitay et al., 2016; Füllgrabe & Rosen, 2016; Ruggles & Shinn-Cunningham, 2011), suggesting that cognitive functions other than working memory may be better associated with SiN performance in those with normal hearing sensitivity. Moreover, converging evidence (Anderson et al., 2013; Gazzaley & Nobre, 2012; Koeritzer et al., 2018) and the modified ELU model (Rönnberg et al., 2013) also underline the importance of considering the interaction between attention and working memory in SiN recognition.

Attention plays a critical role in coordinating everyday activities. Although the auditory system alone can conduct auditory scene analysis based on the characteristics of sounds, it still entails the attention system to refine the sound stream segregation process (Sussman et al., 2005).

Living in a noisy world filled with complex auditory and visual stimuli requires individuals to carefully allocate the limited attentional capacity to process relevant information, and simultaneously inhibit irrelevant information; therefore, inhibitory control is a prerequisite for successful SiN recognition (Janse, 2012; Knight & Heinrich, 2017). For example, focused and divided attention of response inhibition are shown to be critical in predicting SiN performance in complex listening environments (Heinrich et al., 2015, 2016; Janse, 2012). However, due to a large variation in individuals' cognitive abilities and the sensitivity of varying neuropsychological tasks to detect deficits in cognitive functions, the relationship between SiN performance and varying cognitive performance is not always explicit (Getzmann et al., 2015; Ruggles & Shinn-Cunningham, 2011).

## 1.5 Aim of the Dissertation

To summarize, the findings of previous studies indicate two major gaps that need to be addressed. First, even though various methods were used to study cognitive control in tinnitus, none has proven to be sufficient when used alone. For example, ERP or task-based fMRI studies that have included some forms of behavioral or cognitive tasks often did not show consistent results between the behavioral and objective measures (e.g., Amaral & Langers, 2015; Husain et al., 2015). With that said, a thorough evaluation of cognitive control may require various methods, especially when there are doubts about how sensitive behavioral tasks alone can detect subtle changes in cognitive control. Secondly, no direct evidence has been shown to underpin the assumption that the observed SiN difficulties in tinnitus (Ivansic et al., 2017) can be attributed to deficits in cognitive control. This is mainly because SiN studies in tinnitus rarely include behavioral or objective measures on cognitive control. Therefore, multimodal approaches probing both cognitive functions and SiN abilities in a cohort with tinnitus can be critical in delineating the effect of cognitive control on SiN performance (Tai & Husain, 2019).

The primary aim of this dissertation research was to examine the relationship between cognitive control and SiN recognition in individuals with tinnitus and normal hearing. To address this aim, three studies were conducted, linking clinically relevant behavioral measures with brain imaging measures to advance audiological practices and neuroscience of tinnitus. As a continuation of our previous work (Tai & Husain, 2018), SiN ability was evaluated using the Quick Speech-in-Noise test (QuickSIN: Killion et al., 2004) in all three studies. However, instead of using the signal-to-noise ratio (SNR) loss commonly reported for standard QuickSIN, percent correct of word or consonant recognition was used for SiN performance (which will be described in detail for each study in later chapters). Building on the previous work of Tai and Husain (2018) that suggests the perceptual factor of tinnitus loudness can affect SiN performance, the first study examined the effect of another perceptual characteristic of tinnitus, the perceived pitch of tinnitus, on the recognition of consonants in noise at various frequency ranges. The first study aimed to investigate the effect of tinnitus pitch on SiN recognition and to further assess cognitive control deficits in individual with tinnitus. The second study, using voxel-based morphometry (VBM), investigated neuroanatomical differences in gray matter (GM) volume in auditory and cognitive processing regions between individuals with and without tinnitus, and how GM volumes correlated with their SiN performance. The third study examined whether neural alterations reflected by ERPs during tasks of inhibitory control are associated with SiN performance in individuals with tinnitus. Together, the findings from the three studies will lead to a better interpretation of how cognitive control affects SiN in individuals with tinnitus from perceptual, neuroanatomical, and electrophysiological aspects.

# CHAPTER 2: STUDY 1

## Study 1: Association between tinnitus pitch and consonant recognition in noise

### 2.1 Abstract

**Purpose:** Difficulties in speech-in-noise (SiN) understanding are often reported in individuals with tinnitus. Building on our previous findings that SiN performance is correlated with subjective loudness of tinnitus, the present study aimed to investigate the effect of tinnitus pitch on consonant recognition in noise.

**Method:** Pure-tone audiometry and Quick Speech-in-Noise test (QuickSIN) were conducted on 66 participants categorized into four groups by their hearing sensitivity and self-report of tinnitus. Consonant recognition scores at various frequency ranges were obtained at the 5-dB signal-to-noise ratio condition of QuickSIN. Participants with tinnitus also completed a tinnitus pitch-matching procedure. Correlation analyses were conducted between tinnitus pitch and the frequency of the worst consonant recognition, and the error rates based on word and sentence position were compared.

**Results:** Regardless of hearing sensitivity, tinnitus pitch did not correlate with frequency of the worst consonant recognition. Sentence-initial word recognition was affected by hearing impairment, whereas sentence-final word recognition was not affected by hearing impairment or tinnitus. In contrast to individuals with normal hearing, participants with hearing impairment varied in full sentence recognition, with those reporting tinnitus exhibiting significantly higher error rates.

**Conclusions:** The findings suggest that the effect of tinnitus on consonant recognition in noise may involve higher-level functions more than perceptual factors, specifically as related to tinnitus pitch. Further, for individuals with SiN concerns, clinical evaluation should address both

hearing sensitivity and the presence of tinnitus. Future SiN studies should incorporate cognitive tests and possibly brain imaging to parse out the contribution of cognitive factors, such as cognitive control, in SiN in tinnitus.

## 2.2 Introduction

Chronic tinnitus can cause detrimental effects on an individual's quality of life, including impaired concentration, depression, anxiety, and sleep disturbances (Tyler et al., 2014). Among those effects, impaired concentration has been shown to be a significant predictor that contributes 46% of the variance in quality of life in individuals reporting severe tinnitus (Erlandsson & Hallberg, 2000). Moreover, deficits in communication in a variety of listening environments, which are related to cognitive abilities, may severely impact an individual's quality of life (Heinrich et al., 2015). Individuals with tinnitus often report difficulties understanding speech in adverse listening environments (Tyler & Baker, 1983; Vielsmeier et al., 2015). Commonly, they attribute such difficulties to the overpowering nature of tinnitus, which makes them unable to perceive the acoustic stimuli properly (Manchaiah et al., 2018). However, those reported problems can be incorrectly ascribed to tinnitus. A causal relationship between tinnitus and difficulties understanding speech in noise cannot be explicated without ruling out hearing impairment, because both tinnitus and hearing impairment can reduce overall cognitive performance (Watts et al., 2018).

Regardless of hearing sensitivity, poorer speech-in-noise (SiN) performance has been found in individuals with tinnitus compared with hearing-matched controls (Gilles et al., 2016; Hennig et al., 2011; Jain & Sahoo, 2014; Moon et al., 2015; Newman et al., 1994; Ryu et al., 2012). However, our recent study on individuals with tinnitus and normal hearing sensitivity does not support a general SiN deficit in tinnitus (Tai & Husain, 2018). Instead, our findings show that individuals with tinnitus performed significantly worse than hearing-matched controls only at the 5-dB signal-to-noise ratio (SNR) condition of the Quick Speech-in-Noise test (QuickSIN: Killion et al., 2004), which is a challenging listening condition in QuickSIN. Additionally, the SiN performance in individuals with tinnitus was found to be significantly correlated with the perceptual factors related to the loudness of tinnitus. Building on our previous findings, we speculated that perceiving tinnitus at a certain frequency may interfere with the processing of incoming stimuli at the same frequency.

### 2.2.1 Psychoacoustic Measures of Tinnitus

Similar to chronic pain, the presence or severity of chronic tinnitus cannot as yet be validated using objective measures (Henry et al., 2013). Although patients often describe their tinnitus based on dimensions of perception such as pitch, loudness, or laterality that resembles an external sound, it has been known that tinnitus, as an internally-generated sound, behaves differently from external sounds (Fournier et al., 2019; Henry & Meikle, 2000). Nonetheless, psychoacoustic measures, including loudness matching, pitch matching, residual inhibition, and minimal masking level have been used clinically for decades (Meikle et al., 2008). These measures remain popular as counseling tools to provide reassurance to patients that tinnitus is real and quantifiable, even though they demonstrate limited diagnostic significance because of their poor reliability and their high dependence on patients' previous listening experience (Henry et al., 2013; Henry & Meikle, 2000; Manning et al., 2019; Tyler, 2000).

#### ***Tinnitus Pitch***

Tinnitus pitch refers to the perceived frequency of tonal tinnitus or the most prominent frequency of non-tonal tinnitus such as a hissing sound (Henry, 2016; Tyler, 2000). Tinnitus pitch is typically matched at frequencies above 3 kHz (Henry, 2016; Henry & Meikle, 2000; Pan et al., 2009; Roberts et al., 2006; Tyler, 2000), and the determination of one distinct tinnitus pitch has been widely used to reduce testing time (Norena et al., 2002). The matched pitch can vary over several octaves, even with repeated measures within a session, suggesting that tinnitus pitch matching can be highly variable in individuals (Henry, 2016; Norena et al., 2002). Moreover, patients' subjective descriptions can be unreliable, especially when they experience tinnitus with complex percept (Sereda et al., 2011). Therefore, recent psychoacoustic measures have begun to emphasize the importance of considering various pitch components that contribute to the "tinnitus spectrum" by using a tinnitus likeness rating across frequencies (Hoare et al., 2014; Norena et al., 2002; Roberts et al., 2006, 2008; Sereda et al., 2011).

### ***The Relationship between Tinnitus Pitch and Hearing Sensitivity***

Because the prevalence of tinnitus is high among individuals with hearing impairment (Shargorodsky et al., 2010), tinnitus pitch has been modeled as being within frequencies of hearing loss or the edge of hearing loss to identify possible mechanisms of tinnitus (e.g., Pan et al., 2009). On the one hand, tinnitus pitch is believed to fall in the frequency region of hearing loss (Norena et al., 2002; Roberts et al., 2006; Schecklmann et al., 2012; Sereda et al., 2011), which supports the model of increased neural activity in the deafferented or hearing loss region (Eggermont & Roberts, 2004). On the other hand, the perceived tinnitus pitch has been found to correspond to the edge frequency of the hearing loss region (Kiani et al., 2013; König et al., 2006; Moore et al., 2010), indicating a tonotopic reorganization or expansion at frequencies near the boundary of regions between normal hearing and hearing loss (Rauschecker, 1999).

However, the relationship between tinnitus pitch and hearing impairment does not always fall into the dichotomic models. Several studies failed to replicate the above-mentioned studies with results suggesting no significant correlation between tinnitus pitch and hearing loss or the edge frequency (Figueiredo et al., 2010; Flores et al., 2016; Pan et al., 2009; Seimetz et al., 2016). Moreover, a significant correlation between tinnitus pitch and hearing loss or edge frequency might only be found in select subject groups: for example, in individuals with bilateral tonal tinnitus and mild-to-moderate hearing loss (Moore et al., 2010), or in those with unilateral, acute tinnitus (Ochi et al., 2003). Still, little is known about how tinnitus pitch can add to the knowledge of other audiological configurations such as in normal hearing sensitivity, as it usually implies no accessible hearing impairment in the conventional testing frequencies.

### 2.2.2 Consonant Recognition in Speech-in-Noise Test

Presently, there is insufficient evidence to rank SiN tests regarding their clinical efficacy due to fundamental differences in target speakers, type of background noise, and availability of semantic cues. According to Wilson et al. (2007), the Words-in-Noise test (WIN: Wilson, 2003) and QuickSIN are both sensitive in detecting SiN deficits in individuals with hearing loss. In the present study, QuickSIN was selected over WIN for a continuation of our previous study (Tai & Husain, 2018), and to prevent duplication of the word lists used for the speech-in-quiet test. In Tai and Husain (2018), QuickSIN performance at each SNR condition was obtained in percentage after dividing the number of keywords repeated correctly by the pre-defined five keywords in each sentence. Nevertheless, words and sentences may not be the best stimuli for SiN assessments because the lexical effects in words and the context information in sentences can improve the performance and potentially mask the effect of unfavorable conditions such as hearing impairment or tinnitus (Phatak et al., 2009; Zaar & Dau, 2015).

In contrast to word or sentence scoring, phoneme scoring, which refers to the percent correct based on vowel and consonant recognition, has been used to examine SiN performance in individuals with varying hearing sensitivity (Boothroyd, 2008; Gelfand, 1998). Advantages of phoneme scoring include, 1) it increases the number of items scored in the same amount of time, decreases inter-subject variability, and improves test-retest reliability, 2) it provides a better estimation about the perception of acoustical cues of speech, with less involvement of lexical content that might be affected by individuals' vocabulary knowledge, 3) phoneme scores can replace word scores because there is a strong word-to-phoneme correlation, and 4) phoneme scores do not decrease rapidly as word scores when the SNR decreases, thus, they are less variable than word scores (Billings et al., 2015; Boothroyd, 2008; Gelfand, 1998; Gelfand & Gelfand, 2012; McCreery et al., 2010; Olsen et al., 1997). For the present study, only consonant recognition was considered because consonants are more vulnerable in the presence of noise than vowels (Phatak & Allen, 2007). Consonant recognition of QuickSIN may incorporate short-term stimuli (e.g., consonant-vowel combinations such as /ba/ or /ta/) within a framework of meaningful speech units (words or sentences). Additionally, it allows for the possibility of associating consonants with their frequency distribution based on the speech "banana" in the audiogram (e.g., Northern & Downs, 2002, p.18), a tool which is often used for clinical consultation.

Note, however, that the overall performance of consonant recognition can be influenced by the position of a word in a sentence. Significantly higher word recognition scores have been found for sentence-initial words than second words (Gelfand, 1998). Moreover, sentence-final word identification in noise depends on the interaction of factors such as word/target expectancy, SNR, and cognitive abilities (Lash et al., 2013). One aspect of cognition implicated in speech recognition in challenging conditions is cognitive control (part of the central executive function), which refers to a variety of top-down processes such as attention or inhibitory control that human beings use to complete their daily tasks (Diamond, 2013). It has been shown that sentence-final words with high predictability are identified more accurately than those with low predictability in challenging SNR conditions (Hunter & Pisoni, 2018; Lash et al., 2013). Because QuickSIN comprises words with low predictability (Killion et al., 2004), correct identification of sentence-final words may rely on how well a listener attends to the phonetic or lexical information than relying on the content (Hunter & Pisoni, 2018). Thus, cognitive control can be critical for the suppression of task-irrelevant information when identifying low-predictable words or sentences that are highly degraded by noise (Cahana-Amitay et al., 2016). However, previous attempts have only been parsing the effect of age and hearing acuity on sentence-final word recognition (Cahana-Amitay et al., 2016; Hunter & Pisoni, 2018; Lash et al., 2013). As yet, it is unknown how the presence of tinnitus, which is task-irrelevant and has been shown to impact cognitive control (Andersson & McKenna, 2006; Mohamad et al., 2016; Tegg-Quinn et al., 2016; Trevis et al., 2016, 2018), can influence the recognition of words or sentences at various positions in low predictable speech materials.

### 2.2.3 Aims and Hypotheses

The aims of this study were 1) to investigate the effect of tinnitus pitch on consonant recognition, specifically at the 5-dB SNR condition of QuickSIN, because a significant between-group difference was found only in this condition previously (Tai & Husain, 2018), and 2) to examine if tinnitus can affect sentence-initial or -final word recognition, as well as full-sentence recognition. According to “biased competition” (Shinn-cunningham, 2008), if more salient sound streams (e.g., tinnitus) can take over automatically, attention towards the tinnitus pitch/spectrum might mask consonants at tinnitus pitch/spectrum, leading to poorer consonant recognition scores in those frequencies than in non-pitch frequencies. Such impact might be more pronounced in individuals with tinnitus and normal hearing due to a reduced effect of hearing loss on consonant recognition. Thus, a significant correlation between tinnitus pitch and frequency of the worst consonant recognition was hypothesized. Further, we hypothesized that attention towards tinnitus might impact cognitive control, manifested by the increased difficulty in processing sentence-final words or full sentences when the listening condition becomes challenging (e.g., from 10-dB SNR to 5-dB SNR condition).

## 2.3 Method

### 2.3.1 Participants

Participants aged between 21 and 64 years were recruited from the surrounding Urbana-Champaign area under the University of Illinois at Urbana-Champaign Institutional Review Board protocol 15955. Written informed consent was obtained from all participants before the initiation of the study. Individuals were excluded if they reported a history of traumatic brain injury, neurological disorders, Meniere’s disease, post-traumatic stress disorder, and psychological disorders except for currently managed anxiety or depression. Only those who reported American English as their native language were included. Monetary compensation was provided to each participant upon completion of the study.

Participants were grouped based on the presence of chronic tinnitus (at least six months in duration) and their hearing sensitivity: normal hearing was defined as less than or equal to 25 dB HL from 0.25 to 4 kHz in both ears, whereas hearing loss was defined as hearing thresholds greater than 25 dB HL but less than 70 dB HL in any frequency from 0.25 to 4 kHz in either ear.

### 2.3.2 Behavioral Procedures

#### *Audiological Assessments*

Otoscopic inspection, tympanometry, and acoustic reflexes were conducted on all participants to rule out outer ear, middle ear, or retrocochler pathologies. Pure-tone audiometry included octave frequencies between 0.25 and 16 kHz and inter-octave frequencies of 3 and 6 kHz in each ear. Bilateral high-frequency pure-tone average (HFPTA), which is considered as a good predictor of speech perception (Humes, 1996), was obtained by taking the averaged thresholds of 1, 2, and 4 kHz in both ears. Word recognition score (WRS) of the Northwestern University Auditory Test No. 6 list (NU-6: Tillman & Carhart, 1966) was obtained in each ear for the speech-in-quiet test. All participants included in the study had a WRS higher than 80% in either ear.

### ***Self-Reported Questionnaires***

All participants completed an in-house intake form asking questions about their healthcare history. Individuals with tinnitus were also asked to complete the Tinnitus Functional Index (TFI: Meikle et al., 2012). The TFI contains 25-items with a 0-10 or 0%-100% rating scale that covers problems in eight tinnitus-related domains: cognitive, auditory, intrusive, sleep, relaxation, quality of life, emotional, and sense of control. The score of TFI ranges from 0 to 100: a score less than 25 indicates mild tinnitus, and a score greater than or equal to 25 implies significant problems with tinnitus that might require intervention (Henry et al., 2016).

### ***Tinnitus Pitch Matching***

Tinnitus pitch matching was conducted using an audiometer by having individuals with tinnitus select a tone between 0.25 and 8 kHz (including inter-octave frequencies of 0.75, 3, and 6 kHz) that matches the most prominent pitch of their perceived tinnitus. The pitch matching process started with a 1-kHz pulsed tone presenting at 10 dB sensation level for around three seconds, and the frequency of tone increased or decreased in one octave or inter-octave step based on the participant’s response. The presentation level for the remaining frequencies was adjusted accordingly to ensure the stimuli were audible throughout the matching process. To examine the relation between tinnitus pitch and frequency of the worst consonant recognition, a distinct tinnitus pitch instead of the spectrum was measured. To facilitate the comparison between the matching tone and tinnitus and to avoid octave confusion, the matching tones were presented to the ear with non-dominant tinnitus for individuals with bilateral (or head) tinnitus and to the contralateral ear for those with unilateral tinnitus (Henry et al., 2013; Henry & Meikle, 2000). For those who did not report a dominant ear for tinnitus, the ear with a better pure-tone average (PTA: mean hearing threshold of 0.5, 1, and 2 kHz) was used, and the right ear was used if there is no difference of between-ear PTAs. The estimate of tinnitus pitch was taken from the average of three repetitions to account for intra-subject variability during tinnitus pitch matching. Due to the study design (speech banana only contains consonants up to 8 kHz) and limitations of our equipment, pitch matching was only obtained up to 8 kHz. Therefore, for one individual with hearing loss and two individuals with normal hearing, the highest frequency of 8 kHz was reported as their tinnitus pitch even though their true tinnitus pitch was above 8 kHz.

### ***Quick Speech-in-Noise Test (QuickSIN)***

The QuickSIN test was conducted using built-in sound files of the audiometer. Each QuickSIN list consists of six sentences spoken by a female speaker, with five target words per sentence. Participants were instructed to repeat the sentences spoken by the target female talker and ignore the four-talker background noise. The SNR decreases after the presentation of each sentence in 5-dB steps from 25 to 0 (the most difficult condition). As advised in the QuickSIN user manual, the presentation level was set at 70 dB HL for all participants because their PTAs were all less than 45 dB HL. Lists 1 to 4 were used, with two lists presented monaurally to each ear. The SNR loss, defined as the increase in dB SNR required for an individual with hearing loss relative to those with normal hearing to understand speech in noise, was obtained by subtracting total correct words in each list from 25.5, which is the typical scoring method of QuickSIN. Because the aim of the study was not to compare the between-ear performance, bilateral SNR loss was obtained by averaging the SNR loss of all four lists.

For the analysis of consonant recognition, participants' responses were recorded using a Boocosa digital voice recorder (model: VR-001; 1536 Kbps quality of recording). The recording was then transcribed by two native American English speakers who were not involved in data collection. Because Spearman's correlation test indicated a strong and significant correlation of the transcription between the two transcribers ($r_s = 0.96$, $p < 0.001$), only the transcription of one transcriber was used for further analysis.

**Frequency of the Worst Consonant Recognition.** Consonant recognition scores were obtained for the six SNR conditions using all the words in QuickSIN lists 1 to 4, with the exclusion of all articles ("a" or "the"). Seventeen consonants were identified at the 5-dB SNR condition and categorized into different frequency ranges (Table 2.1) based on the speech banana of Northern and Downs (2002, p.18). Because an estimated frequency of the consonant /t/ was not reported in Northern and Downs (2002), it was thus defined according to Humes (1991). The total consonant recognition score was weighted based on different frequency distributions of consonants (Table 2.1). Further, frequency of the worst consonant recognition at the 5-dB SNR condition was determined in participants with tinnitus. An average of multiple frequencies was used in one participant with hearing loss because the worst score was obtained at more than one frequency. Additionally, one participant with normal hearing scored 100% for consonant recognition across frequencies; thus, frequency of the worst consonant recognition could not be determined.

**Percent Error of Sentence-Initial Words, Sentence-Final Words, and Full Sentence.** To understand if an individual's performance was affected by word position or by the increased difficulties in concentrating on the task when the listening condition became challenging, transcriptions of the 5-dB SNR condition were used to obtain the percent error of sentence-initial words ("it," "crouch," "pick," and "stems") and sentence-final words ("wide," "mark," "pack," and "broke"). Error for full sentence recognition was determined when an individual failed to repeat any word of a 5-dB SNR sentence; under the condition of full-sentence omission, both sentence-initial and sentence-final words were considered as being incorrectly repeated.

### 2.3.3 Equipment/Testing Environment

Audiological assessments, tinnitus pitch matching, and QuickSIN were conducted using an Interacoustics Equinox 2.0 clinical audiometer with the ER-3A insert earphones for frequencies from 0.25 to 8 kHz. Pure-tone thresholds between 9 and 16 kHz were obtained using the Sennheiser HDA 200 headphones. Tympanometry and acoustic reflexes were conducted using the Interacoustics Titan Ver. 4.0 tympanometer. The audiometer, tympanometer, and the transducers were calibrated annually according to the ANSI S3.6-2010 standard (ANSI, 2010). To control for the validity and reliability of the study, the assessments were conducted in a single-chamber IAC or Acoustic Systems sound-attenuating booth, both satisfied the ANSI S3.1-1999 (R2003) standard (ANSI, 2003).

### 2.3.4 Statistical Analysis

After checking the normality of data with Shapiro-Wilk tests, Kruskal-Wallis rank sum tests for nonparametric data were used to examine demographic differences in age, bilateral HFPTA, WRS, SNR loss, and percent error of the full sentence among groups. Linear mixed effect models, which do not require the data to be normally distributed or balanced, were used for comparison among groups of 1) hearing threshold at each frequency, 2) consonant recognition at the six SNR conditions, 3) consonant recognition score at each frequency range, and 4) percent error of sentence-initial and -final words. Post hoc tests were conducted using Bonferroni correction for multiple comparisons. Between tinnitus groups, comparisons in tinnitus duration or severity were conducted by using the Mann-Whitney U test for nonparametric data. Within tinnitus group correlations between tinnitus pitch and frequency of the worst consonant recognition were examined using Spearman's correlation tests. All statistical analyses were performed using the R statistical software (version 3.5.1) with a significance level set at 0.05.

## 2.4 Results

Sixty-six participants who fulfilled the inclusion criteria were categorized into four groups: 1) tinnitus with normal hearing (TIN_NH, n = 17), 2) controls with normal hearing and no tinnitus (CON_NH, n = 17), 3) tinnitus with hearing loss (TIN_HL, n = 17), and 4) controls with hearing loss and no tinnitus (CON_HL, n = 15). The demographic information of participants is shown in Table 2.2.

### 2.4.1 Demographic and Hearing Thresholds

The results of Kruskal-Wallis rank sum tests (Table 2.2) indicated significant differences in age ($H(3) = 18.033$, $p < 0.001$), bilateral HFPTA ($H(3) = 31.595$, $p < 0.001$), and bilateral SNR loss ($H(3) = 18.694$, $p < 0.001$). Post hoc analyses with Bonferroni correction showed no significant difference in age, bilateral HFPTA, and bilateral SNR loss between hearing-matched groups (TIN_NH vs. CON_NH or TIN_HL vs. CON_HL). However, TIN_HL had significantly older age, higher bilateral HFPTA, and higher bilateral SNR loss than the two normal hearing groups, whereas CON_HL had significantly older age and higher bilateral HFPTA than the two normal hearing groups. In summary, the results suggest that although both TIN_HL and CON_HL had significantly worse hearing sensitivity compared with the two normal hearing groups, only TIN_HL presented a significantly worse SNR loss relative to that of the normal hearing groups.

#### ***Mean Hearing Thresholds***

Figure 2.1 shows the mean hearing thresholds from 0.25 to 8 kHz in both ears among groups; hearing thresholds between 9 and 16 kHz were not reported because consonants of the speech banana spanned only between 0.25 and 8 kHz of testing frequencies. Linear mixed effect model with Group and Frequency (eight frequencies from 0.25 to 8 kHz, including 3 and 6 kHz) as the fixed effect, and each individual as the random effect showed a significant main effect of Group ($F(3, 62) = 24.047$, $p < 0.001$), main effect of Frequency ($F(7, 434) = 41.008$, $p < 0.001$), and interaction effect of Group x Frequency ($F(21, 434) = 9.699$, $p < 0.001$). Post hoc *t* tests with Bonferroni correction suggested that comparing the two groups with normal hearing, TIN_HL had significantly higher thresholds at 3, 4, 6, and 8 kHz, and CON_HL had significantly higher thresholds at 4, 6, and 8 kHz. Mean hearing thresholds were not significantly different between the two groups with normal hearing or those with hearing loss across frequencies, although a trend toward significant difference was found between CON_HL and TIN_HL at 3 kHz ($t(62) = -3.37$, $p = 0.06$).

### 2.4.2 Consonant Recognition

#### ***Consonant Recognition at the Six SNR Conditions***

Figure 2.2 shows mean consonant recognition scores across various SNR conditions among groups. Linear mixed effect model with the Group and SNR conditions (six conditions from 0 to 25 dB SNR) as the fixed effect, and each individual as the random effect showed a significant main effect of Group (*F*(3, 62) = 7.517, $p < 0.001$), main effect of SNR condition (*F*(5, 310) = 1624.924, $p < 0.001$), and interaction effect of Group x SNR condition (*F*(15, 310) = 4.776, $p < 0.001$). Post hoc analyses with Bonferroni correction for multiple comparisons indicated that the two groups with hearing loss had significantly poorer consonant recognition score at the 5-dB SNR condition than those with normal hearing, but significant difference in consonant recognition between hearing-matched groups was not found at this condition. No significant difference in percent correct among groups was observed at any other SNR conditions. The findings echo our previous study (Tai & Husain, 2018) that showed the 5-dB SNR condition is the most sensitive condition to detect a between-group difference in SiN performance.

### *5-dB SNR Consonant Recognition across Frequencies*

Figure 2.3 shows consonant recognition scores across frequency ranges in each group. Linear mixed effect model with Group and Frequency as the fixed effect, and each individual as the random effect showed significant main effects of Group (*F*(3, 62) = 7.011, $p < 0.001$) and Frequency (*F*(7, 434) = 16.562, $p < 0.001$), but a non-significant interaction effect of Group x Frequency (*F*(21, 434) = 1.187, $p = 0.259$). Post hoc analyses with Bonferroni correction for multiple comparisons indicated that TIN_HL had significantly worse performance than CON_NH or TIN_NH, and the overall performance was significantly poorer at 2 and 3 kHz. Poor consonant recognition at 2 kHz may be attributed to the relatively low number of consonants accounted for this frequency (Table 1). Poor consonant recognition at 3 kHz might be related to an overall high percent error of sentence-initial or -final words because the 3-kHz consonants are mainly distributed in sentence-initial or -final words.

### 2.4.3 Percent Error of Sentence-Initial Words, Sentence-Final Words, and Full Sentences

Linear mixed effect model with the Group and Word Position (initial or final) as the fixed effect, and each individual as the random effect did not show a main effect of Word Position ($F(1, 62) = 2.523$, $p = 0.117$), suggesting that word position did not affect the overall performance of participants. However, there was a significant main effect of Group ($F(3, 62) = 6.01$, $p < 0.001$) and a significant interaction effect of Group x Word Position ($F(3, 62) = 6.157$, $p < 0.001$). Post hoc analyses with Bonferroni correction for multiple comparisons indicated that percent error was significantly higher in the groups with hearing loss than in the groups with normal hearing. Additionally, for sentence-initial words, mean percent error in CON_HL (mean 60%, SD 24.64%) was significantly higher than that in TIN_NH (mean 23.53%, SD 18.68%) and in CON_NH (mean 23.53%, SD 16.47%), whereas the mean percent error in TIN_HL (mean 47.06%, SD 24.82%) showed a trend of significance ($p = 0.057$) compared with either group with normal hearing (Figure 2.4A). For the sentence-final words (Figure 2.4B), no significant difference in mean percent error was found among groups (CON_NH: mean 39.71%, SD 23.48%; TIN_NH: mean 38.24%, SD 23.58%; CON_HL: mean 40%, SD 28.03%, TIN_HL: mean 57.35%, SD 26.17%).

For full sentence recognition, the results of Kruskal-Wallis rank sum test indicated a significant difference in mean percent error among groups ($H(3) = 14.786$, $p = 0.002$). Post hoc analyses with Bonferroni correction showed that TIN_HL had a significantly higher rate of missing the full sentence (mean 19.12%, SD 22.59%) than the two groups with normal hearing (both had mean 1.47% and SD 6.06%). TIN_HL also showed a higher percent error of the full sentence compared with CON_HL (mean 8.33%, SD 15.43%), although the difference did not reach statistical significance after correcting for multiple comparisons (Figure 2.4C).

### 2.4.4 Comparison and Correlations in the Groups with tinnitus

#### *Between Group Comparison*

The characteristics of tinnitus in TIN_NH and TIN_HL are shown in Table 2.3. The mean TFI scores were greater than 25 in both groups, suggesting significant problems with tinnitus. Although the mean duration and the TFI score were higher in TIN_HL than in TIN_NH, no significant between-group difference was found. Bilateral tinnitus and ringing or whistling tinnitus sounds were reported in most cases. The mean tinnitus pitch was also not significantly different between TIN_NH and TIN_HL.

#### *Within Group Correlations*

Figure 2.5 depicts the association between tinnitus pitch and frequency of the worst consonant recognition. The frequency of the worst consonant recognition in TIN_HL was sparser than that in TIN_NH, which mainly clusters at 2 or 3 kHz, this is consistent with the overall poorer performance at these two frequencies compared with other frequencies. Although a higher correlation between tinnitus pitch and frequency of the worst consonant recognition was found in TIN_NH ($r_s = 0.349$, $p = 0.185$) than in TIN_HL ($r_s = 0.196$, $p = 0.452$), the correlation in either group was not significant. Likewise, the correlation between the two variables was not significant with pooled data of the two tinnitus groups ($r_s = 0.282$, $p = 0.113$). The non-significant correlations suggest that tinnitus pitch does not mask consonants at the same frequency.

## 2.5 Discussion

This study aimed to examine the effect of tinnitus pitch on consonant recognition in noise in individuals with varying hearing sensitivity. To our knowledge, this is the first study to explicitly investigate any interference in consonant recognition by the pitch of the tinnitus percept. To better understand the effect of tinnitus on cognitive control abilities, error rates of sentence-initial words, sentence-final words, and full sentences in noise were also investigated. Between hearing-matched groups, we did not find any significant difference in consonant recognition score at the 5-dB SNR condition (Figure 2.2); however, individuals with hearing loss showed significantly poorer consonant recognition at this condition than those with normal hearing. Regardless of the hearing sensitivity, the results showed non-significant correlations between tinnitus pitch and frequency of the worst consonant recognition, indicating that perceiving tinnitus at a certain frequency does not interfere with consonant recognition at that frequency. Compared to individuals with normal hearing, individuals with hearing loss and no tinnitus showed greater difficulties in processing sentence-initial words, whereas those with both tinnitus and hearing loss had greater difficulties in processing full sentences in challenging listening conditions.

### 2.5.1 Effect of Tinnitus Pitch on Consonant Recognition

Previous studies on consonant recognition mainly categorized consonants based on the place or manner of articulation (Helfer & Huntley, 1991; Woods et al., 2012). To examine the effect of tinnitus pitch on consonant recognition, an experimental approach that categorized consonants based on their frequency distribution of the speech banana was applied. As was hypothesized, individuals with normal hearing had a higher correlation between tinnitus pitch and frequency of the worst consonant recognition than those with hearing loss, indicating that the impact of tinnitus pitch on consonant recognition might be more pronounced when the effect of hearing impairment was reduced. However, the non-significant correlations between tinnitus pitch and the frequency of the worst consonant suggest that at the perceptual level, tinnitus does not mask heard consonants at the tinnitus pitch. Using a cough or a 1000-Hz tone to replace a phoneme in a sentence, Warren (1970) demonstrated that listeners had an illusory perception of the missing phoneme, leading to a replacement of the correct phoneme. Thus, one interpretation is that even if tinnitus pitch overlaps with the frequency of some consonants, a listener's language skills would enable the use of redundancies in speech at the phonemic level, which leads to automatic restoration of missing speech sounds. Another explanation lies in the difference of the tuning curves between tinnitus pitch (an internal sound) and an external sound. Even with tonal tinnitus, tinnitus tuning curves can still show low frequency selectivity with a flat, rather than a traditional V-shape configuration typically seen in psychophysical tuning curves (Fournier et al., 2019), indicating the unfeasibility of a tinnitus sound to mask sounds at a specific frequency. Taken together, the finding implies that tinnitus percept does not significantly change the source-induced variability of the speech stimuli (Zaar & Dau, 2015), as the perceptual differences caused by the variations of speech and noise remain the same despite the perception of tinnitus.

The non-significant correlation between tinnitus pitch and the frequency of worst consonant recognition also indicates that factors other than tinnitus percept might better explain the performance of consonant recognition in tinnitus. This finding echoes a recent neuroimaging study, which showed that in comparison to control frequency, stimuli matching tinnitus frequency elicited greater activity in cognitive or emotional regions of the brain instead of the auditory region (Hullfish et al., 2018).

### 2.5.2 Role of Word/Sentence Position in SiN

In contrast to our hypothesis, the results did not suggest an effect of tinnitus on the recognition of sentence-final words (Figure 2.4B), even though the mean score of tinnitus severity indicated significant problems. This finding implies that reduced cognitive control abilities caused solely by tinnitus might not be sufficient to impact the performance on a single SiN task with low predictability words, which requires less cognitive load compared with a dual-task paradigm (Degeest et al., 2017; Hunter & Pisoni, 2018). Nonetheless, there seems to be an effect of hearing loss on processing sentence-initial words: both groups with hearing loss showed a higher percent error of sentence-initial word recognition compared with the two normal hearing groups (Figure 2.4A). In individuals with normal hearing sensitivity, Gelfand (1998) found a first-word advantage with the score for the first word significantly higher than the second word for a three-word repetition. In the present study, individuals with hearing impairment did not seem to benefit from such first-word advantage. As the effect of hearing impairment on sentence-initial word recognition has not been fully explored in previous studies, it warrants further examination, especially when the sentence-initial word is the first word being heard during the transition from a relatively easy condition (10-dB SNR) to a challenging condition (5-dB SNR).

A higher rate of missing full sentences at the 5-dB SNR condition in the groups with hearing loss than in those with normal hearing (Figure 2.4C) may suggest that individuals with hearing loss could no longer engage in sentence recognition as the listening condition became progressively challenging (from 10-dB SNR to 5-dB SNR). Because a significantly higher percent error of full sentence was only found in TIN_HL than in the groups with normal hearing, it might imply that a decrease in cognitive control abilities during a single SiN task is only evident when tinnitus and hearing impairment co-occur. This assumption can be supported by the differential involvement in the auditory attention and short-term memory network found in hearing impairment with and without tinnitus: during discrimination tasks, individuals with tinnitus and hearing impairment showed a decreased response in the attentional network relative to those with hearing impairment only, even though behavioral performance did not differ significantly between groups (Husain, Pajor, et al., 2011). Likewise, Prestes and Gil (2009) found that the co-occurrence of tinnitus and hearing impairment had more of an impact on quality of life than having tinnitus alone. Thus, clinical evaluation should address both aspects for individuals who report SiN difficulties.

### 2.5.3 Clinical Implications and Future Directions

The non-significant correlation between tinnitus pitch and frequency of the worst consonant recognition by no means implies tinnitus pitch has no useful information as a clinical tool. Measuring tinnitus pitch is valuable in assuring that tinnitus is quantifiable for clinical consultation (Henry, 2016). For some tinnitus interventions, further reduction of tinnitus loudness or tinnitus handicap has been achieved by using customized sound therapies or amplification that enrich sound experiences at a frequency range corresponding to tinnitus pitch (Mahboubi et al., 2017; McNeill et al., 2012; Schaette et al., 2010; Searchfield et al., 2017). Therefore, even though tinnitus pitch does not add to our knowledge in understanding SiN difficulties, it can still be essential for clinical consultation and tinnitus management.

Although not statistically significant, the groups with high-frequency hearing loss showed more difficulties identifying consonants at both high (3.5 and > 4 kHz) and low frequencies (0.25, 0.5, and 0.75 kHz) than those with normal hearing (Figure 2.3), even though they had normal hearing thresholds below 2 kHz (Figure 2.1). Such findings are not surprising, as it has been suggested that damage to the basal region of the cochlea may cause impaired low-frequency speech discrimination (Horwitz et al., 2002). Additionally, studies have shown a significant correlation between low-frequency hearing thresholds and overall SiN performance in individuals with normal hearing thresholds up to 2 kHz (Gelfand et al., 1986; Valderrama et al., 2018). This implies that low-frequency thresholds may need to be accounted for in individuals who report SiN difficulties.

Further, the results suggest that the effect of tinnitus on SiN recognition is not at the perceptual level, indicating other factors such as higher-level cognitive functions need to be considered. However, without examining cognitive control abilities explicitly, a direct association between SiN recognition and cognitive control cannot be established. Future endeavors should incorporate cognitive testing or objective measures such as brain imaging to examine alterations of brain regions related to cognitive control during SiN processing, and to establish a direct link between cognitive control and SiN recognition in tinnitus.

### 2.5.4 Caveat

Some limitations should be noted. Firstly, the hearing loss groups in the present study were significantly older than the normal hearing groups. As speech perception problems in noise can readily be seen in adults between 50 and 60 years (Goossens et al., 2017), it might be imprudent to attribute the observed poor SiN performance in the hearing loss groups solely to their hearing sensitivity without considering the effect of aging. Secondly, using the predominant tinnitus pitch may not fully evaluate the complexity of tinnitus percept in individuals who experience tinnitus as a spectrum of frequencies (Hébert, 2018; Henry, 2016; Norena et al., 2002). Thirdly, in contrast to studies that used manually generated stimuli to control for parameters such as duration or central frequency of consonants (e.g., Phatak & Allen, 2007), we used consonants in the QuickSIN sentences. Sentence stimuli can inevitably contain lexical information that potentially improves listeners' performance, even though these sentences consist of low-predictable words. Fourthly, speech bananas differ from one audiogram to another, and it is impractical to consolidate all speech bananas to determine the best frequency of a consonant. Simply categorizing consonants to fixed frequency ranges may not account for the wide span of consonant formants and formant transitions in different consonant-vowel combinations (Johnson et al., 2011; Kewley-Port, 1982). Fifthly, although QuickSIN recording was transcribed by two native American English speakers, tester and transcriber biases can remain present while scoring or interpreting the data (Billings et al., 2015). Lastly, most clinical SiN tests, including the QuickSIN, do not reflect challenges such as reverberation or speakers from different spatial orientations that listeners may experience in real-world environments (Brungart et al., 2014; Phatak et al., 2018), nor consider audiovisual benefit in speech processing (Moradi et al., 2017).

### 2.5.5 Conclusion

To conclude, we found that tinnitus pitch did not affect consonant recognition in noise, which indicates that the effect of tinnitus is not restricted to the perceptual level. While tinnitus *per se* does not affect SiN recognition, a combined effect of tinnitus and hearing impairment on SiN performance was noted, which might be attributed to reduced cognitive control abilities in this group. The findings underline the importance of incorporating questionnaires, cognitive testing, brain imaging techniques, and more ecologically valid SiN tests to better understand SiN difficulties and cognitive control deficits in tinnitus. Such information can advance cognitive-based aural rehabilitation to improve communication challenges and quality of life in individuals with tinnitus.

## 2.6 Tables and Figures

**Table 2.1** Consonant distribution at various frequency ranges of the QuickSIN 5-dB SNR sentences (lists 1 to 4).

| Frequency (kHz) | Prevalence of consonants (represented in letter) | Total (%) |
|---|---|---|
| 0.25 | j = 1, z = 4, m = 4, n = 5 | 14 (21.21) |
| 0.5 | v = 2, d = 6, b = 3, l = 4 | 15 (22.73) |
| 0.75 | r = 9 | 9 (13.64) |
| 1 | p = 4 | 4 (6.06) |
| 2 | g = 1, ch = 2 | 3 (4.55) |
| 3 | k = 8 | 8 (12.12) |
| 3.5 | t = 6 | 6 (9.09) |
| > 4 | f = 1, s = 5, th = 1 | 7 (10.61) |

**Table 2.2** Participants' demographics. Numbers are mean (SD), and range.

| **Demographics** | **Groups with Normal Hearing** | | **Groups with Hearing Loss** | | **H** |
|---|---|---|---|---|---|
| | ***TIN_NH*** | ***CON_NH*** | ***TIN_HL*** | ***CON_HL*** | |
| **Number** | 17 | 17 | 17 | 15 | – |
| **Gender** | 5 females | 11 females | 9 females | 5 females | – |
| **Age (years)** | 42.82 (13.77), 22-62 | 47.12 (10.72), 21-61 | 57.12 (6.01), 45-64 | 55.73 (7.93), 38-64 | 18.033*** |
| **HFPTA (dB HL)** [a] | 12.4 (4.2), 5.83-20 | 11.18 (3.47), 5-18.33 | 24.36 (9.07), 10.83-42.5 | 20.22 (7.16), 11.67-33.33 | 31.595*** |
| **WRS (%)** [a] | 99.88 (0.49), 98-100 | 99.88 (0.49), 98-100 | 99.65 (0.79), 98-100 | 99.07 (3.1), 88-100 | 1.788 |
| **SNR Loss** [a] | 1.85 (1.06), 0.5-4.25 | 1.72 (0.95), 0.25-3.5 | 3.59 (1.53), 0.75-5.5 | 2.85 (1.15), 0.5-5 | 18.694*** |

[a] Obtained bilaterally.

***$p < 0.001$

CON_HL, controls with hearing loss; CON_NH, controls with normal hearing; H, Kruskal-Wallis rank sum test; HFPTA, high-frequency pure-tone average of 1, 2, and 4 kHz; SNR Loss, signal-to-noise ratio loss measured in QuickSIN; TIN_HL, tinnitus with hearing loss; TIN_NH, tinnitus with normal hearing; WRS, word recognition score.

**Table 2.3** Tinnitus characteristics in the groups with tinnitus. Numbers are mean (SD), range unless otherwise stated.

| **Characteristics** | **TIN_NH** | **TIN_HL** | **U** |
|---|---|---|---|
| **Duration (years)** | 7.58 (14.01), 0.5-35 | 13.72 (14.96), 0.67-55 | 177 |
| **Tinnitus pitch (Hz)** | 3808.82 (2192.11), 750-8000 | 3455.88 (2195.35), 250-8000 | 128 |
| **Tinnitus severity** | | | |
| *TFI* | 25.74 (15.92), 3.6-60.4 | 33.98 (22.75), 7.6-77.6 | 173 |
| **Laterality** | ***n (%)*** | ***n (%)*** | |
| *Bilateral* | 12 (70.59) | 14 (82.35) | – |
| *Unilateral* | 2 (11.76) | 2 (11.76) | – |
| *Head* | 3 (17.64) | 1 (5.88) | – |
| **Tinnitus sounds** | | | |
| *Ringing or whistling* | 12 (70.59) | 11 (64.71) | – |
| *Roaring or rushing* | 1 (5.88) | 3 (17.64) | – |
| *Humming* | 2 (11.76) | – | – |
| *Buzzing* | 1 (5.88) | – | – |
| *Hissing* | 1 (5.88) | 1 (5.88) | – |
| *Cricket-like* | – | 2 (11.76) | – |

TFI, Tinnitus Functional Index; TIN_NH, tinnitus with normal hearing; TIN_HL, tinnitus with hearing loss; U: Mann-Whitney U test.

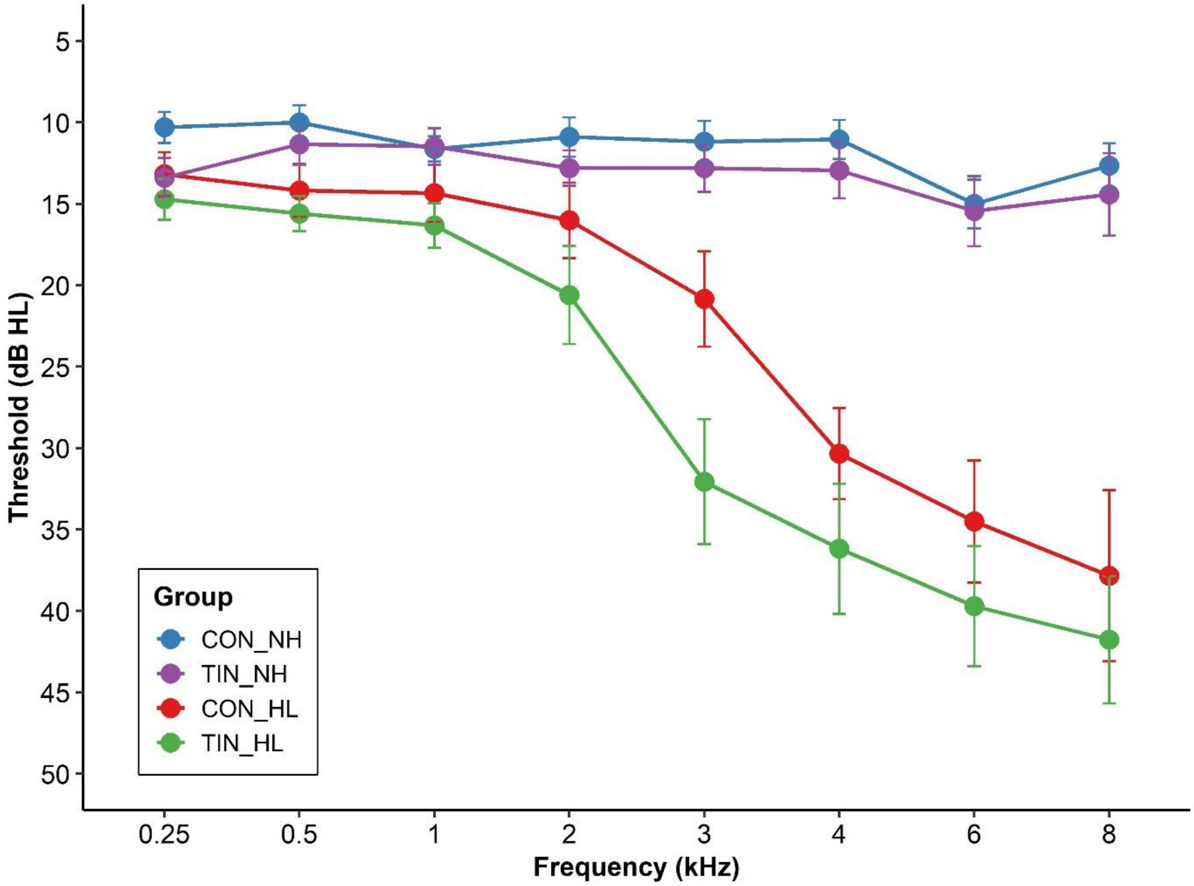


**Figure 2.1** Mean hearing thresholds from 0.25 to 8 kHz in both ears. Error bars indicate one standard error of the mean. The two groups with hearing loss had significantly higher thresholds from 4 to 8 kHz compared with those with normal hearing. CON_HL, controls with hearing loss; CON_NH, controls with normal hearing; TIN_HL, tinnitus with hearing loss; TIN_NH, tinnitus with normal hearing.

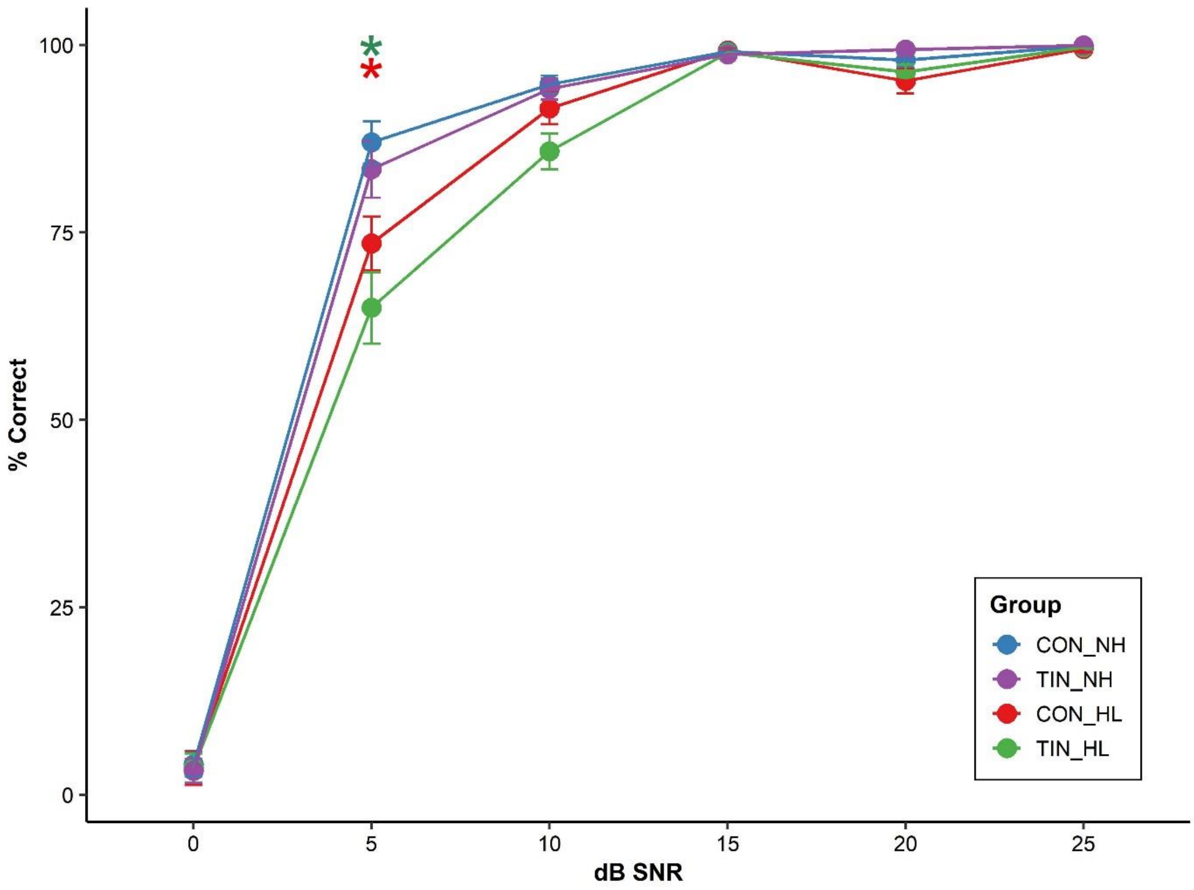


**Figure 2.2** Mean consonant recognition scores in percent correct at various SNR conditions. Error bars indicate one standard error of the mean. The two groups with hearing loss had significantly poorer consonant recognition scores at 5-dB SNR condition (marked with asterisks) compared with those with normal hearing. CON_HL, controls with hearing loss; CON_NH, controls with normal hearing; TIN_HL, tinnitus with hearing loss; TIN_NH, tinnitus with normal hearing.

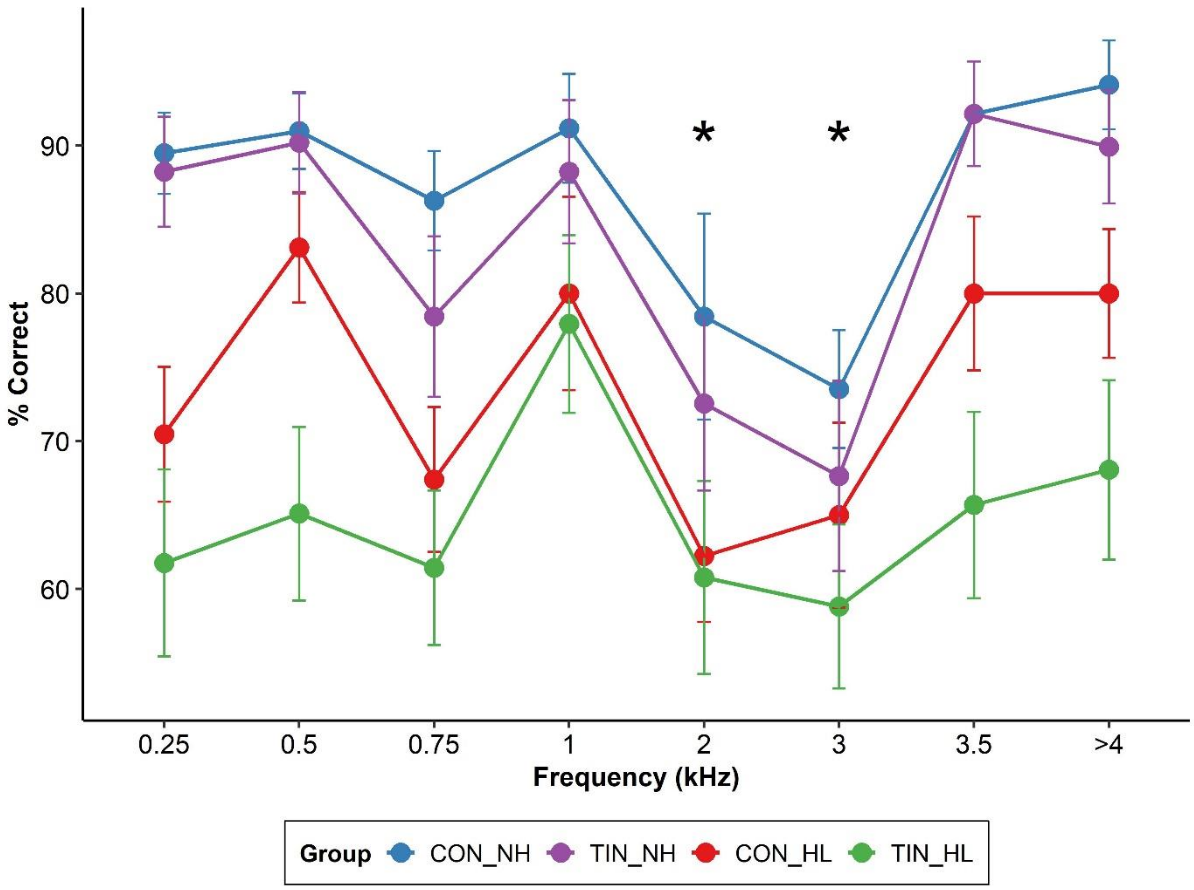
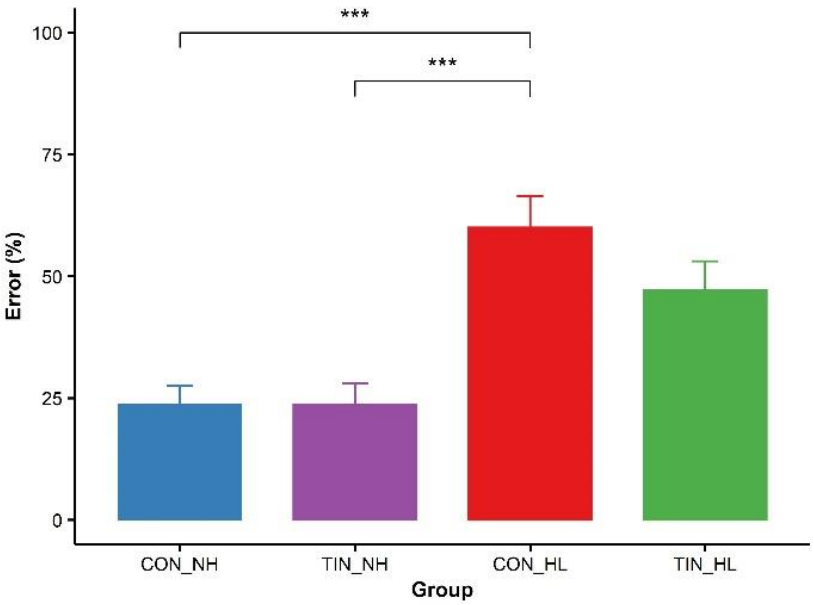
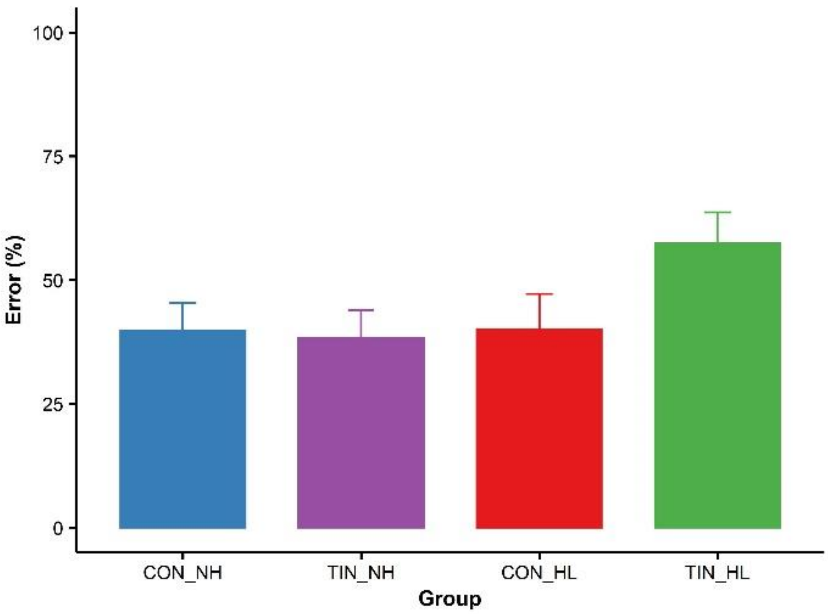


**Figure 2.3** Mean consonant recognition scores at various frequency ranges in the 5-dB SNR condition. Error bars indicate one standard error of the mean. In all groups, consonant scores were significantly poorer at 2 and 3 kHz (marked with asterisks) compared with other frequencies. CON_HL, controls with hearing loss; CON_NH, controls with normal hearing; TIN_HL, tinnitus with hearing loss; TIN_NH, tinnitus with normal hearing.



(A) Sentence-initial words



(B) Sentence-final words

**Figure 2.4** Mean percent error of sentence-initial words (A), sentence-final words (B), and full sentence (C) in each group. Error bars indicate one standard error of the mean. CON_HL had a significantly higher error rate of sentence-initial words compared to the two groups with normal hearing, whereas TIN_HL had a significantly higher error rate of the full sentence compared to the two groups with normal hearing. The asterisks represent significance after Bonferroni correction for multiple comparisons (**, $p < 0.01$; ***, $p < 0.001$). CON_HL, controls with hearing loss; CON_NH, controls with normal hearing; TIN_HL, tinnitus with hearing loss; TIN_NH, tinnitus with normal hearing.

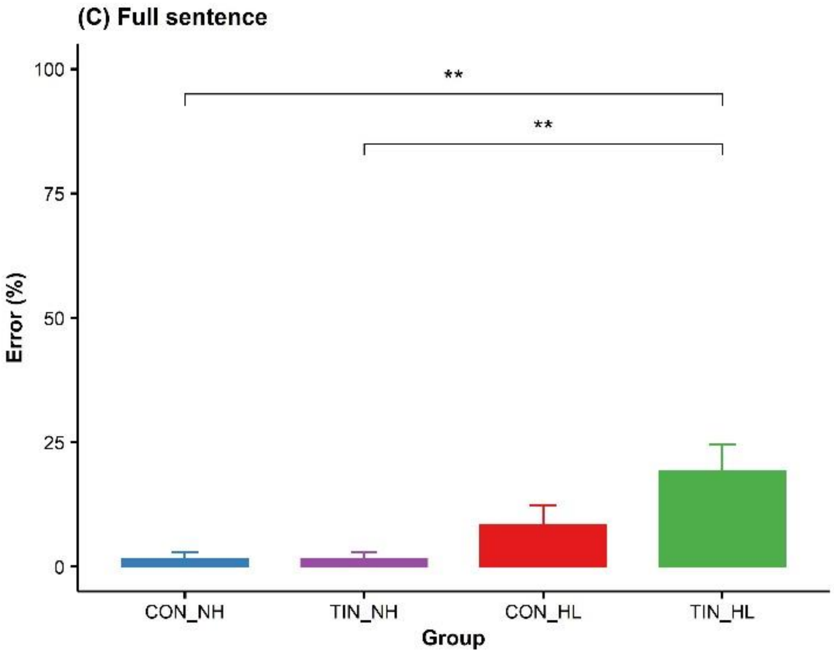


**Figure 2.4 (cont.)** Mean percent error of sentence-initial words (A), sentence-final words (B), and full sentence (C) in each group. Error bars indicate one standard error of the mean. CON_HL had a significantly higher error rate of sentence-initial words compared to the two groups with normal hearing, whereas TIN_HL had a significantly higher error rate of the full sentence compared to the two groups with normal hearing. The asterisks represent significance after Bonferroni correction for multiple comparisons (**, $p < 0.01$; ***, $p < 0.001$). CON_HL, controls with hearing loss; CON_NH, controls with normal hearing; TIN_HL, tinnitus with hearing loss; TIN_NH, tinnitus with normal hearing.

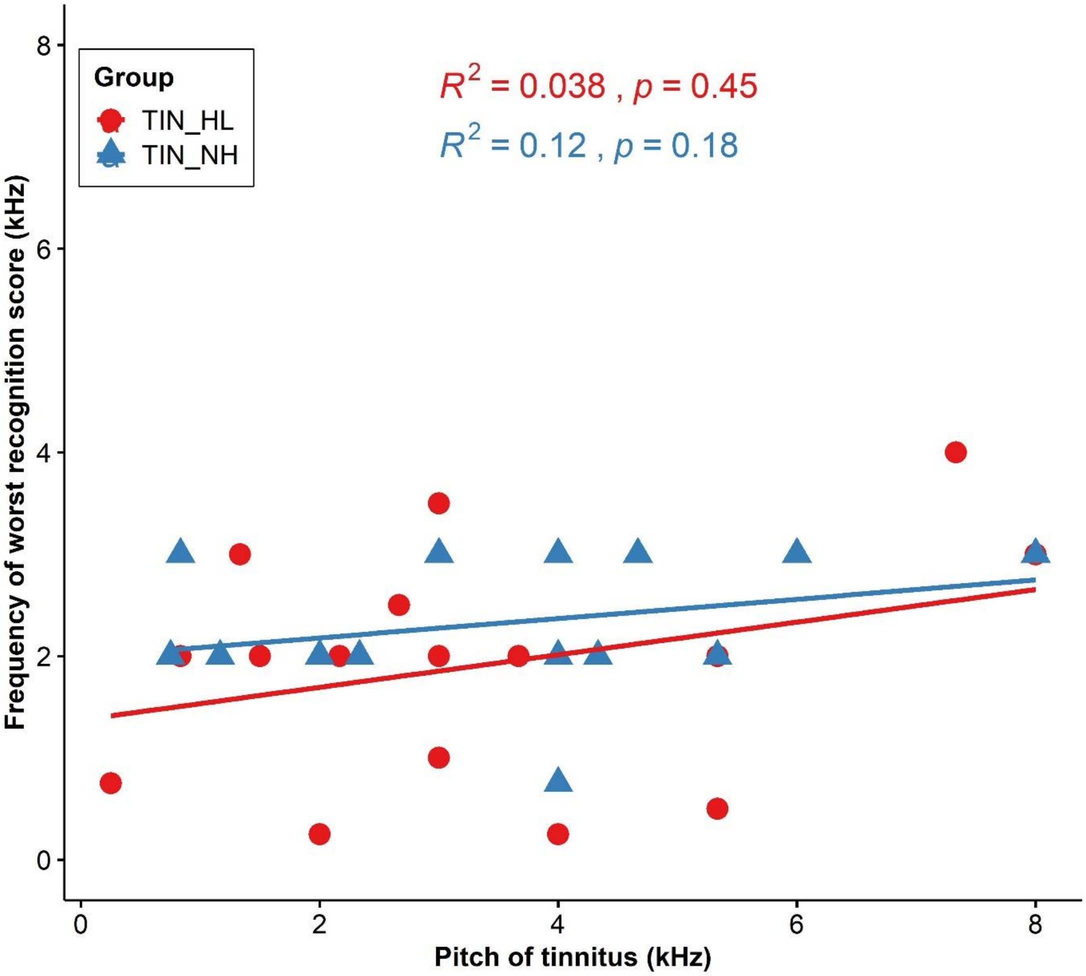


**Figure 2.5** Scatter plot that shows pitch of tinnitus and frequency of the worst consonant recognition at 5-dB SNR of individuals with tinnitus, separated by hearing sensitivity. The regression lines indicated that only 12% and 3.8% of variance in frequency of the worst consonant recognition can be explained by tinnitus pitch in the group with normal hearing and the group with hearing loss, respectively. Data of one participant in TIN_NH was removed due to perfect score of consonant recognition of all frequencies. TIN_HL, tinnitus with hearing loss; TIN_NH, tinnitus with normal hearing.

# CHAPTER 3: STUDY 2

## Study 2: Gray matter volume changes and speech-in-noise performance in tinnitus patients with normal hearing sensitivity

### 3.1 Abstract

**Purpose:** Speech-in-noise (SiN) difficulties are often reported in patients with tinnitus regardless of their hearing sensitivity. Although brain structural changes such as reduced gray matter (GM) volume in auditory and cognitive processing regions have been reported in adults with tinnitus relative to controls, such changes as of yet have not been linked to their SiN performance. The current study aimed to examine if SiN recognition is related to the GM volume in the auditory and cognitive processing regions in individuals with tinnitus.

**Method:** Pure-tone audiometry and Quick Speech-in-Noise test were conducted on individuals with tinnitus and normal hearing (less than or equal to 25 dB HL from 0.25 to 8 kHz) and hearing-matched controls. T1-weighted structural MRI images were obtained from all participants. After preprocessing, GM volumes were compared between tinnitus and control groups using whole-brain and region-of-interest analyses. Further, regression analyses were performed to examine the correlation between regional GM volume and SiN scores in each group.

**Results:** With similar SiN performance, the results showed decreased GM volume in the bilateral inferior frontal gyri in the tinnitus group relative to the control group. In the tinnitus group, SiN performance showed a negative correlation with GM volume in the left cerebellum (Crus I/II) and the left superior temporal gyrus; no significant correlation between SiN performance and regional GM volume was found in the control group.

**Conclusions:** Even with clinically defined normal hearing and comparable SiN performance, the presence of tinnitus appears to change the relationship between SiN recognition and regional GM volume, relative to healthy controls. This change may reflect compensatory mechanisms utilized by individuals with tinnitus who maintain behavioral performance.

### 3.2 Introduction

Self-reported speech comprehension difficulties are common in the tinnitus population (Tyler & Baker, 1983; Vielsmeier et al., 2016). Compared with hearing-matched controls, individuals with tinnitus and normal hearing have been shown to have poorer speech-in-noise (SiN) performance (see Ivansic et al., 2017 for a review). Nonetheless, instead of showing a general SiN deficit, our recent study (Tai & Husain, 2018) suggested that individuals with tinnitus and normal hearing sensitivity only had poorer SiN performance compared with hearing-matched controls at the 5-dB signal-to-noise ratio (SNR) condition of the Quick Speech-in-Noise test (QuickSIN: Killion et al., 2004). Moreover, a significant between-ear difference in SiN performance was found in the tinnitus group despite symmetrical hearing, possibly resulting from neuroanatomical differences between the two cerebral hemispheres or some as yet unknown factors (Tai & Husain, 2018). In the present study, we investigated the first of these hypotheses, specifically structural differences in gray matter between individuals with and without tinnitus, and examined the relationship between SiN performance and neuroanatomical measures in brain regions that are crucial for cognitive control.

The development of brain imaging techniques has made it possible to examine structural and functional changes related to tinnitus. Among brain imaging tools, voxel-based morphometry (VBM) has been extensively used to analyze structural magnetic resonance images to understand the difference in gray matter (GM) volume in various populations (Ashburner &

Friston, 2000, 2001). Through VBM, the anatomical magnetic resonance imaging (MRI) data are segmented into tissue types such as GM, white matter, and cerebrospinal fluid. Further, VBM permits the examination of regional GM volume for between-group comparisons (Ashburner & Friston, 2000), as well as the investigation of the association between brain structural measures and varying behavioral or neuropsychological assessments outside the MRI scanner on the same cohort of participants (Kanai & Rees, 2011).

Several tinnitus studies have reported structural changes in various brain regions. One of the first such studies found decreased GM volume in the subcallosal region and increased GM concentration in the posterior auditory thalamus in individuals with tinnitus and normal hearing sensitivity relative to controls (Mühlau et al., 2006). Their findings affirmed that neuroanatomical changes in patients with tinnitus can involve both auditory and emotion-related regions, which has been supported by many fMRI studies in tinnitus (see Husain, 2016 for a review). Additionally, brain structural changes in regions related to cognitive control such as the ventromedial prefrontal cortex (vmPFC) and the anterior cingulate cortex (ACC) have been reported in other fMRI studies in tinnitus (Leaver et al., 2011, 2012; Schmidt et al., 2018; Vanneste et al., 2015). As SiN recognition relies on cognitive control ability, or the ability to retrieve task-relevant information and ignore task-irrelevant information (Janse, 2012; Peelle, 2018), morphological changes in cognitive processing regions not only can be critical in interpreting the generation and persistence of tinnitus but also might elucidate SiN deficits reported in the tinnitus population (Ivansic et al., 2017).

### 3.2.1 VBM Studies in Tinnitus

Previous VBM studies yield mixed findings even with proper control of individuals' hearing profiles (Table 3.1). Landgrebe et al. (2009) found structural changes in both auditory and limbic systems in individuals with tinnitus; however, different brain regions were reported. Additionally, two other studies that included individuals with tinnitus and normal hearing sensitivity did not find definitive differences in GM volume or concentration between their tinnitus and control groups (Allan et al., 2016; Melcher et al., 2013). Instead, Melcher et al. (2013) found that GM volume negatively correlated with the mean hearing thresholds at extended high frequencies (above 8 kHz) in several midline regions, including the ventral posterior cingulate cortex, dorsomedial prefrontal cortex, and vmPFC. The negative findings of Melcher et al. (2013) led the authors to postulate that rather than tinnitus, hearing thresholds above 8 kHz may better explain the myriad observations in previous VBM studies (Husain, Medina, et al., 2011; Landgrebe et al., 2009; Mühlau et al., 2006).

Studies in individuals with both tinnitus and hearing loss suggest that changes in GM volume in those individuals might be attributed to their hearing impairment, rather than tinnitus (Allan et al., 2016; Boyen et al., 2013; Husain, Medina, et al., 2011; Vanneste et al., 2015). The effect of hearing loss on GM changes have been confirmed by varying tinnitus studies: for example, decreased GM volume in the left inferior colliculus and the bilateral medial geniculate nuclei (Allan et al., 2016) or the occipital lobe and hypothalamus (Boyen et al., 2013) have been reported in groups with hearing loss disregarding the presence of tinnitus. Similarly, a study in a large cohort of 154 patients with tinnitus confirmed that an increase in hearing loss was associated with a decrease in GM concentration in the cerebellum, ventral lateral prefrontal cortex, somatosensory cortex, auditory cortex, posterior cingulate cortex, and superior parietal cortex (Vanneste et al., 2015). Overall, previous findings suggest that the impact of hearing impairment may dominate over that of tinnitus when it comes to neuroanatomical changes.

Therefore, controlling the effect of hearing impairment on regional GM volume can be critical for VBM studies in tinnitus.

### 3.2.2 Relationship Between Structural Changes in Cognitive Processing Regions and SiN Recognition

Brain regions related to cognitive control have been shown to play an important role in speech perception in suboptimal listening conditions in fMRI studies. In conjunction with the activation of auditory processing regions (e.g., superior temporal gyrus, or STG), regions related to cognitive control such as the ACC, superior frontal gyrus (SFG), middle frontal gyrus (MFG), and inferior frontal gyrus (IFG) are found to be significantly more responsive to speech in noise than in quiet in young adults with normal hearing sensitivity (Obleser et al., 2007; Zekveld et al., 2012), in older adults with relatively intact hearing (Eckert et al., 2008; Wong et al., 2009) or with hearing impairment (Harris et al., 2009), and in listeners with reduced working memory capacity (Zekveld et al., 2012).

In contrast, findings of structural MRI studies are disjointed: on the one hand, findings suggest that only the GM volume in the auditory processing regions can predict word recognition scores in demanding listening conditions (Harris et al., 2009). On the other hand, cortical thickness of several cognitive processing regions (e.g., SFG and IFG) has been confirmed to be positively correlated with speech stimuli processing (Deschamps et al., 2016). Moreover, using surface-based morphometry for deriving GM volume, Wong et al. (2010) found that in older adults with high-frequency hearing loss, the larger or the thicker the left IFG, the better was the ability to perceive speech in the most challenging condition (0-dB SNR condition) of the QuickSIN test. Similarly, in a large-scale study in a nonclinical, middle-aged cohort (n = 8701, mean age = 62.3 years, SD = 7.4 years), larger GM volume in bilateral STG and right MFG was associated with better speech reception threshold in noise (Rudner et al., 2019). Such a finding delineates possible changes in the relationship between GM volume in cognitive processing regions and SiN performance to accommodate inter-individual differences (e.g., hearing loss vs. no hearing loss). Albeit with some discrepancies, the results from functional and structural MRI underpin the importance of considering both auditory and cognitive processing regions for SiN recognition.

### 3.2.3 Aims and Hypotheses

In summary, some of the previous VBM studies in the tinnitus population suggest decreased GM volume in the subcallosal area, limbic cortex, auditory cortex, and regions in the auditory pathway relative to controls (Allan et al., 2016; Landgrebe et al., 2009; Mühlau et al., 2006; Schneider et al., 2009). Additionally, putative brain regions that are critical for cognitive control and SiN recognition (e.g., vmPFC and ACC) have been noted in the functional brain imaging literature in tinnitus (Leaver et al., 2011, 2012; Schmidt et al., 2018; Vanneste et al., 2015), although no direct relationships have been tested prior. As yet, the association between SiN difficulties and cognitive deficits in the tinnitus population has been postulated (Ivansic et al., 2017; Tai & Husain, 2019), but only been supported by indirect behavioral evidence in either SiN or cognitive control studies. Therefore, a better understanding of how structural changes of the brain are related to SiN recognition is needed.

To reduce the effect of hearing impairment on changes in GM volume in the current study, we examined the relationship between SiN performance and GM volume in individuals with tinnitus and normal hearing sensitivity. Specifically, we aimed to investigate if GM volume in the auditory and cognitive processing regions are related to SiN performance at the 5-dB SNR condition of the QuickSIN test, which is the only condition that showed a between-group difference in Tai and Husain (2018). We hypothesized that similar to studies on aging and hearing impairment (Wong et al., 2010), a positive correlation between GM volume in cognitive processing regions and SiN performance will be found in the tinnitus group.

## 3.3 Methods

### 3.3.1 Participants

Individuals between 21 and 64 years old were recruited from the surrounding Urbana-Champaign area. Written informed consent, under the University of Illinois at Urbana-Champaign Institutional Review Board protocol 15955, was obtained from all participants before the initiation of the study. Participants were excluded if they reported a history of pulsatile tinnitus, neurological health issues such as epilepsy, traumatic brain injury, Meniere's disease, post-traumatic stress disorder, and psychological disorders except for currently managed anxiety or depression. Because handedness is not an exclusion criterion, participants only reported their handedness as right, left, or both in the in-house health history form developed for the study. For the safety of MRI scans, individuals who reported any metal implants or pieces in the body were excluded.

The study consists of two main components: behavioral assessment (audiological testing and QuickSIN) and MRI scan. All participants went through the screening process of behavioral assessment before being included for the MRI scan, which was done within one month of the behavioral assessment. Participants were grouped into the tinnitus (TIN) or control group (CTR) depending on the presence of chronic tinnitus (more than six months). Only the data of those who had normal hearing sensitivity (less than or equal to 25 dB HL from 0.25 to 8 kHz in both ears) and who reported American English as their native language were included in the analyses.

### 3.3.2 Behavioral Assessment

To control for the validity and reliability of the data, behavioral assessment, except for the tinnitus questionnaire, were conducted in a single-chamber IAC or Acoustic Systems sound-attenuating booth, with both satisfied the ANSI S3.1-1999 [R2003] standard (ANSI, 2003).

#### *Audiological Testing*

All participants underwent otoscopic inspection, tympanometry, and acoustic reflexes to rule out outer ear, middle ear, or retrocochler pathologies. Pure-tone audiometry was conducted from 0.25 to 16 kHz in each ear. Similar to Melcher et al. (2013), extended high-frequency pure-tone average (EHFPTA) was obtained by taking the average thresholds from 9 to 14 kHz in both ears. Word recognition score (WRS) of the NU-6 lists was obtained in each ear for the speech-in-quiet test. All participants in the current study had a WRS greater than 80% in both ears. Additionally, loudness discomfort level (LDL) was obtained for each ear using pure tones (0.5 and 4 kHz) and spondee words; participants were excluded for the MRI scan if they showed hypersensitivity to loud sounds with an LDL lower than 75 dB HL at any stimuli.

Audiological assessments were conducted using an Interacoustics Equinox 2.0 clinical audiometer with the ER-3A insert earphones for frequencies from 0.25 Hz to 8 kHz, and the Sennheiser HDA 200 headphones for frequencies from 9 to 16 kHz. Tympanometry and acoustic reflexes were conducted using the Interacoustics Titan Ver. 4.0 tympanometer. The audiometer, tympanometer, and the transducers were calibrated annually according to the ANSI S3.6-2010 standard (ANSI, 2010).

#### *Quick Speech-in-Noise test (QuickSIN)*

The QuickSIN test (Killion et al., 2004) was conducted via the built-in sound files of the audiometer. Each QuickSIN list consists of six sentences spoken by a female talker with five target words per sentence. After each presentation of the sentence, the SNR decreases in 5-dB steps from 25 dB SNR to 0 dB SNR. The presentation level was at a loud but comfortable level of 70 dB HL for all participants, as suggested in the QuickSIN user manual. Lists 1 to 4 were used with two lists presented monaurally to each ear. Participants were instructed to repeat the sentences spoken by the target female talker and ignore the four-talker background noise; they were also told to guess if they were not sure about what they heard. Different from the standard administration of the QuickSIN that incorporating the number of target words repeated correctly in sentences across six SNR conditions, the main outcome measure of SiN performance was calculated as percent correct, derived from the number of correctly repeated target words divided by the total five target words at the 5-dB SNR condition. An average score of the four lists at the 5-dB SNR condition was used as the bilateral SiN score for each participant.

### ***Tinnitus-Related Questionnaire***

As an estimation of tinnitus severity, the Tinnitus Functional Index (TFI: Meikle et al., 2012) was completed during the MRI session by individuals with tinnitus. The TFI is a validated 25-item tinnitus questionnaire that contains problems in eight tinnitus-related domains: cognitive, auditory, intrusive, sleep, relaxation, quality of life, emotional, and sense of control. Each question of the TFI is evaluated by a 0-10 or 10-100% Likert-type response scale, with a total of 100 being the maximum possible score. Five levels of severity based on the total TFI score are 1) not a problem, ranging from 0 to 17, 2) small problem, ranging from 18 to 31, 3) moderate problem, ranging from 32 to 53, 4) big problem, ranging from 54 to 72, and 5) very big problem, ranging from 73 to 100 (Henry et al., 2016).

#### *Statistical Analyses*

Between-group comparisons in demographic, audiological, and speech measures were conducted using the Mann-Whitney U test for nonparametric data, except for examining gender distribution ($\chi^2$ test was used instead). A linear mixed effect model that does not require the data to be normally distributed was used to examine the between-group difference in extended high-frequency thresholds. Spearman's correlations between bilateral SiN score and other variables, including age and EHFPTA, were obtained in each group and in all participants. Additionally, Spearman's correlation was conducted between bilateral SiN score and TFI score or tinnitus duration in the tinnitus group. All statistical analyses for behavioral measures were performed using the R statistical software (version 3.5.1) at a significance level of 0.05.

### 3.3.3 Imaging Data Acquisition and Analyses

#### *Imaging Acquisition*

Brain imaging data were collected on a 3T Siemens MAGNETOM Prisma scanner. The following parameters were used to acquire the high-resolution, T1-weighted sagittal MPRAGE image: TR = 2300 ms, TE = 2.32 ms, flip angle = 8°, 192 slices, voxel size = 0.9 x 0.9 x 0.9 $mm^3$.

#### *Image Preprocessing*

The T1-weighted structural magnetic resonance images were preprocessed using the Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat/index.html) with the Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK). The images were first segmented into GM, white matter, and cerebrospinal fluid using tissue probability map, affine and non-linear registrations, and bias correction for non-uniform intensities. The GM images were then spatially normalized into a standard Montreal Neurological Institute (MNI) space using DARTEL registration, with a 1.5 mm isotropic resolution. The Jacobian determinant of deformation fields was used to scale intensities disrupted by registration, resulting in modulated warped GM. The images were inspected for potential outliers using the Mahalanobis distance between mean correlations and weighted overall image quality. Subsequently, all images were smoothed where each voxel was convolved with an 8-mm full-width-half-maximum Gaussian kernel.

The preprocessed GM volumes were then used for two main statistical analyses. First, the regional GM volume between tinnitus and control groups was compared using a two-sample t-test with correction for total intracranial volume (TIV), age, and gender. Secondly, the relationship between regional GM volume and bilateral SiN score in each group was examined using linear regression models, with GM volumes as the response variable and bilateral SiN score as the predictor, while removing the effects of TIV, age, and gender. Both statistical methods were used for whole-brain or ROI analysis. The significance level was set to $p < 0.001$ for the uncorrected threshold, and $p < 0.05$ for family-wise error (FWE) correction for multiple comparisons at either cluster or voxel level. An extent threshold of a minimum cluster size of 50 voxels was used.

### *Region-of-Interest (ROI) Analysis*

To reduce Type I error caused by the number of statistical tests in the whole-brain analysis, ROI analyses with fewer voxels were conducted. The ROIs included previously defined bilateral auditory processing regions (Mühlau et al., 2006) that have been used in VBM studies in the tinnitus population: ventral and dorsal cochlear nuclei, superior olivary complex, inferior colliculus, and medial geniculate nucleus. Additionally, the following auditory and cognitive processing regions that are important for SiN (based on Wong et al., 2010) were defined bilaterally using the Wake Forest University PickAtlas toolbox (version 3.0.5: Maldjian et al., 2003, 2004): STG, primary auditory cortex, pars opercularis of the IFG, pars triangularis of the IFG, rostral MFG, caudal MFG, SFG, and dorsal anterior cingulate gyrus. All 24 ROIs were 8-mm spheres centered at the MNI coordinates noted in Table 3.2.

## 3.4 Results

Behavioral and structural brain data of 14 individuals in the tinnitus group (TIN) and 14 individuals in the control group (CTR) were included. All participants had normal hearing up to 8 kHz in both ears. The demographic information and behavioral data are shown in Table 3.3.

### 3.4.1 Behavioral Data

The results of the Mann-Whitney U tests and the $\chi^2$ test indicated no significant difference in age, gender, bilateral WRS, EHFPTA, and SiN score between TIN and CTR (Table 3.3). The individual and mean hearing thresholds in each group are shown in Figure 3.1. Because normal hearing thresholds at extended high-frequency were not required for the study, a linear mixed effect model with Group and Frequency (six frequencies from 9 to 16 kHz) as the fixed effect, and each individual as the random effect was used to examine the between-group difference in extended high-frequency thresholds. The results showed a significant main effect of Frequency ($F(5, 130) = 72.91$, $p < 0.001$), but no significant main effect of Group ($F(1, 26) = 0.96$, $p = 0.34$) or interaction effect of Group x Frequency ($F(5, 130) = 0.44$, $p = 0.82$). The findings suggest that thresholds at any frequency from 9 to 16 kHz were not significantly different between groups.

Table 3.4 shows tinnitus characteristics in individuals with tinnitus. Only one participant reported having recent-onset tinnitus (longer than six months but less than 1 year) as defined by Schmidt et al. (2018), the remainder of the participants reported long-term tinnitus (more than one year). Overall, participants with tinnitus reported a low TFI score, leading to a mean TFI of

18.97 categorized as a small problem at the group level. Most participants reported having bilateral tinnitus with a ringing or whistling sound. Spearman's correlations (Table 3.5) showed that bilateral SiN score was significantly correlated with EHFPTA in TIN ($r_s = -0.56$, $p = 0.036$) or with EHFPTA in the combined group ($r_s = -0.44$, $p = 0.02$), but not in CTR ($r_s = -0.19$, $p = 0.5$). Bilateral SiN score was not significantly correlated with age in either group or in the combined group. It was also not significantly correlated with the TFI score ($r_s = -0.2$, $p = 0.49$) or tinnitus duration ($r_s = -0.26$, $p = 0.4$) in TIN.

### 3.4.2 VBM Data

#### *Between-Group Difference in GM Volume*

Using whole-brain analysis, significantly greater GM volume in CTR than in TIN was found in two clusters (Table 3.6 and Figure 3.2), with one cluster located at the right IFG and the other spanning both left insula and left IFG (using a less stringent corrected threshold as $p \leq 0.056$). No significant between-group difference in GM volume was found for the contrast of TIN greater than CTR. Likewise, no significant results were noted for the ROI analysis for either comparison.

#### *Relationship between GM Volume and SiN Performance*

At the corrected threshold at cluster level, whole-brain multiple regression analysis indicated that bilateral SiN score was negatively associated with GM volume in the left cerebellum in the tinnitus group, specifically at Crus I/II (Table 3.6, Figure 3.3A). Moreover, multiple regression analyses using ROIs showed a significant negative correlation between bilateral SiN score and GM volume in the left STG in the tinnitus group at the voxel level (Table 3.6 and Figure 3.3B). Note that in the tinnitus group, a negative correlation between bilateral SiN score and GM volume in the left STG (-50, 3, -4 mm) was also found using whole-brain multiple regression analyses, but the correlation was not significant at the corrected threshold (FWE corrected $p = 0.138$ at cluster level and $p = 0.225$ at voxel level). In the control group, no significant correlation at the corrected threshold was found between SiN score and GM volume in any brain region using either whole-brain or ROIs for regression analyses.

## 3.5 Discussion

In this study, we examined neuroanatomical differences in GM volume between individuals with tinnitus and age- and hearing-matched controls; both groups had clinically defined normal hearing thresholds. To investigate the relationship between GM volume and SiN performance, regression analyses were conducted in each group while controlling for age, gender, and total brain volume. Although no significant between-group difference was found in SiN performance, individuals in the tinnitus group showed decreased GM volume in bilateral IFG relative to controls. Further, some behavioral and neuroanatomical measures were significantly correlated with SiN performance in the tinnitus group alone; these measures include: 1) EHFPTA, 2) GM volume in the left cerebellum (Crus I/II), and 3) GM volume in the left STG. Overall, the results suggested that better SiN performance in the tinnitus group was related to better EHFPTA and smaller GM volume in the left cerebellum and the left STG.

### 3.5.1 GM Volume Difference between Groups

#### *Comparison with Previous VBM Studies in Tinnitus and Normal Hearing*

Several subsequent studies after the pioneering work of Muhlau et al. (2006) have intended to replicate the neuroanatomical changes in individuals with tinnitus and normal hearing sensitivity (Allan et al., 2016; Landgrebe et al., 2009; Melcher et al., 2013). Although these studies underpin the assumption that brain structural reorganization can occur after changes in sensory input such as in tinnitus (Merabet & Pascual-Leone, 2010), findings have diverged.

Lately, additional analytical techniques have been used to better identify neuroanatomical biomarkers of tinnitus; for example, machine learning techniques applied by Liu et al. (2019). In their study, 61 brain regions that were reported in existing studies to be associated with tinnitus but not with hearing loss were set as the ROIs. They found 13 brain regions as potential neuroanatomical biomarkers of tinnitus, which include bilateral hypothalami, right insula, bilateral STG, left rostral MFG, bilateral inferior temporal gyri, right inferior parietal lobule, right transverse temporal gyrus, right middle temporal gyrus (MTG), right cingulate gyrus, and left SFG (Liu et al., 2019). A recent study using meta-analyses on eight previous VBM studies also suggested structural changes in STG, MTG, SFG, and right inferior parietal in individuals with tinnitus, although the effect of hearing impairment was not precluded (Cheng et al., 2020). In the present study, a significant between-group difference in GM volume was only found in bilateral IFG, which did not echo any of the previous VBM findings. The disparate observations may be accounted for by the use of varying brain imaging methodologies and high heterogeneity in tinnitus (Adjamian et al., 2014; Scott-Wittenborn et al., 2017).

### *The Implication of Decreased GM Volume in Bilateral IFG in tinnitus*

At the corrected threshold, individuals with tinnitus and normal hearing had reduced GM volume in bilateral IFG compared with hearing-matched controls. The IFG, along with STG and MTG, is part of the core speech network whose activation is required for acoustic, semantic, and syntactic analyses for intelligible sentences (Harris et al., 2009; Peelle, 2018; Peelle & Wingfield, 2016). Increased activation of bilateral IFG has been observed while processing high-ambiguity sentences (Rodd et al., 2005), with the left IFG playing a critical role for ambiguity resolution of semantic and syntactic information (Davis et al., 2011; Rodd et al., 2010) and SiN recognition (Evans et al., 2016; Golestani et al., 2013; Obleser et al., 2007; Wild et al., 2012). Although it may be fairly straight forward to understand SiN using functional brain imaging, linking it to neuroanatomy is challenging. This is because there is a many-to-many mapping between structure and function and a specific brain region can participate in several functional networks. Activity in several interconnected functional networks in turn leads to observed behavior such as button pressing or SiN. Thus, observed anatomical differences between groups may be due to increases or decreases in gray matter and have to be cautiously interpreted when there are no differences in behavior.

Published neuroanatomical findings suggest that cortical GM thickness or volume in IFG is positively correlated with SiN recognition (Wong et al., 2010), executive control of attention (Kanai & Rees, 2011), cognitive flexibility and psychomotor speed (Newman et al., 2007), statistical structure processing of auditory sequence (Deschamps et al., 2016), and crystallized or spatial intelligence (Colom et al., 2013). Given the importance of IFG in cognitive processing and SiN, significantly lower GM volume in bilateral IFG in the tinnitus group relative to the control group might imply an increased SiN difficulty in tinnitus. However, the non-significant between-group difference in SiN performance does not support the assumption.

One possible explanation of the observed between-group GM volume differences lies in the need to constantly ignore the tinnitus sound during daily tasks, which increases cognitive load and likely results in continuous recruitment of bilateral IFG; thus, it is more difficult for individuals with tinnitus than those without to preserve GM in these regions. In other words, relative to individuals with tinnitus, those without tinnitus use cognitive resources in daily tasks more efficiently, which may result in increased or better-preserved GM volume in bilateral IFG. Although such a functional-structural relationship cannot be confirmed without using both functional and structural brain imaging techniques in the same cohort, long-term changes in functional recruitment have been found to associate with long-term structural changes in the brain (Merabet & Pascual-Leone, 2010; Peelle & Wingfield, 2016). In a series of longitudinal studies, Draganski et al. (2004, 2006) demonstrated learning-induced structural changes in the GM. In their studies, GM expansion in visual areas was found in the group with a three-month training of three-ball cascade juggling, but not in the non-juggling group (Draganski et al., 2004). Likewise, significantly increased GM in the hippocampus was found in medical students after three months of study for a medical exam; this stimulus-induced effect extended beyond the learning period, manifesting by a continuous GM increase in the hippocampus after another three months (Draganski et al., 2006). These studies corroborate that neural plasticity allows functional and structural reorganization following short-term or prolonged sensory/cognitive changes throughout the lifespan (Cardin et al., 2013; Draganski et al., 2004, 2006; Lövdén et al., 2013). Thus, with a tinnitus duration ranging from 10 months to 45 years in our tinnitus group (Table 3.3), structural reorganization in bilateral IFG caused by the constantly heard tinnitus sound may be conceivable.

### 3.5.2 Relationship between Regional GM Volume and SiN performance

For the whole-brain or ROI analysis, GM volume in the left STG did not significantly differ between groups at the corrected threshold; however, our findings suggest that reduced GM volume in left STG correlated with better SiN performance in the tinnitus group. Although it has been proposed that speech can be processed in bilateral STG (Hickok & Poeppel, 2000; Kennedy-Higgins et al., 2020), the left-lateralized view for speech perception has been largely supported by neuroimaging studies showing that the left STG plays an essential role in analyzing intelligible speech (Davis et al., 2011; Narain et al., 2003), in reacting to increased background noise during speech processing (Wong et al., 2008), and in extracting target speech from an attended auditory scene (Evans et al., 2016; Vander Ghinst et al., 2016). Therefore, a significant correlation between GM volume in the left STG and SiN performance is not surprising. One might speculate that such a correlation is questionable as the participants' handedness was not properly controlled for in the present study (Table 3.3); however, studies have confirmed that right-hemisphere dominance for speech rarely occurs even in individuals who are left-handed or ambidextrous (Khedr et al., 2002; Pujol et al., 1999).

A recent animal study suggested that the cerebellum can be an important but non-obligatory generator of tinnitus (Bauer et al., 2013). Notably, one intriguing finding of the present study is that in the tinnitus group, smaller GM volume in the left cerebellum (Crus I/II) correlated with better SiN performance. Although the historic view of cerebellar functions mainly involves sensorimotor control (Manto et al., 2012), increasing evidence has suggested that the cerebellum works like a computational system which facilitates adaptive changes in behavior through continuously monitoring sensory, motor, and cognitive tasks to ensure better signal processing in the prefrontal and temporal-parietal cortices (Bauer et al., 2013; Guediche et al., 2015; Mathiak et al., 2002; Petacchi et al., 2005; Stoodley & Schmahmann, 2009). Both the left Crus I and Crus II of the lateral cerebellum have been shown to be consistently activated during paradigms related to language, working memory, cognitive, emotional, and spatial processing (Durisko & Fiez, 2010; Stoodley & Schmahmann, 2009). Specifically, the left Crus I has a distinct role in auditory processing and speech perception (Guediche et al., 2015; Petacchi et al., 2005), and the removal of the left Crus I may result in impaired fundamental auditory processing such as deficits in pitch perception (Petacchi et al., 2005). Taken together, both left Crus I and Crus II of the cerebellum are associated with auditory and cognitive functions that are critical for SiN recognition. However, these regions may only join the core speech network when further computational support is required for speech processing (Mathiak et al., 2002).

The counterintuitive relationship between SiN performance and GM volume in either the left STG or the left cerebellum warrants further examination. Studies targeting older or wider age groups found that larger regional GM volume in the prefrontal cortex (PFC) corresponds to better performance in cognitive tasks (Elderkin-Thompson et al., 2008; Newman et al., 2007; Ren et al., 2018; Ruscheweyh et al., 2013; Vibha et al., 2018), which suggest that heterogeneity in age can reinforce the positive correlation between PFC volume and executive performance (Yuan & Raz, 2014). On the contrary, studies including young adults, especially college students, found that smaller regional GM volume in PFC predicts better performance in varying cognitive tasks (Breukelaar et al., 2017; Salat et al., 2002; Smolker et al., 2015; Takeuchi et al., 2012, 2013, 2017). This negative correlation in young adults is not surprising, as the maturation of the human brain involves neuronal pruning processes, which leads to a reduction in GM volume (Kanai & Rees, 2011). Notably, Genon et al. (2017) found that correlation patterns between GM volume in the premotor cortex and the performance of several neuropsychological tasks varied across small samples; depending on the selected sample, negative correlations were equally likely as positive ones. Therefore, the direction of correlation might be affected by the small sample size, participants' age, and possible other comorbid conditions, such as tinnitus in our study.

Through VBM analyses, only macroscopic alterations such as changes in GM volume are examined. Without understanding the involved microstructural changes (e.g., neuronal cell bodies, synapses, and dendrites) and the subsequent effects caused by these changes, it might be imprudent to conclude a negative correlation being an artifact (Draganski et al., 2004; Kanai & Rees, 2011; Lövdén et al., 2013; Yuan & Raz, 2014). The negative correlation may imply the conventional “more is better” view cannot be generalized in the tinnitus population. This can explain why an additive effect of greater GM volume loss was not observed in individuals with both tinnitus and hearing loss than in those with hearing loss only (Husain, Medina, et al., 2011). Through constantly having tinnitus as a distractor, individuals with tinnitus may have developed a more efficient way than those without while reacting to background noise, and this adaptation is reflected at the neuroanatomical level. Thus, to ensure a comparable SiN performance, lesser GM volume was used to process task-irrelevant stimuli in individuals with tinnitus. Nonetheless, a link between SiN performance and GM volume in auditory and cognitive processing regions lateralized to the left hemisphere may corroborate the right-ear (left-hemisphere) advantage in SiN performance previously reported in individuals with tinnitus (Tai & Husain, 2018).

### 3.5.3 The Association among Hearing Sensitivity, Tinnitus, SiN Performance, and GM Volume

Even with similar EHFPTA and SiN performance, the results suggest that in the tinnitus group, better SiN performance correlated with lower extended high-frequency thresholds and lower GM volume in brain regions related to auditory or cognitive processing. Notably, such correlations were not found behaviorally or neuroanatomically in the control group. The findings suggest that even with clinically defined normal hearing, the presence of tinnitus might change the relationship between SiN recognition and extended high-frequency thresholds or regional GM volume. As the functional network of speech perception in noise can involve IFG, STG, and cerebellum (Guediche et al., 2015), the negative correlation between SiN and regional GM volume in the left cerebellum and STG may entail a compensatory mechanism within this network in reacting to the reduced GM volume in bilateral IFG. Because complementary cognitive functions after sensory changes can improve top-down auditory processing and lead to better cognitive performance (Peelle & Wingfield, 2016), a correlation between SiN and regional GM volume might also suggest potential modification of top-down pathway (from the brain to the cochlea) to compensate for the effect of EHFPTA on SiN recognition. This assumption is underpinned by a recent study of Bures et al. (2019), which suggested that with a similar SiN performance, elder adults with tinnitus used temporal information more efficiently than those without tinnitus to compensate the changes in sensory input caused by tinnitus. In sum, the findings may suggest that structural reorganization in tinnitus is inevitable for maintaining behavioral performance in suboptimal conditions.

### 3.5.4 Clinical Implication

Previous VBM studies mainly focused on how structural changes in the brain are related to tinnitus pathophysiology (Landgrebe et al., 2009; Mühlau et al., 2006) or the co-occurrence of tinnitus and hearing loss (Allan et al., 2016; Husain, Medina, et al., 2011). For the present study, we emphasized how the neuroanatomical alterations in tinnitus might relate to individuals' daily tasks, naming SiN recognition. With comparable hearing sensitivity and SiN performance, the tinnitus-specific results indicate that tinnitus, or neural reorganization caused by tinnitus, might mediate the relationship between hearing impairment (at the extended high-frequency range) and SiN recognition. The significant clusters found in auditory and cognitive processing regions might affirm the importance of integrating peripheral auditory acuity, cognitive functions, and neuroanatomical changes in one model while examining the effect of tinnitus on SiN recognition. Similar to aural rehabilitation for sensory changes (Merabet & Pascual-Leone, 2010), considering how the brain adapts to the presence of tinnitus to maintain daily activities can be important for tinnitus rehabilitation. Additionally, not showing reduced behavioral performance cannot be a clear indication of no structural changes in the brain. If stimulus-dependent alterations truly happen in the macroscopic structure of the tinnitus brain (e.g. in Draganski et al., 2004, 2006), auditory and cognitive training might be beneficial to reduce further impacts of tinnitus on behavioral performance.

### 3.5.5 Caveat

One major shortcoming of the present study is the small sample size. Individuals with tinnitus and normal hearing sensitivity comprise less than 10% of the tinnitus population (Barnea et al., 1990), and further recruitment criteria such as being native American English speakers and being able to complete both behavioral and MRI sessions greatly reduced the possibility of a large-scale study. With similar mean age and hearing sensitivity, Melcher et al. (2013) found no significant difference in GM volume between 24 individuals with tinnitus and 24 controls who were carefully matched by age, gender, and hearing thresholds up to 16 kHz. Thus, the divergence between the present study and Melcher et al. (2013) may be caused by individual variability relevant to the sample size. Moreover, it has been shown that greater between-ear asymmetry of extended high-frequency thresholds can cause poorer inhibitory control or poor global executive function resulting from more cognitive resources required for everyday tasks to compensate the ear asymmetry (Brännström et al., 2018). Therefore, one cannot preclude the effect of between-ear asymmetry in each group on the correlation between EHFPTA and SiN performance. Further, even though the relationship between tinnitus duration and changes in GM volume is not explicit (Landgrebe et al., 2009; Vanneste et al., 2015; Yoo et al., 2016), the effect of tinnitus duration on regional GM volume cannot be ruled out in the present study. Lastly, in a cross-sectional study, it is impossible to determine if the observed structural changes started after the onset of tinnitus, or if further neuroanatomical changes happened between the behavioral and MRI measures. Accordingly, a longitudinal study in a large cohort of individuals with tinnitus is necessary to monitor changes in regional GM volume. Future endeavors should also be establishing a causal relationship between regional GM volume and SiN performance in tinnitus through the support of fMRI studies with techniques that reduce the impact of acoustic scanner noise (Peelle, 2014).

### 3.5.6 Conclusion

In conclusion, we have shown that in individuals with normal hearing sensitivity, the associations among peripheral auditory acuity, neuroanatomy, and SiN performance can be changed by the presence of tinnitus. More importantly, the findings suggest that neuroanatomical alterations following sensory changes such as chronic tinnitus might not be manifested as difficulty performing behavioral tasks, although the effort needed to perform a task may differ between the tinnitus and control groups. Nonetheless, it can be valuable for future longitudinal studies or studies targeting varying tinnitus subgroups to apply multimodal approaches that incorporate both behavioral and brain imaging measures. Such approaches can be critical for monitoring changes caused by tinnitus across the lifespan, identifying the critical period for tinnitus intervention, and helping patients overcome the impact of tinnitus in everyday life.

## 3.6 Tables and Figures

**Table 3.1** Summary of voxel-based morphometry studies in tinnitus.

| | | Age (years) | | Tinnitus Severity | Gray Matter Volume | |
|---|---|---|---|---|---|---|
| **Study** | **N** | ***Range*** | ***Mean (SD)*** | ***Mean (SD)*** | ***Tinnitus > Control*** | ***Tinnitus < Control*** |
| ***Normal hearing*** | | | | | | |
| Muhlau et al., 2006 | 28 | 26-53 | 40 | TQ: 25 (16) | R medial geniculate nucleus | Subcallosal area<br>Nucleus accumbens |
| Landgrebe et al., 2009 | 28 | | 32.2 (9.4) | TQ: 32.9 (13.9) | – | R inferior colliculus<br>L hippocampus |
| Melcher et al., 2013 | 24 | 33-62 | 47.33 (8.03) | TRQ: 26.71 (26.96) | – | – |
| Allan et al., 2016 | 15 | 24-80 | 47.6 (16.66) | - | – | – |
| ***Hearing loss*** | | | | | | |
| Schneider et al., 2009 | 26 | | 39 (2.5) | TQ: 14.2 (2.1) | – | Medial Heschl's gyrus |
| Leaver et al., 2011 | 11 | 20-64 | 33.3 (16) | – | – | Subcallosal area<br>vmPFC |
| Husain et al., 2011 | 8 | 42-64 | 56.13 (7.04) | THI: 17.25 (5.01) | Bil superior frontal gyri<br>Bil medial frontal gyri<br>Bil superior temporal gyri | – |
| Leaver et al., 2012 | 23 | 23-66 | 47.4 (2.9) | – | – | vmPFC<br>dmPFC<br>L supramarginal gyrus |
| Boyen et al., 2013 | 31 | 31-75 | 56 (9) | THI: 29 (20) | L primary auditory cortex | Bil inferior temporal area<br>Bil limbic area |
| Allan et al., 2016 [a] | 73 | 24-80 | 58.38 (12.41) | – | Superior olivary complex | R Heschl's gyrus |
| Allan et al., 2016 [b] | 16 | 24-80 | 55.06 (15.53) | – | – | – |
| Schmidt et al., 2018 | 15 | - | 55.13 (6.89) | THI: 9.33 (6.4) | Anterior cingulate cortex | – |

[a] All tinnitus participants (normal hearing and hearing loss).

[b] Participants with severe tinnitus.

Bil, bilateral; dmPFC, dorsomedial prefrontal cortex; L, left; N, number of tinnitus patients; R, right; THI, Tinnitus Handicap Inventory (maximum possible = 100); TQ, Tinnitus Questionnaire (maximum possible = 84); TRQ: Tinnitus Reaction Questionnaire (maximum possible = 104); vmPFC, ventromedial prefrontal cortex.

**Table 3.2** Twenty-four seed regions used for regions of interest analyses. Regions were 8-mm spheres centered at the listed Montreal Neurological Institute (MNI) coordinates.

| | Coordinates (MNI) | | |
|---|---|---|---|
| **Seed Region** | ***x*** | ***y*** | ***z*** |
| ***Auditory processing regions*** | | | |
| Bilateral ventral and dorsal cochlear nuclei | ±10 | -38 | -45 |
| Bilateral superior olivary complex | ±13 | -35 | -41 |
| Bilateral inferior colliculus | ±6 | -33 | -11 |
| Bilateral medial geniculate nucleus | ±17 | -24 | -2 |
| R superior temporal gyrus | 54 | -19 | 1 |
| L superior temporal gyrus | -57 | -20 | 1 |
| R primary auditory cortex | 50 | -21 | 7 |
| L primary auditory cortex | -52 | -19 | 7 |
| ***Cognitive processing regions*** | | | |
| R pars opercularis of the inferior frontal gyrus | 49 | 12 | 17 |
| L pars opercularis of the inferior frontal gyrus | -48 | 13 | 17 |
| R pars triangularis of the inferior frontal gyrus | 46 | 26 | 7 |
| L pars triangularis of the inferior frontal gyrus | -47 | 27 | 6 |
| R rostral middle frontal gyrus | 23 | 55 | 7 |
| L rostral middle frontal gyrus | -23 | 55 | 4 |
| R caudal middle frontal gyrus | 35 | 39 | 31 |
| L caudal middle frontal gyrus | -39 | 34 | 37 |
| R superior frontal gyrus | 22 | 26 | 45 |
| L superior frontal gyrus | -22 | 24 | 44 |
| R dorsal anterior cingulate gyrus | 6 | 33 | 16 |
| L dorsal anterior cingulate gyrus | -5 | 39 | 20 |

L, left; R, right.

**Table 3.3** Demographic and behavioral data. Numbers are mean (SD), range unless otherwise stated.

| Measures | TIN | CTR | Test Statistic |
|---|---|---|---|
| **Number of subjects** | 14 | 14 | – |
| **Gender (male:female)** | 7:7 | 5:9 | $\chi^2 = 0.583^{ns}$ |
| **Handedness (right:left:both)** | 11:2:1 | 13:1:0 | – |
| **Age (years)** | 45.14 (10.7), 25-61 | 47.36 (9.12), 35-60 | $U = 109.5^{ns}$ |
| **EHFPTA (dB HL)** [a] | 31.71 (13.8), 4.5-48 | 26.39 (13.15), 7.5-46.5 | $U = 79.5^{ns}$ |
| **WRS (%)** [a] | 99.86 (0.53), 98-100 | 100 (0) | $U = 105^{ns}$ |
| **SiN score (%)** [a] | 79.29 (16.85), 45-100 | 84.29 (10.89), 65-100 | $U = 110^{ns}$ |

[a] Obtained bilaterally

[ns] Not significant

CTR, control group; EHFPTA, extended high-frequency pure-tone average from 9 to 14 kHz; SiN, speech-in-noise; TIN, tinnitus group; WRS, word recognition score in quiet.

**Table 3.4** Tinnitus characteristics (*N* = 14).

| **Characteristics** | **Mean (SD)** | **Min, Max** |
|---|---|---|
| **Duration (years)** | 12.63 (12.39) | 0.83, 45 |
| **Tinnitus Functional Index** | 18.97 (13.44)<br>0-17, not a problem (*n* = 7)<br>18-31, small problem (*n* = 4)<br>32-53, moderate problem (*n* = 3) | 1.2, 40.8 |
| **Laterality** | Bilateral, equally loud (*n* = 6)<br>Bilateral, louder in the right ear (*n* = 1)<br>Bilateral, louder in the left ear (*n* = 4)<br>Left ear (*n* = 1)<br>In the right side of head (*n* = 1)<br>In the left side of head (*n* = 1) | |
| **Tinnitus sounds** | Ringing or whistling (*n* = 9)<br>Buzzing (*n* = 2)<br>Humming (*n* = 2)<br>Hissing (*n* = 1) | |

**Table 3.5** Spearman's correlations between bilateral speech-in-noise (SiN) score and other variables.

| **Variables** | **Bilateral SiN Score** | | |
|---|---|---|---|
| | ***All (n = 28)*** | ***TIN (n = 14)*** | ***CTR (n = 14)*** |
| **Age** | -0.14 | -0.50 | 0.34 |
| **EHFPTA** | -0.44* | -0.56* | -0.19 |
| **Tinnitus duration** | – | -0.26 | – |
| **TFI** | – | -0.20 | – |

*$p < 0.05$

CTR, control group; EHFPTA, averaged pure-tone threshold from 9 to 14 kHz in both ears; SiN, speech-in-noise; TIN, tinnitus group; TFI, Tinnitus Functional Index.

**Table 3.6** Brain morphological results in gray matter. Only clusters that met the corrected threshold ($p < 0.05$) at either cluster or voxel level were reported.

| | **Coordinates** | | | ***P* FWE corrected** | | | | |
|---|---|---|---|---|---|---|---|---|
| **Condition** | **X** | **Y** | **Z** | **Cluster level** | **Voxel level** | **Cluster size (k)** | **Z score** | **Brain regions** |
| ***(1) Whole-brain t-tests****: Uncorrected $p < 0.001$ and FWE corrected $p \le 0.056$ at cluster level, $k = 50$* | | | | | | | | |
| CTR > TIN | 39 | 29 | -6 | 0.040 | 0.367 | 646 | 4.13 | R inferior frontal gyrus |
| | -32 | 29 | 11 | 0.056 | 0.299 | 586 | 4.21 | L insula/inferior frontal gyrus |
| ***(2) Whole-brain multiple regression to predict SiN score by group****: Uncorrected $p < 0.001$ and FWE corrected $p < 0.05$ at cluster level, $k = 50$* | | | | | | | | |
| TIN **(-)** | -44 | -57 | -44 | 0.013 | 0.847 | 542 | 4.01 | L cerebellum (Crus I/II) |
| ***(3) Multiple regression using ROIs to predict SiN score by group****: uncorrected $p < 0.001$ and FWE corrected $p < 0.05$ at voxel level, $k = 50$* | | | | | | | | |
| TIN **(-)** | -48 | 3 | -5 | 0.196 | 0.022 | 111 | 4.66 | L superior temporal gyrus |

Regions are listed in Montreal Neurological Institute (MNI) coordinates.

CTR, control group; FWE, family-wise error; L, left; R, right; ROIs, regions of interest; SiN, speech-in-noise; TIN, tinnitus group; (-), negative correlation.

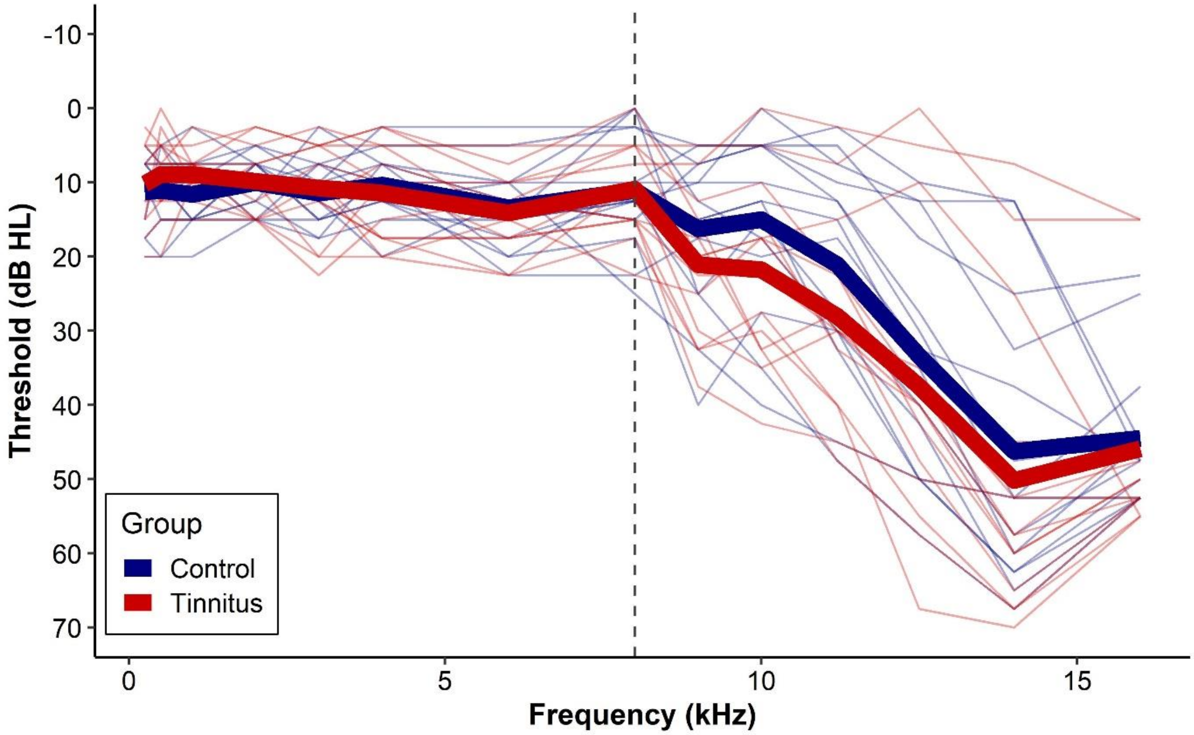


**Figure 3.1** Mean hearing thresholds (thick lines) and individual hearing thresholds (thin lines) from 0.25 to 16 kHz in both ears. The dashed line indicates the cutoff (8 kHz) between conventional testing frequencies and extended high frequencies. No significant between-group difference in threshold was found at any frequency between 9 and 16 kHz.

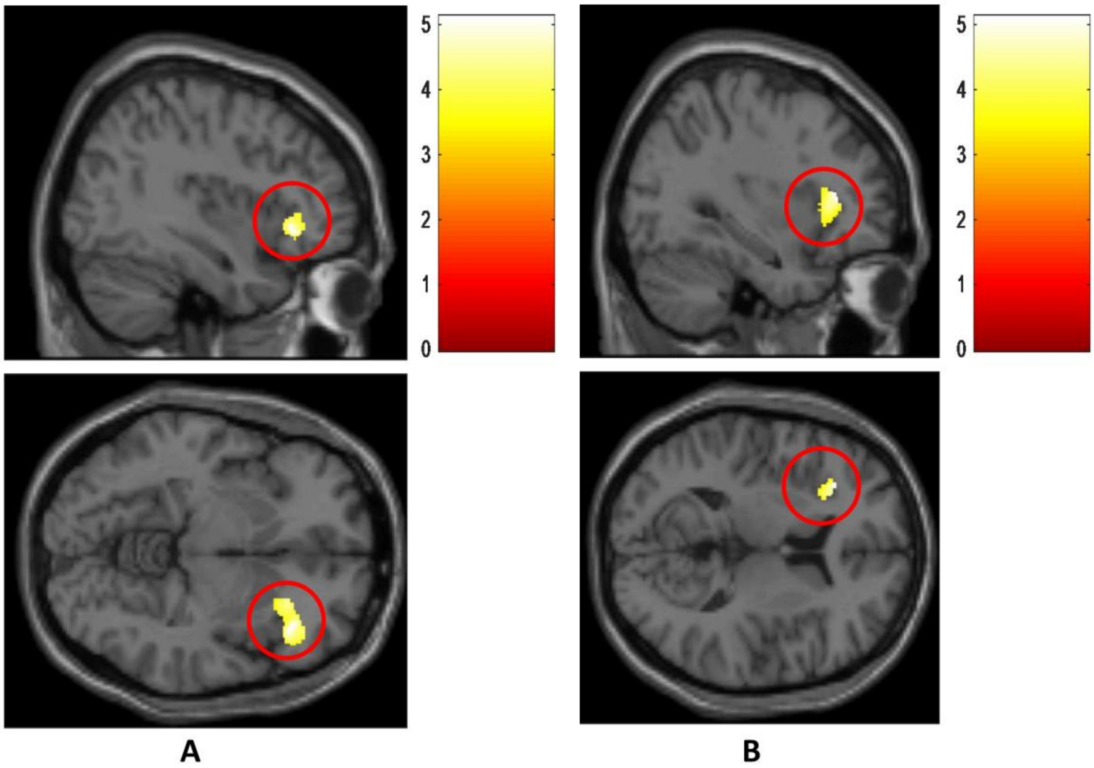


**Figure 3.2** Clusters showing significant difference (family-wise-error corrected $p \leq 0.056$ at cluster level; whole-brain analysis) in gray matter volume between tinnitus and control groups: larger gray matter volume was found in the control group than in the tinnitus group in right inferior frontal gyrus (A) and in left insula/inferior frontal gyrus (B).

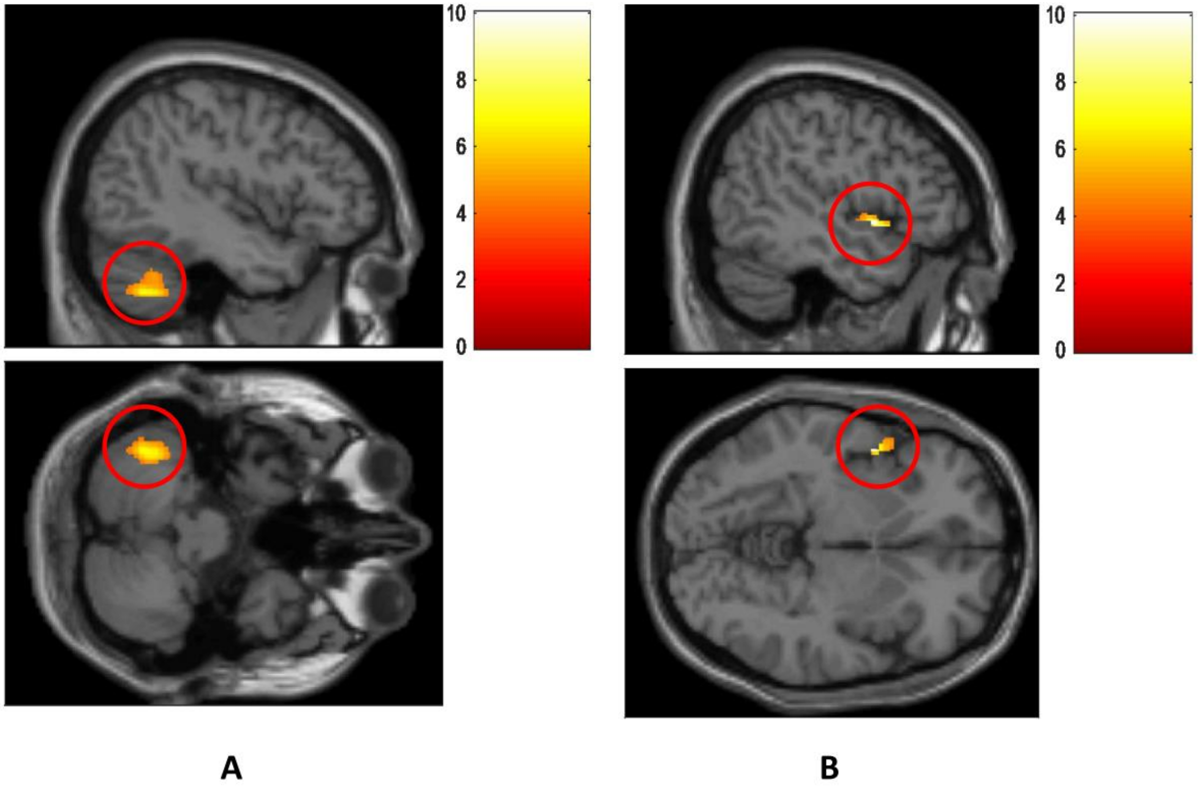


**Figure 3.3** Clusters showing significant negative correlations in the tinnitus group between bilateral speech-in-noise score and gray matter volume in (A) left cerebellum Crus I/II (family-wise-error corrected $p < 0.05$ at cluster level; whole-brain analysis), and in (B) left superior temporal gyrus (family-wise-error corrected $p < 0.05$ at voxel level; region-of-interest analysis).

# CHAPTER 4: STUDY 3

## Study 3: Examining cognitive control deficits in tinnitus patients using behavioral and ERP measures

### 4.1 Abstract

**Purpose:** Inhibitory control has been reported to be a key to understanding the generation or persistence of tinnitus and a prerequisite for SiN understanding. Although the effect of tinnitus on various cognitive functions and speech-in-noise (SiN) recognition is commonly reported, there is no evidence on how the neural underpinnings of inhibitory control are associated with SiN performance. This study aimed to incorporate both behavioral and electrophysiological measures to better understand how inhibitory control relates to SiN performance in individuals with tinnitus and normal hearing sensitivity.

**Methods:** Audiological assessments, Quick Speech-in-Noise test, and neuropsychological measures were conducted on individuals with normal hearing sensitivity, grouping based on the presence of tinnitus. Additionally, participants completed two visual Go/Nogo tasks of semantic categorization during the recording of electroencephalogram. Between-group comparisons on behavioral measures and event-related potentials (ERPs) components that correspond to inhibitory control processing (N2 and P3) were conducted. Further, the relationship between SiN performance and Nogo ERP measures was examined.

**Results:** Hearing sensitivity, SiN recognition, neuropsychological performance, and Go/Nogo response times and error rates did not significantly differ between tinnitus and control groups. However, relative to the control group, neural alterations that suggest deficits in inhibitory control, manifested as prolonged latency and reduced amplitude of the N2, were found in the tinnitus group. Additionally, Nogo-N2 latency significantly correlated with SiN performance in the tinnitus group.

**Conclusions:** The findings suggest that even in the absence of poor behavioral performance, inhibitory control alterations in tinnitus can be detected by measuring neural underpinnings of the N2 component. Inhibitory control ability seems to be relatively more important for SiN recognition in individuals with tinnitus than those without. Future studies should include behavioral and electrophysiological approaches to better understand neural alterations and their relation to overt behavioral changes over the progression of tinnitus.

## 4.2 Introduction

Recent functional magnetic resonance imaging (fMRI) studies confirmed that tinnitus not only relates to central mechanisms of processing auditory signals but also associates with cognitive control regions in emotion and attention (Carpenter-Thompson et al., 2015; Husain, 2016; Husain et al., 2015), indicating that cognitive control may be relevant to the generation and sustention of tinnitus (Jastreboff, 1990; Roberts et al., 2013; Trevis et al., 2016). Likewise, behavioral and electrophysiological studies on the relation between tinnitus and cognitive control abilities also corroborated fMRI findings (Andersson et al., 2000; Degeest et al., 2017; Hallam et al., 2004; Houdayer et al., 2015; Jackson et al., 2014; Mannarelli et al., 2017; Rossiter et al., 2006; Stevens et al., 2007; Waechter & Brännström, 2015). However, converging evidence does not suggest a general cognitive control deficit in the tinnitus population. Overall, previous findings support preserved alerting and orienting attentional networks (Heeren et al., 2014), but impaired selective and inhibitory control of attention, conceivably due to reduced attentional resources resulted from an increased focus on tinnitus (Andersson & McKenna, 2006; Clarke et al., 2020; Heeren et al., 2014; Mannarelli et al., 2017; Mohamad et al., 2016; Stevens et al., 2007; Tegg-Quinn et al., 2016).

Nonetheless, the effect of tinnitus on cognitive control abilities in individuals with normal hearing sensitivity is still debated. Although some studies demonstrated that relative to hearing-matched controls, individuals with tinnitus and normal hearing have deficits in selective attention and cognitive processing (Gabr et al., 2011) and increased listening effort in dual-task conditions (Degeest et al., 2017), others suggested that tinnitus without the presence of hearing impairment is inadequate to cause cognitive control deficits (Brannstrom & Waechter, 2018; Houdayer et al., 2015; Waechter & Brännström, 2015). The myriad observations across studies may imply that using behavioral and neuropsychological measures alone are not sensitive to reveal cognitive control deficits, especially when the hearing status is controlled for.

Poorer speech-in-noise (SiN) performance, as a manifestation of potential consequences of cognitive control deficits, has been consistently reported in individuals with tinnitus and normal hearing sensitivity relative to hearing-matched controls (Gilles et al., 2016; Hennig et al., 2011; Huang et al., 2007; Jain & Sahoo, 2014; Moon et al., 2015; Ryu et al., 2012). However, our previous study (Tai & Husain, 2018) did not suggest a general SiN deficit in individuals with tinnitus and normal hearing. Instead, the findings showed that the tinnitus group performed significantly worse in the left ear than in the right ear, even though bilateral tinnitus percept and symmetrical hearing were reported (Tai & Husain, 2018). Although the between-ear difference in SiN performance in the tinnitus group can result from a right-ear advantage (or more precisely, a left-ear disadvantage) in speech processing, such findings might not be solely attributed to the structural differences in hemispheres because the right-ear advantage can be influenced by cognitive functions such as attention or working memory (Hiscock & Kinsbourne, 2011). The findings of Tai and Husain (2018) underline the importance of including neuropsychological and neurophysiological assessments to unveil neural alterations, to better understand the impact of cognitive control on SiN recognition in tinnitus.

### 4.2.1 Inhibitory Control and SiN Performance

As one aspect of central executive function, inhibitory control is a cognitive process that allows individuals to suppress their thoughts, attention, or emotion to avoid prepotent responses to task-irrelevant stimuli, in order to make the most appropriate decision for daily tasks (Diamond, 2013). Inefficient inhibitory control can lead to a decline in processing complex cognitive tasks when more task-irrelevant information enters working memory and being processed with task-relevant information (Hasher & Zacks, 1988). Therefore, inhibitory control plays a critical role in mediating higher-order cognition such as working memory or matrix reasoning (Darowski et al., 2008; Hasher & Zacks, 1988; Lustig et al., 2001, 2007; Mostofsky & Simmonds, 2008), and greater resistance to proactive interference predicts better SiN performance (Ellis & Rönnberg, 2014; Peelle, 2018; Stenbäck et al., 2015). Converging evidence suggests that inhibitory control is a prerequisite for speech-in-speech processing such as at a cocktail party, where listeners with decreased inhibition capacities tend to activate more semantic information from an irrelevant speech stream (Cahana-Amitay et al., 2016; Perrone-Bertolotti et al., 2017). Some studies also indicated that the generation or persistence of tinnitus may be attributed to the altered top-down inhibitory control mechanisms, as tinnitus can be considered task-irrelevant (Araneda, De Volder, Deggouj, & Renier, 2015; Trevis et al., 2016).

Inhibitory control can be sub-categorized into response and interference inhibition (also known as selective attention) (Diamond, 2013). Different from measures of interference inhibition such as the Stroop task, tasks that directly tag response inhibition only involve the suppression of prepotent responses (Clarke et al., 2020; Diamond, 2013; Mostofsky & Simmonds, 2008). Two widely used measures include the Go/Nogo task, which requires an individual to respond to the target stimuli and withhold responses to non-target stimuli, and the Stop-Signal task, which requires one to restrain the prepotent response after seeing a stop signal (Diamond, 2013). As yet, most tinnitus studies greatly focused on interference inhibition (attention), and only a few studies have evaluated response inhibition in the tinnitus population (Araneda, De Volder, Deggouj, & Renier, 2015; Krick et al., 2017; Trevis et al., 2016). Studies probing response inhibition showed consistent findings that individuals with chronic tinnitus have impaired inhibitory control as manifested by increased response times and error in either auditory or visual inhibitory control tasks, even though the response inhibition requirements differ from the Go/Nogo to the Stop-Signal tasks (Verbruggen & Logan, 2008). However, it is unclear if the impaired response inhibition is solely ascribed to tinnitus without proper control of participants' hearing sensitivity. Thus, whether such deficits can also be observed behaviorally in individuals with tinnitus and normal hearing sensitivity is still unknown.

### 4.2.2 Go/Nogo Task and Event-Related Potentials (ERPs)

Building on our previous findings (Tai & Husain, 2018) that suggest a lack of general SiN deficits in the tinnitus group with normal hearing, visual Go/Nogo tasks with electroencephalography (EEG) recordings were included in the present study to better examine if an early indication of neural alterations related to inhibitory control is present in this population. Objective measures such as EEG or fMRI are shown to be sensitive in detecting neural alterations before behavioral changes can be observed (Getzmann et al., 2015; Husain, Pajor, et al., 2011; Husain et al., 2015; Mudar et al., 2015). For example, Getzmann et al. (2015) found that with a comparable performance of neuropsychological assessments, older adults with lower

SiN performance showed significantly decreased attention and inhibitory control (manifested by lower amplitudes in ERP components) than those with higher SiN performance. Simultaneous EEG recordings with Go/Nogo tasks allow the observed changes in the ERP components to be used as markers of neural alterations of inhibitory control and conflict monitoring.

When inhibiting a motor response in the Nogo trials, increased amplitudes can be observed in ERP components of N2 and P3 (Falkenstein et al., 1999). The N2 component is a negative deflection believed to reflect ACC activity (Folstein & Van Patten, 2008, Nieuwenhuis et al., 2003), with a latency around 150 to 400 ms after stimulus onset and a maximum measured at the Fz electrode (Maguire et al., 2009). The P3 component is a positive shift believed to involve multiple neural generators such as anterior insula, IFG, and posterior cingulate (Baumeister et al., 2014; Johnson, 1993), with a latency around 300 to 500 ms and a maximum observed at the Fz and Cz electrodes (Maguire et al., 2009). Using the same Go/Nogo paradigm in the context of semantic categorization, our preliminary study (Nguyen, Shende, et al., 2017, unpublished abstract) suggested a significantly decreased Nogo-P3 amplitude in individuals with age-related hearing loss than in age-matched controls with normal hearing. Such neural alteration was found to be related to participants' SiN performance (Nguyen, Shende, et al., 2017). The preliminary results demonstrate a link between SiN performance and inhibitory control that can be supported using both behavioral and electrophysiological assessments.

Because cognitive functions are generally not modality-specific (George et al., 2007; Peelle, 2018), visual Go/Nogo tasks instead of auditory ones were used in the present study to reduce the potential effect of hearing disorders such as hearing loss or tinnitus on auditory stimuli. Similar approaches have been proposed for assessing SiN recognition: for example, the Text Reception Threshold, an analogy of speech reception threshold in the visual modality that is found to be associated with SiN performance, has been used to explain cognitive abilities required for SiN recognition when hearing impairment is present (George et al., 2007; Zekveld, Deijen, et al., 2007; Zekveld, George, et al., 2007).

### 4.2.3 Aims and Hypotheses

The present study aimed to investigate the relationship between SiN performance and ERP components related to inhibitory control in individuals with tinnitus and normal hearing. Based on previous behavioral findings of reduced inhibitory control abilities in tinnitus (Araneda, De Volder, Deggouj, & Renier, 2015; Krick et al., 2017), we hypothesized that relative to hearing-matched controls, individuals with tinnitus will demonstrate behavioral indicators or neural alterations showing inefficient inhibitory control, which include: 1) higher error rates during the Nogo trials (commission errors), and 2) reduced amplitudes and prolonged latencies in the Nogo-N2 and Nogo-P3 components. Moreover, we expected that there will be a significant correlation between the neural alterations in Nogo ERPs and SiN recognition. It is possible that in a group with mild tinnitus severity, changes in inhibitory control might not be observed behaviorally; therefore, we further hypothesized that in this scenario the between-group difference in the amplitudes and latencies of the Nogo ERPs will still be significant to indicate subtle signs of alterations to inhibitory control; such alterations may become more profound with higher indices of tinnitus severity.

## 4.3 Methods

### 4.3.1 Participants

Individuals between the ages of 21 to 55 years with tinnitus for more than six months and normal hearing (defined as less than or equal to 25 dB HL from 0.5 to 4 kHz in both ears), and age-, gender- and hearing-matched controls were recruited from the surrounding Urbana-

Champaign area. Participants who reported the following history or conditions were excluded before the initiation of the study: corrected vision was not sufficient to see the visual stimuli on a computer screen, history of traumatic brain injury, Meniere's disease, post-traumatic stress disorder, other psychological disorders except for currently managed depression or anxiety, or a history of neurological disorders including epilepsy. Participants who were in any medical condition that may cause cognitive dysfunction (e.g., brain tumor) or who took medication that can affect cognitive functioning were also excluded. Written informed consent was obtained from each participant before the initiation of data collection under the University of Illinois at Urbana-Champaign Institutional Review Board protocol 19411.

The Montreal Cognitive Assessment (MoCA: Nasreddine et al., 2005), Beck Depression Inventory (BDI: Beck et al., 1996), and Beck Anxiety Inventory (BAI: Beck et al., 1988) were used to screen participants' cognitive ability and psychological states; participants with exceptional scores (MoCA < 26, BDI > 30, or BAI > 25) were excluded. The Edinburgh Handedness Inventory (Oldfield, 1971) was used to ensure all participants included in the study are right-handed. All participants reported being native American English speakers.

### 4.3.2 Procedures

#### *Self-Reported Questionnaires*

Participants completed an in-house healthcare questionnaire probing history of tinnitus and hearing loss. Additionally, the 12-item version of the Speech, Spatial, and Qualities of Hearing scale (SSQ12: Noble et al., 2013) was used to investigate concerns about participants' hearing ability in various listening environments. The score of SSQ12 ranges from 0 to 10, with a lower score suggesting more difficulties understanding speech in adverse listening environments. The SSQ12 has been validated in a large clinical research sample (Noble et al.,

2013) and has been shown to yield similar results as the original 49-item SSQ (Gatehouse & Noble, 2004).

Individuals with tinnitus also completed the Tinnitus Functional Index (TFI: Meikle et al., 2012), which is a validated questionnaire that comprises questions probing eight tinnitus-related dimensions: cognitive, auditory, intrusive, sleep, relaxation, quality of life, emotional, and sense of control. The TFI contains 25 questions rating through a 0-10 or 0-100% scale for each question, with 100 being the maximum possible score. A score below 25 suggests relatively mild tinnitus, whereas a score equal to or above 25 suggests significant problems with tinnitus that require intervention (Henry et al., 2016). The overall score of TFI was used to estimate tinnitus severity of individuals with tinnitus.

### ***Audiological Testing and SiN Recognition***

Audiological assessments included tympanometry and acoustic reflexes to examine middle ear function and to rule out possible retrocochlear pathologies. Distortion product otoacoustic emissions (DPOAEs) were also obtained to rule out outer hair cell dysfunction. All subjects had measurable DPOAEs. Pure-tone thresholds of conventional and extended high frequencies between 0.25 and 16 kHz were obtained for each ear; extended high-frequency pure-tone average (EHFPTA) was calculated using the mean thresholds of frequencies between 9 and 16 kHz. Speech reception threshold and word recognition score (WRS) were obtained to ensure participants have adequate speech-in-quiet recognition. All participants had a WRS above 80% bilaterally.

SiN recognition was evaluated by using built-in sound files of the Quick Speech-in-Noise test (QuickSIN: Killion et al., 2004) in the audiometer. Each list of the QuickSIN contains six sentences spoken by a female talker with five target words in each sentence. The task difficulty of each sentence increases gradually with the decrease of signal-to-noise ratio (SNR). The test was conducted in the following order: 1) standard QuickSIN (lists 1 to 4): target speech was fixed at 70 dB HL and the multi-babble background noise increased from 45 to 70 dB HL after the presentation of each sentence (from 25-dB to 0-dB SNR), with lists 1 and 2 presented to one ear and lists 3 and 4 to the other ear, and 2) modified QuickSIN (lists 5 and 6): to increase task difficulty, target speech and babble were fixed at 70 dB HL and 65 dB HL, respectively, with list 5 presented to one ear and list 6 presented to the other ear. The test always began with list 1, while the start ear was counterbalanced across participants. As our previous tinnitus study (Tai & Husain, 2018) showed no between-group difference in SiN performance using the score of standard QuickSIN, the standard QuickSIN was conducted only to familiarize listeners with various SNR conditions. The main outcome measure of SiN performance was calculated using the mean percent correct at 5-dB SNR of the modified QuickSIN, which was obtained through dividing the number of correctly-repeated target words by the total five keywords in each sentence, with an average score of 12 sentences in lists 5 and 6.

Pure-tone audiometry, speech audiometry, and QuickSIN test were conducted using the Interacoustics Equinox 2.0 PC-based audiometer and ER-3A insert earphones in a single-chamber Acoustic Systems sound-attenuating booth satisfied the ANSI S3.1-1999 [R2003] standard (ANSI, 2003). The Sennheiser HDA 200 headphones were used only for obtaining extended high-frequency thresholds. DPOAEs were assessed using Scout SPORT PC-based diagnostic OAE system. Tympanometry and acoustic reflexes were conducted using an Interacoustics Titan 4.0 clinical tympanometer. All equipment was calibrated annually based on the ANSI S3.6-2010 standard (ANSI, 2010).

### *Neuropsychological Testing*

Participants completed a battery of neuropsychological testing in the following order: Trail-Making Test (part A and B), Stroop Color-Word Interference test, and the Test of Everyday Attention (TEA: Robertson et al., 1996).

**Trail-Making Test (TMT).** The TMT consists of two parts, with part A (TMT-A) requiring an individual to connect numbers in ascending order (1, 2, 3, etc.) and part B (TMT-B) requiring one to connect alternately between numbers and letters (1, A, 2, B, etc.); the time for completing each trail was recorded (Tombaugh, 2004). Participants completed TMT-A before TMT-B. The TMT-A mainly involves processing speed, whereas the TMT-B involves attention, cognitive flexibility, and sequencing (Ellis et al., 2016; Gabr et al., 2011; Jozefowicz-Korczynska et al., 2005; Pajor et al., 2013). For statistical analysis, the derived score of TMT-A to TMT-B ratio (TMT-B/A) was used, as it has been shown to best represent the executive function probed by TMT (Arbuthnott & Frank, 2000).

**The Stroop Task.** The present study used the Color-Word Interference Test of the Delis-Kaplan Executive Function System (D-KEFS: Delis et al., 2001), which is one version of the standard color-word Stroop task (Stroop, 1935). The Stroop task engages various cognitive processes, including executive attention, cognitive flexibility, and processing speed (Getzmann et al., 2015; Mohamad et al., 2016). The test consists of four conditions: 1) color naming, which requires individuals to name the colors of patches, 2) word reading, which requires individuals to read the printed words, 3) inhibition, individuals need to inhibit the prepotent response by ignoring the printed words (incongruent and irrelevant information) and by naming ink colors (relevant information), and 4) inhibition/switching, individuals repeat what they have done for condition 3 but read a printed word if the word is inside a square. The participants were instructed to complete each condition as quickly as possible without making mistakes, with the response time (RT) being recorded. The Stroop interference (SI) was calculated based on the difference in RT between the color naming (congruent) and inhibition condition (incongruent).

**The Test of Everyday Attention (TEA).** Participants completed two visual subtests of TEA (Robertson et al., 1996): Map Search and Visual Elevator. For the Map Search, participants were instructed to search for fork-and-knife symbols (with a total of 80 symbols) on a colored map in two minutes. The Map Search taps selective attention of the target symbol while inhibiting distractors on the map. For the Visual Elevator, participants were instructed to count which floor they were at by following a series of photos representing elevators or arrows (indicating the up or down direction of the elevator). The test involves individuals' abilities in attentional switching or cognitive flexibility to reach a correct response. For correct items, the time taken was divided by the number of switches to obtain the time-per-switch measure.

### *Experimental Paradigm and Procedures*

Participants completed two visual Go/Nogo tasks at different levels of semantic categorization detailed in Maguire et al. (2009) and Mudar et al. (2015). At the basic categorization level (single-car task or SiC), participants pressed a button after seeing a single line-drawing image of a car (Go) or withheld button press after seeing a dog (Nogo). Repeated images were used in the SiC task to facilitate discrimination between items. At the superordinate level (object-animal task or ObA), participants pressed the button after seeing examplars of objects (Go) and inhibited button press after seeing animals (Nogo). Different examplars of objects and animals were used in the ObA task. Each task contained 200 images with 80% of Go images (160 images) and 20% of Nogo images (40 images) to increase the tendency of prepotent response to the Go trials. Each image was presented for 300 ms, followed by a fixation "+" sign with an interstimulus interval of 1700 ms. The completion time for each task was around seven minutes. The order of the stimuli in each task was pseudorandomized and the task order was counterbalanced across participants to minimize the effect of a testing order.

### *EEG Data Acquisition and Processing*

Participants wore a 64-electrode Neuroscan elastic cap for the acquisition of continuous EEG during the Go/Nogo tasks. The Scan 4.5 software (sampling rate: 1 kHz, DC-200 Hz) and a Neuroscan SynAmp2 amplifier were used for the recording, with the typical electrode impedances lower than 10 kΩ and the reference electrodes set at the midline between Cz and CPz. A pair of electrodes were placed above and below the left eye for the vertical electrooculogram (VEOG). Electrodes that functioned poorly were identified through visual inspection and were excluded for further analysis (3.41% in the tinnitus and 3.44% in the control group). The raw EEG data were high pass filtered at 0.15 Hz and processed offline to correct for eye blinks using spatial filtering of the Neuroscan software. The data were epoched 200 ms before and 1200 ms after the onset of the stimuli, and re-referenced to the average potential over the entire scalp except for the VEOG and poorly functioning electrodes. A digital band-pass filter was then applied, with a lower cutoff value of 1 Hz to remove slow voltage shifts and a higher cutoff value of 30 Hz to minimize high-frequency noise. Baseline correction was conducted by subtracting the mean amplitude of the pre-stimulus interval (-200 ms to 0 ms) from each time point. Artifact rejection was done by rejecting peak signal amplitudes of more than 75 μV; the mean rejection rates were 8.82%/8.33% in Go and 6.79%/9.5% in Nogo trials for the tinnitus/control group. ERP average of each subject was obtained separately for the correct trials of the Go and Nogo response types; only trials with an RT between 100 ms and 1000 ms were included for further analysis.

***ERP Analysis***

For each individual, mean ERP was obtained for the four conditions: SiC-Go, SiC-Nogo, ObA-Go, and ObA-Nogo. The N2 and P3 electrode sites were selected based on what was reported in previous studies (Maguire et al., 2009; Mudar et al., 2015, 2016; Nguyen, Mudar, et al., 2017). After estimating latency variability across tinnitus and control groups, peak latency and baseline-to-peak amplitude were measured automatically between 180 and 320 ms for N2 and between 320 and 550 ms for P3 at two midline electrodes (Fz, FCz) for both Go and Nogo trials, using the Neuroscan software.

### 4.3.3 Statistical Analysis

Mann-Whitney U test for nonparametric data was used for between-group comparison in demographics, emotional, audiological, and neuropsychological measures. The $\chi^2$ test was used to examine the between-group difference in gender. Behavioral measures during Go/Nogo tasks were reported as RTs and error rates. The error rates were calculated as omission errors when a participant incorrectly inhibited button press during Go trials and commission errors when a participant failed to inhibit during Nogo trials. Standard general linear models (GLM) were used to examine behavioral measures (RTs and error rates) and ERP measures (latency and amplitude of N2 and P3) to investigate the effects of the following variables: group (tinnitus/control), task (SiC/ObA), and response type (Go/Nogo). Because RTs were only available during the Go trials, response type was not applied in the GLM when RT serves as a dependent variable. Moreover, due to the unequal trial-averaged responses and the unequal number of Go and Nogo trials, weights based on the number of trials for calculating each ERP measure were employed in the GLMs for the ERP measures. Spearman’s correlation analyses were used to examine the relationship between SiN recognition and the latency and amplitude of Nogo-N2 and Nogo-P3 components. All statistical analyses were conducted using the R statistical software (version 3.5.1) with a significance level set at 0.05.

## 4.4 Results

Eleven individuals with chronic tinnitus (TIN) and 10 hearing-matched controls (CTR) were included. Demographic information and self-reported measures were shown in Table 4.1. The two groups did not differ in age, gender, and any self-report measures (BAI, BDI, and SSQ12). Participants with tinnitus reported a low TFI score, with a mean TFI of 13.96 (categorized as a small problem); only one participant (9.09%) reported a score greater than 25, indicating a significant problem that might require intervention.

### 4.4.1 Audiological and Neuropsychological Data

Bilateral mean and individual hearing thresholds in each group are shown in Figure 4.1. Mann-Whitney U tests indicated no significant difference in bilateral WRS, EHFPTA, and SiN performance at the fixed 5-dB SNR condition between TIN and CTR (Table 4.2). Moreover, no significant between-group difference was found in any neuropsychological assessments, including MoCA, TMT-B/A, SI, and Map Search and Visual Elevator subtests of the TEA.

### 4.4.2 Behavioral Results of the Go/Nogo Tasks

Table 4.3 shows the mean RTs and error rates of the Go/Nogo tasks in each group.

#### *Reaction Times*

Statistical analyses of the Go-RTs (Table 4.4) indicated a main effect of task ($F(1, 38) = 10.42$, $p = 0.001$), with significantly longer RTs in the ObA task (mean 378.24 ms) than in the SiC task (mean 298.44 ms). No other significant main effect or interaction effects were found.

### *Error Rates*

Statistical analyses of the error rates (Table 4.4) showed the main effect of response type ($F(1, 73) = 23.37$, $p < 0.001$), with higher error rates to Nogo (mean 10.06%) than to Go stimuli (mean 2.94%). No other significant main effect or interaction effects were found.

### 4.4.3 ERP Results

Mean latency and amplitude of N2 and P3 measured at the Fz and FCz electrodes are reported in Table 4.5, separated by group. The results of statistical analyses are shown in Table 4.6 for the Fz electrode and Table 4.7 for the FCz electrode.

### *N2 Latency*

A significant main effect of group was found at both Fz ($F(1, 76) = 4.67$, $p = 0.031$) and FCz ($F(1, 76) = 5.79$, $p = 0.016$), with TIN having longer latency than CTR (Fz: 227.27 ms > 212.61 ms; FCz: 224.54 ms > 211.4 ms). No other main or interaction effects were significant. Figure 4.2 shows the grand average ERPs of each group at the Fz and FCz electrodes, disregarding the task or response type.

### *N2 Amplitude*

A significant main effect of group was found at both Fz ($F(1, 76) = 6.02$, $p = 0.014$) and FCz ($F(1, 76) = 7.14$, $p = 0.008$), with TIN having lower amplitude than CTR (Fz: -1.8 μV < -2.42 μV; FCz: -1.22 μV < -1.79 μV; Figure 4.2). No other main or interaction effects were significant.

### *P3 Latency*

A significant main effect of task was found at both Fz ($F(1, 76) = 6.41$, $p = 0.011$) and FCz ($F(1, 76) = 11.62$, $p < 0.001$), with longer latency in ObA than in SiC (Fz: 415.34 ms > 378.46 ms; FCz: 397.95 ms > 357.07 ms). No other main or interaction effects were significant.

Figure 4.3 shows grand average ERPs of the SiC and ObA tasks at the Fz and FCz electrodes, disregarding the group and response type.

### *P3 Amplitude*

A significant main effect of response type was found at both Fz ($F(1, 76) = 5.27$, $p = 0.022$) and FCz ($F(1, 76) = 11.13$, $p < 0.001$), with higher amplitude of Nogo than Go stimuli (Fz: 2.8 μV > 1.74 μV; FCz: 2.62 μV > 1.4 μV). No other main or interaction effects were significant. Figure 4.4 shows grand average ERPs of the Go and Nogo response at the Fz and FCz electrodes, disregarding the group and task.

### *Correlation between ERP Measures and SiN Performance*

Table 4.8 shows the Spearman's correlations between SiN performance and Nogo ERP measures in each group and in all participants. The only significant correlation was found between Nogo-N2 latency and SiN performance ($r_s = -0.68$, $p = 0.02$) in TIN, suggesting that longer Nogo-N2 latency related to poorer SiN recognition in the tinnitus group (Figure 4.5); such correlation was not observed in the control group. Due to the small sample size for separated correlation analyses in each group, the confidence intervals with 1000 replicates, obtained via a bootstrapping procedure, were also calculated to confirm the correlation between Nogo-N2 latency and SiN performance (TIN: 95% CI [-0.92, -0.11]; CTR: 95% CI [-0.21, 1]).

## 4.5 Discussion

This study aimed to examine inhibitory control ability in individuals with tinnitus and normal hearing, and its relationship with SiN performance through behavioral and electrophysiological approaches. Behaviorally, the results showed no significant between-group difference in SiN recognition, neuropsychological performance, and Go/Nogo RTs and error rates when age, hearing sensitivity, psychological states, and self-reported SiN difficulty were matched between the tinnitus and control groups. However, relative to individuals without tinnitus, those with tinnitus demonstrated longer latency and lower amplitude of the N2 component, indicating neural alterations related to inhibitory control. Further, the latency of Nogo-N2 significantly correlated with SiN performance in the tinnitus group, but not in the control group.

### 4.5.1 Behavioral Findings

#### *Neuropsychological Performance*

With matched age and hearing sensitivity between TIN and CTR, the results of SiN and neuropsychological testing did not suggest deficits in SiN recognition or cognitive control in TIN. Particularly, the neuropsychological findings on TMT or Stroop task did not corroborate with previously observed cognitive control deficits in the tinnitus population (Andersson et al., 2000; Gabr et al., 2011; Jackson et al., 2014; Jozefowicz-Korczynska et al., 2005; Pajor et al., 2013; Stevens et al., 2007). However, previous findings on neuropsychological performance seem to be highly driven by the potential effect of hearing impairment, as several studies either included individuals with both tinnitus and hearing impairment (e.g., Andersson et al., 2000) or did not rule out hearing loss in their participants by conducting an audiological assessment (e.g., Jackson et al., 2014). In individuals with tinnitus and normal hearing, Waechter and Brannstrom (2015) showed no significant differences in RTs or accuracy between their tinnitus and control groups for any conditions in the standard Stroop task. Our results echo those of Waechter and Brannstrom (2015) and confirm their claim that cognitive control deficits may not be evident in overt behavior, or the interference effect of tinnitus on cognitive performance cannot be examined by using the Stroop task in individuals with tinnitus and normal hearing.

### *Go/Nogo Behavioral Measures*

The behavioral findings of Go/Nogo tasks suggested comparable response inhibition ability between TIN and CTR, with no significant between-group difference in RTs and error rates irrespective of the Go or Nogo response type or the difficulty of the task. Similarly, Araneda, De Volder, Deggouj, and Renier (2015) only found longer RTs and more commission errors in their chronic tinnitus group than in the control group in the auditory, but not in the visual Go/Nogo task. Different from our findings, Krick et al. (2017) found that individuals with chronic tinnitus demonstrated longer RTs in a visual Go/Nogo task than healthy controls. A recent study using meta-analysis also confirmed the effect of tinnitus on RTs of tasks measuring inhibitory control (including tasks for both response and interference inhibition), but not on error rates (Clarke et al., 2020). The contradictory findings between the present and previous studies may be attributed to the additive effect of tinnitus and hearing impairment on inhibitory control, as most previous studies did not control for hearing sensitivity in their participants. Additionally, recent-onset (less than six months) or more severe tinnitus have been shown to negatively impact the RTs and commission errors of inhibitory control tasks (Clarke et al., 2020; Krick et al., 2017; Mohamad et al., 2016). Thus, it might not be surprising that the behavioral measures of Go/Nogo tasks did not show inhibitory control deficits in our group with long-term chronic, mild tinnitus and normal hearing sensitivity.

## 4.5.2 ERP Findings

### *Prolonged Latency and Reduced Amplitude of N2 in Tinnitus*

The findings of the present study did not support our hypothesis of longer latency and lower amplitude specifically to the Nogo-N2 and Nogo-P3 components in TIN relative to CTR. However, irrespective of the task and response type, TIN had longer latency and lower amplitude of the N2 component than CTR. The relationship between the N2 component and response inhibition has been long debated, with some suggesting that N2 is related to inhibiting a motor response (Falkenstein et al., 1999; Falkenstein, 2006; Folstein & Van Petten, 2008), and others indicated that N2 reflects conflict monitoring either on different response types or on the correct trials during the task (Donkers & Van Boxtel, 2004; Getzmann et al., 2015; Nieuwenhuis et al., 2003). Albeit with the controversy in existing literature, it is generally agreed that N2 relates to response inhibition to some extent (Jodo & Kayama, 1992; Luck, 2014; Maguire et al., 2009; Smith et al., 2007). Using identical study design of Go/Nogo task, prolonged N2 latency or reduced N2 amplitude has been shown to be neural markers of cognitive deterioration in older adults (Mudar et al., 2015), in individuals with amnestic mild cognitive impairment (Mudar et al., 2016), or in those with untreated age-related hearing loss (Nguyen, Shende et al., 2017). Prolonged N2 latency has also been found in individuals with severe tinnitus and those with co-occurrence of tinnitus and hearing loss using oddball paradigms for examining attention allocation (Attias et al., 1996; Wang et al., 2018). Although such neural alterations usually accompany longer RTs and increased error rates of Go/Nogo tasks (e.g., Mudar et al., 2015), our findings of neural alterations with the absence of poor behavioral performance may underpin the assumption of an early sign of cognitive changes in individuals with tinnitus and normal hearing.

### ***The Effect of Task or Response Type on the P3 Component***

With increasing task difficulty from SiC (basic categorization) to ObA (superordinate categorization), prolonged latency was expected to be found in both the N2 and P3. However, the effect of task was only found in P3. The P3 component has been shown to be related to inhibition (Falkenstein et al., 1999, 2002), response conflict (Smith et al., 2010), and motor-related activation (Verleger et al., 2006). The longer P3 latency found in ObA relative to SiC was consistent with the findings of previous studies using an identical paradigm in other populations (Maguire et al., 2009; Mudar et al., 2015, 2016), suggesting that the categorization task modulates P3 latency similarly regardless of the population. Further, the findings of a larger P3 amplitude to the Nogo than to the Go stimuli are not surprising. The Nogo-P3 has been shown to involve different generators from the Go-P3, and its amplitude increases when the probability of Nogo stimuli decreases (Pfefferbaum et al., 1985; Verleger et al., 2016). With the Nogo stimuli only comprising 20% of the trials in the present study, the enhanced Nogo-P3 amplitude may indicate that neural processing is more effortful to the rare Nogo than to the frequent Go stimuli (Mudar et al., 2016). Nonetheless, our findings with a non-significant main effect of group to the P3 latency or amplitude support previous studies that the P3 component may not be sensitive to group effect (Falkenstein et al., 1999).

### *The Relationship between SiN Performance and Nogo-N2 Latency*

The significant relationship between SiN performance and Nogo-N2 latency, although only in TIN, corroborates our hypothesis that neural alterations in Nogo ERPs relate to SiN recognition. Different from the Go-N2, the Nogo-N2 reflects a mechanism necessary for inhibiting the prepotent responses during Nogo trials (Jodo & Kayama, 1992). Prolonged Nogo-N2 latency has been found in individuals with poor performance in inhibitory control tasks due to late inhibition processing (Falkenstein et al., 1999). As a growing body of work suggests the importance of inhibitory control in SiN performance (Cahana-Amitay et al., 2016; Heinrich et al., 2015, 2016; Knight & Heinrich, 2019; Perrone-Bertolotti et al., 2017; Yeend et al., 2017), it is conceivable that a longer Nogo-N2 latency pertains to poorer SiN performance. However, a significant negative correlation between Nogo-N2 latency and SiN performance was only found in the tinnitus group. It is not clear why a counterintuitive correlation, although not statistically significant, was found in the control group (Figure 4.5). The findings may indicate that with affected cognitive control abilities (Clarke et al., 2020; Mohamad et al., 2016; Tegg-Quinn et al., 2016), individuals with tinnitus rely more on inhibitory control than those without when processing SiN. Further, different directions of correlation between Nogo-N2 latency and SiN recognition in the two groups may suggest different cognitive processing strategies used to maintain comparable SiN performance.

### 4.5.3 Caveat

In addition to the small sample size that might affect the statistical power of the study, some other limitations should be noted. Firstly, one major shortcoming that precludes us from making a strong claim of the general tinnitus population lies in the inclusion of participants with long-term tinnitus. Regardless of hearing sensitivity, inhibitory control deficits in chronic tinnitus have been shown in previous studies (Araneda, De Volder, Deggouj, & Renier, 2015; Krick et al., 2017). Still, little is known about the behavioral and functional changes during the first six months of tinnitus progression, even though tinnitus can be catastrophic for patients in the first few months of tinnitus onset (Weise et al., 2013). Thus, a better understanding of how tinnitus progresses over time can be critical for early intervention of tinnitus. Secondly, the performance of inhibitory control or SiN tasks can be moderated by factors such as an individual's goal or motivation (Eckert et al., 2016; Hasher & Zacks, 1988; Peelle, 2018). Therefore, the comparable behavioral performances between the tinnitus and control groups may not truly reflect individuals' cognitive control abilities. Lastly, as the results of Go/Nogo behavioral measures can differ between auditory and visual modalities in individuals with tinnitus (Araneda, De Volder, Deggouj, & Renier, 2015), further studies are warranted to confirm if auditory Go/Nogo tasks can elicit similar neural alterations as in visual tasks in individuals with tinnitus and normal hearing.

### 4.5.4 Conclusion

In conclusion, individuals with tinnitus showed altered neural processing associated with inhibitory control during Go/Nogo tasks. Specifically, prolonged latency and reduced amplitude of the N2 component were observed in individuals with tinnitus relative to controls. Our findings support the hypothesis that individuals with mild tinnitus may not exhibit overt cognitive control deficits as measured by behavioral tasks; however, neural alterations related to cognitive control can still be detected through electrophysiological measures. As the measurement of N2 has been proven to be useful for monitoring elder adults with suspected cognitive impairment (Howe, 2014), our findings demonstrate that in a cohort with mild tinnitus and normal hearing, measuring the N2 component can be beneficial for identifying early signs of cognitive control impairment. While the present study sets the foundation of including both behavioral and electrophysiological approaches for a better understanding of cognitive functions and SiN recognition, future examinations on how neural processing of cognitive control changes over the progression of tinnitus or a treatment period can be advantageous for clinical tinnitus intervention.

## 4.6 Tables and Figures

**Table 4.1** Demographic and self-report measures. Numbers are mean (SD), range unless otherwise stated.

| Measures | TIN | CTR | *P*-value |
|---|---|---|---|
| **Number of subjects** | 11 | 10 | – |
| **Gender (male:female)** | 8:3 | 7:3 | 0.89 |
| **Age (years)** | 40.91 (12.62), 21-55 | 39.6 (12.99), 21-54 | 0.916 |
| **BAI** | 2.36 (2.87), 0-9 | 1.2 (1.32), 0-4 | 0.443 |
| **BDI** | 3.09 (4.44), 0-14 | 2.9 (2.51), 0-8 | 0.474 |
| **SSQ12** | 8.49 (1.48), 5-9.75 | 8.05 (1), 6-9.34 | 0.275 |
| **TFI** | 13.96 (14.8), 3.2-56.67 | – | – |

CTR, control group; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; SSQ12, 12-item Speech, Spatial, and Qualities of Hearing scale; TFI, Tinnitus Functional Index; TIN, tinnitus group.

**Table 4.2** Audiological and neuropsychological measures. Numbers are mean (SD), range unless otherwise stated.

| **Measures** | **TIN** | **CTR** | ***P*-value** |
|---|---|---|---|
| ***Audiological (bilateral)*** | | | |
| EHFPTA (dB HL) | 29.55 (17.48), 7.08-47.5 | 29.25 (14.67), 9.17-47.5 | 1 |
| WRS (%) | 99.64 (0.81), 98-100 | 99.8 (0.63), 98-100 | 0.642 |
| SiN performance (%) | 80.15 (9.02), 58.33-90 | 76.67 (7.33), 60-83.34 | 0.407 |
| ***Neuropsychological*** | | | |
| MoCA | 29 (1), 27-30 | 29.4 (0.97), 27-30 | 0.286 |
| TMT-B/A | 2.39 (1.02), 1.46-5.1 | 2.41 (1.8), 1.32-5.1 | 0.916 |
| SI | 19.93 (9.9), 10.35-39.67 | 19.69 (9.12), 6.22-38.14 | 0.972 |
| TEA: Map Search | 70.36 (9.52), 46-79 | 70.4 (8.19), 57-79 | 0.916 |
| TEA: Visual Elevator | 3.59 (0.71), 2.54-4.87 | 3.2 (0.58), 2.37-4.23 | 0.205 |

CTR, control group; EHFPTA, extended high-frequency pure-tone average from 9 to 16 kHz; MoCA, Montreal Cognitive Assessment; SI, Stroop interference; SiN, speech-in-noise; TEA, Test of Everyday Attention; TIN, tinnitus group; TMT-B/A, Trail Making Test part B to part A ratio; WRS, word recognition score in quiet.

**Table 4.3** Behavioral measures of the Go/Nogo tasks. Numbers are mean (SD).

| **Measures** | **TIN** | **CTR** |
|---|---|---|
| ***SiC*** | | |
| Go RT (ms) | 291.09 (32.92) | 306.52 (91.17) |
| Omission errors (%) | 3.49 (5.68) | 1.47 (1.6) |
| Commission errors (%) | 9.32 (8.81) | 11.11 (7.3) |
| ***ObA*** | | |
| Go RT (ms) | 365.89 (49.31) | 391.82 (121.99) |
| Omission errors (%) | 5.22 (4.62) | 1.31 (2.35) |
| Commission errors (%) | 10.5 (9.63) | 9.44 (8.36) |

CTR, control group; ObA, object-animal task; RT, response time; SiC, single-car task; TIN, tinnitus group.

SiC commission errors of 1 subject in the control group and ObA commission errors of 1 subject in each group were not included in this table or for further behavioral analyses due to ≥ 50% of error rates (performance by chance).

**Table 4.4** Statistical results of Go/Nogo behavioral measures.

| **Effects** | **Go-Response Time** | **Error Rates** |
|---|---|---|
| Group | $F(1, 38) = 0.7, p = 0.403$ | $F(1, 73) = 0.84, p = 0.359$ |
| Task | **$F(1, 38) = 10.42, p = 0.001$**** | $F(1, 73) = 0.06, p = 0.802$ |
| Response type | – | **$F(1, 73) = 23.37, p < 0.0001$**** |
| Group x Task | $F(1, 38) = 0.05, p = 0.832$ | $F(1, 73) = 0.63, p = 0.428$ |
| Group x Response type | – | $F(1, 73) = 1.29, p = 0.257$ |
| Task x Response type | – | $F(1, 73) = 0.12, p = 0.733$ |
| Group x Task x Response type | – | $F(1, 73) = 0.03, p = 0.868$ |

******$p < 0.01$

Values in boldface represent significant effects.

**Table 4.5** ERP measures at the Fz and FCz electrodes of Go/Nogo task. Numbers are mean (SD).

| | Fz | | FCz | |
|---|---|---|---|---|
| **ERP measures** | **TIN** | **CTR** | **TIN** | **CTR** |
| ***N2 Latency (ms)*** | | | | |
| SiC-Go | 229.09 (37.43) | 206.9 (19.72) | 221.18 (42.77) | 199.9 (21.27) |
| SiC-Nogo | 233.27 (31.27) | 219.95 (33.3) | 228.09 (27.03) | 220.2 (39.35) |
| ObA-Go | 219.18 (30.16) | 209.65 (25.36) | 221.91 (39.1) | 199.2 (18.86) |
| ObA-Nogo | 227.55 (30.35) | 213.95 (26.18) | 227 (27.46) | 226.3 (30.9) |
| ***N2 amplitude (µV)*** | | | | |
| SiC-Go | -1.41 (0.98) | -2.75 (2.12) | -0.9 (0.72) | -1.87 (1.39) |
| SiC-Nogo | -2.09 (1.4) | -2.31 (1.59) | -1.51 (1.47) | -1.85 (1.18) |
| ObA-Go | -1.82 (1.05) | -2.24 (1.71) | -1.13 (0.75) | -1.53 (1.22) |
| ObA-Nogo | -1.9 (1.47) | -2.38 (1.78) | -1.32 (1.23) | -1.89 (1.52) |
| ***P3 Latency (ms)*** | | | | |
| SiC-Go | 409.82 (84.07) | 363.75 (67.8) | 362.91 (41.21) | 358.4 (68.52) |
| SiC-Nogo | 363.45 (62.59) | 375.2 (61.01) | 349.27 (24.95) | 357.9 (41.45) |
| ObA-Go | 447.09 (90.21) | 411.95 (85.76) | 416.64 (82.86) | 413.7 (89.3) |
| ObA-Nogo | 400 (65.03) | 400.7 (74.37) | 381.18 (42.10) | 380.1 (59.63) |
| ***P3 amplitude (µV)*** | | | | |
| SiC-Go | 1.74 (1.18) | 1.85 (1.09) | 1.45 (1) | 1.65 (0.88) |
| SiC-Nogo | 2.65 (2.01) | 3.16 (2.24) | 2.69 (1.75) | 3.05 (2.35) |
| ObA-Go | 1.51 (1.19) | 1.9 (1.58) | 1.05 (0.72) | 1.49 (0.99) |
| ObA-Nogo | 2.66 (1.91) | 2.77 (1.95) | 2.23 (1.44) | 2.53 (2.23) |

CTR, control group; ObA, object-animal task; SiC, single-car task; TIN, tinnitus group.

**Table 4.6** Statistical results of ERP measures at the Fz electrode.

| Effects | Latency | Amplitude |
|---|---|---|
| ***N2*** | | |
| Group | **$F(1, 76) = 4.67, p = 0.031$*** | **$F(1, 76) = 6.02, p = 0.014$*** |
| Task | $F(1, 76) = 0.33, p = 0.563$ | $F(1, 76) = 0.03, p = 0.873$ |
| Response type | $F(1, 76) = 0.71, p = 0.399$ | $F(1, 76) = 0.02, p = 0.887$ |
| Group x Task | $F(1, 76) = 0.79, p = 0.376$ | $F(1, 76) = 0.76, p = 0.382$ |
| Group x Response type | $F(1, 76) = 0.04, p = 0.838$ | $F(1, 76) = 0.34, p = 0.559$ |
| Task x Response type | $F(1, 76) = 0.07, p = 0.797$ | $F(1, 76) = 0.02, p = 0.885$ |
| Group x Task x Response type | $F(1, 76) = 0.14, p = 0.707$ | $F(1, 76) = 0.42, p = 0.518$ |
| ***P3*** | | |
| Group | $F(1, 76) = 3.24, p = 0.072$ | $F(1, 76) = 0.71, p = 0.399$ |
| Task | **$F(1, 76) = 6.41, p = 0.011$*** | $F(1, 76) = 0.25, p = 0.62$ |
| Response type | $F(1, 76) = 1.13, p = 0.288$ | **$F(1, 76) = 5.27, p = 0.022$*** |
| Group x Task | $F(1, 76) = 0.02, p = 0.901$ | $F(1, 76) = 0.12, p = 0.727$ |
| Group x Response type | $F(1, 76) = 1.47, p = 0.225$ | $F(1, 76) = 0.002, p = 0.968$ |
| Task x Response type | $F(1, 76) = 0.17, p = 0.68$ | $F(1, 76) = 0, p = 0.996$ |
| Group x Task x Response type | $F(1, 76) = 0.01, p = 0.942$ | $F(1, 76) = 0.25, p = 0.617$ |

*****$p < 0.05$

Values in boldface represent significant effects.

**Table 4.7** Statistical results of ERP measures at the FCz electrode.

| **Effects** | **Latency** | **Amplitude** |
|---|---|---|
| ***N2*** | | |
| Group | **$F(1, 76) = 5.79$, $p = 0.016$*** | **$F(1, 76) = 7.14$, $p = 0.008$**** |
| Task | $F(1, 76) = 0.01$, $p = 0.904$ | $F(1, 76) = 0.08$, $p = 0.783$ |
| Response type | $F(1, 76) = 2.72$, $p = 0.099$ | $F(1, 76) = 0.52$, $p = 0.47$ |
| Group x Task | $F(1, 76) = 0.01$, $p = 0.934$ | $F(1, 76) = 0.6$, $p = 0.44$ |
| Group x Response type | $F(1, 76) = 1.23$, $p = 0.268$ | $F(1, 76) = 0.18$, $p = 0.673$ |
| Task x Response type | $F(1, 76) = 0.002$, $p = 0.968$ | $F(1, 76) = 0.01$, $p = 0.913$ |
| Group x Task x Response type | $F(1, 76) = 0.13$, $p = 0.717$ | $F(1, 76) = 0.32$, $p = 0.574$ |
| ***P3*** | | |
| Group | $F(1, 76) = 0.01$, $p = 0.927$ | $F(1, 76) = 1.29$, $p = 0.256$ |
| Task | **$F(1, 76) = 11.62$, $p = 0.0007$**** | $F(1, 76) = 2.12$, $p = 0.146$ |
| Response type | $F(1, 76) = 1.04$, $p = 0.307$ | **$F(1, 76) = 11.13$, $p = 0.0008$**** |
| Group x Task | $F(1, 76) = 0.003$, $p = 0.959$ | $F(1, 76) = 0.22$, $p = 0.64$ |
| Group x Response type | $F(1, 76) = 0.09$, $p = 0.76$ | $F(1, 76) = 0.1$, $p = 0.758$ |
| Task x Response type | $F(1, 76) = 0.56$, $p = 0.456$ | $F(1, 76) = 0.02$, $p = 0.89$ |
| Group x Task x Response type | $F(1, 76) = 0.01$, $p = 0.916$ | $F(1, 76) = 0.12$, $p = 0.727$ |

*$p < 0.05$; **$p < 0.01$

Values in boldface represent significant effects.

**Table 4.8** Spearman's correlations ($r_s$) between speech-in-noise (SiN) performance and Nogo ERP measures.

| | **SiN Performance at 5-dB SNR** | | |
|---|---|---|---|
| **Nogo ERP measures** | ***All (n = 21)*** | ***TIN (n = 11)*** | ***CTR (n = 10)*** |
| ***N2 Latency*** | -0.25 | **-0.68*** | 0.53 |
| ***N2 Amplitude*** | -0.13 | 0.04 | -0.52 |
| ***P3 Latency*** | -0.11 | -0.23 | -0.01 |
| ***P3 Amplitude*** | 0.1 | 0.11 | 0.29 |

*****$p < 0.05$; Values in boldface represent significant correlations.
CTR, control group; ERP, event-related potential; SNR, signal-to-noise ratio; TIN, tinnitus group.

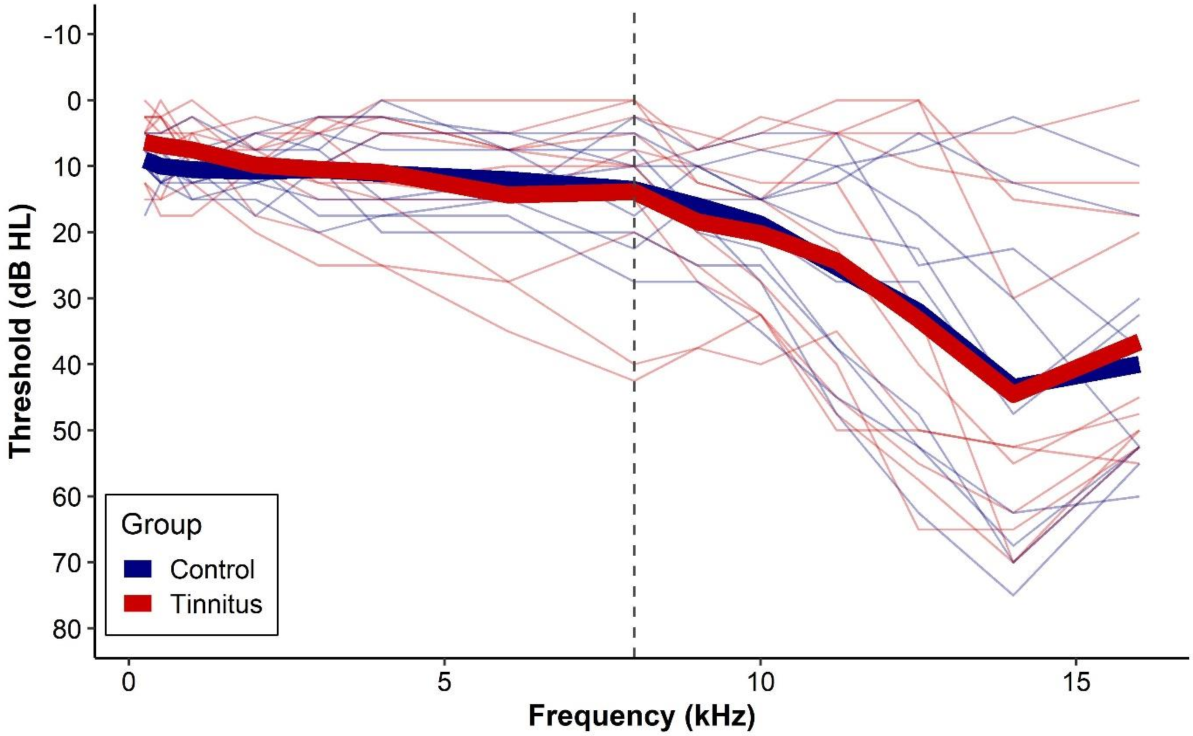


**Figure 4.1** Mean hearing thresholds (thick lines) and individual hearing thresholds (thin lines) from 0.25 to 16 kHz in both ears. The dashed line indicates the cutoff (8 kHz) between conventional testing frequencies and extended high frequencies.

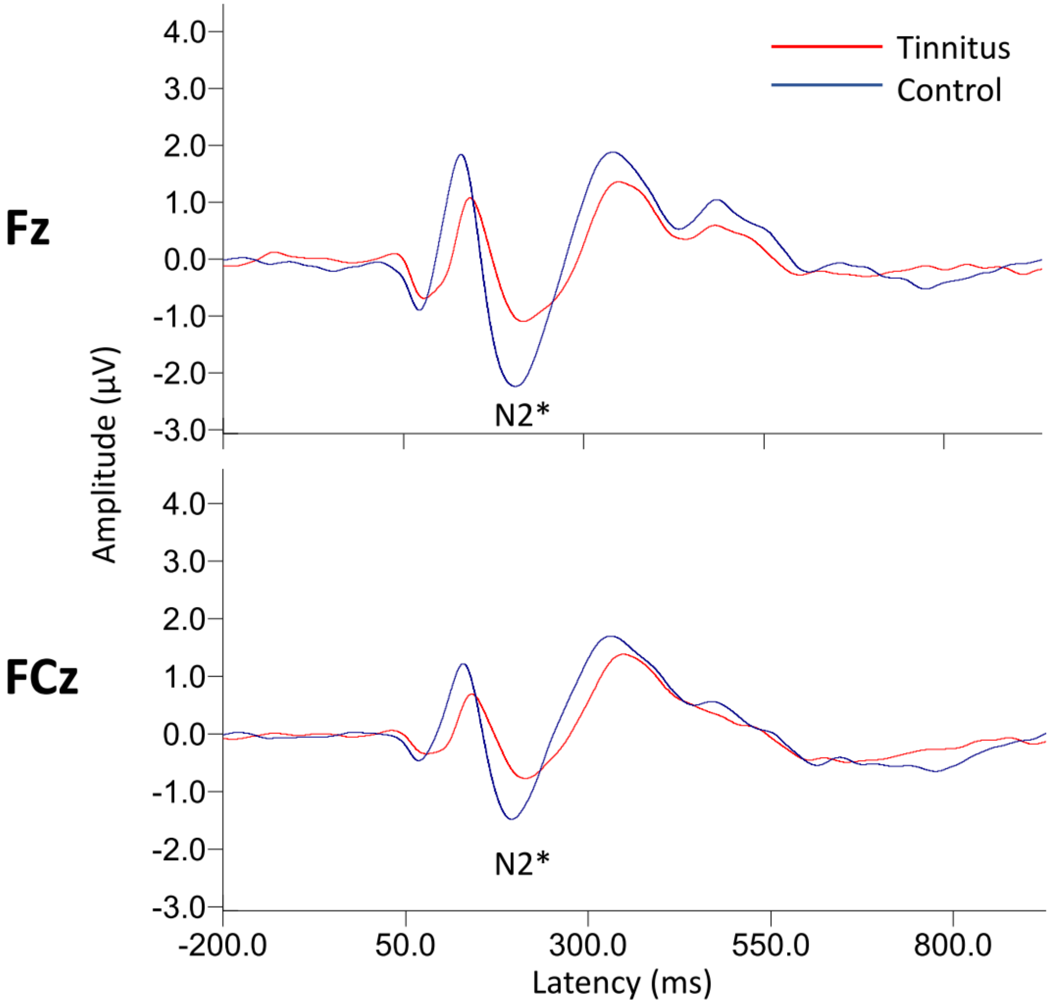


**Figure 4.2** Grand average ERPs at the Fz and FCz electrodes, separated by group. At both electrodes, the N2 component showed significantly longer latency and lower amplitude in the tinnitus group than in the control group (marked with an asterisk). The latency or amplitude of the P3 component at either electrode did not show a significant between-group difference.

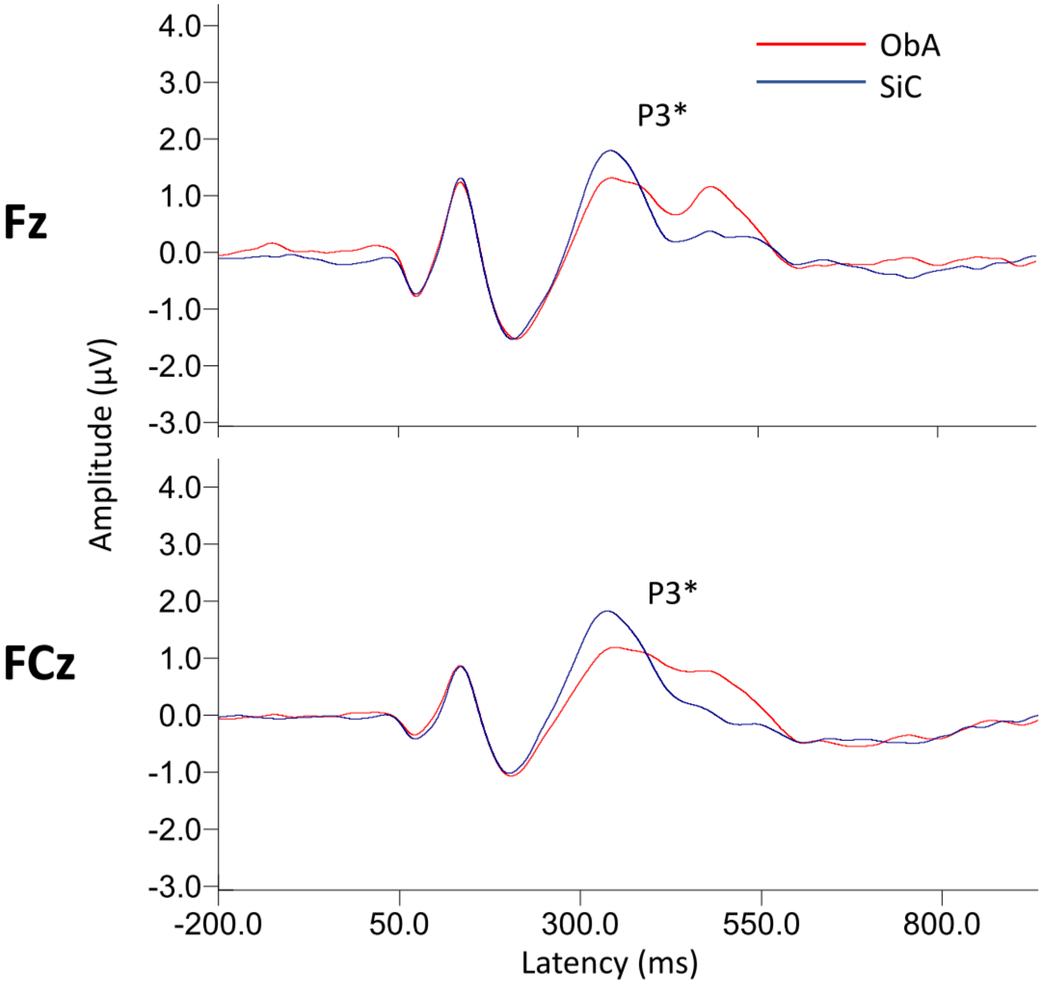


**Figure 4.3** Grand average ERPs of both tinnitus and control groups at the Fz and FCz electrodes, separated by the task. At both electrodes, P3 showed significantly longer latency in the object-animal task (ObA) than in the single-car task (SiC), which is marked with an asterisk. The latency and amplitude of the N2 component were comparable between the two tasks.

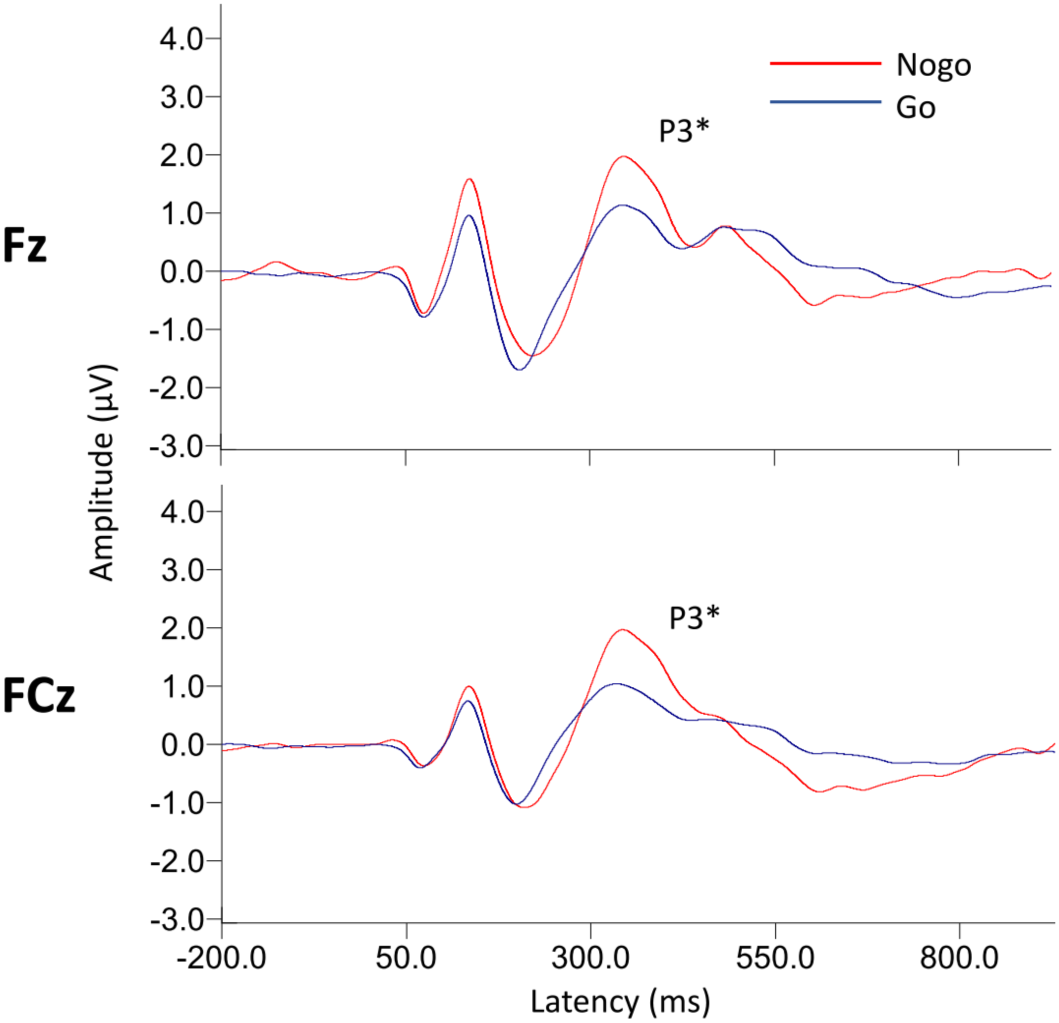


**Figure 4.4** Grand average ERPs of both tinnitus and control groups at the Fz and FCz electrodes, separated by the response type. At both electrodes, P3 showed a significantly larger amplitude to the Nogo than to the Go stimuli (marked with an asterisk). The latency and amplitude of the N2 component were comparable between the response types.

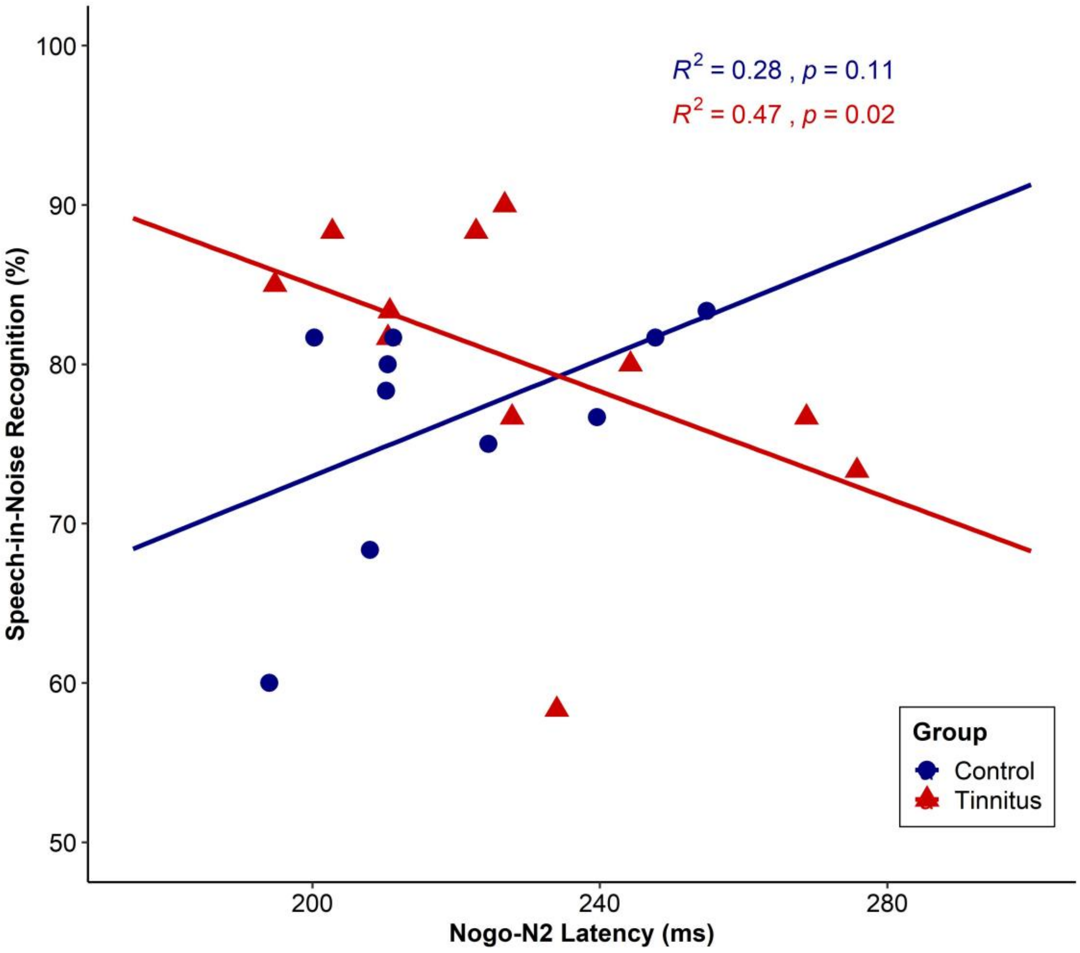


**Figure 4.5** Scatter plot showing N2 latency at the Nogo condition and speech-in-noise recognition at 5-dB SNR, separated by group. The regression lines indicated that 28% and 47% of the variance in speech-in-noise recognition were explained by Nogo-N2 latency in the control and in the tinnitus group, respectively. Longer Nogo-N2 latency significantly related to poorer speech-in-noise recognition in the tinnitus group, but not in the control group.

# CHAPTER 5: CONCLUSION

## 5.1 General Discussion

Using multimodal approaches, the three studies in this dissertation aimed to investigate the relationship between cognitive control and SiN performance in individuals with tinnitus, especially in those with normal hearing. The main findings were: 1) the effect of tinnitus on SiN recognition may involve higher-level cognitive functioning rather than processing solely at the perceptual level, 2) an altered relationship between SiN performance and GM volume in auditory and cognitive processing regions was evident in those with chronic tinnitus, and 3) inhibitory control was important for SiN recognition in individuals with tinnitus, and neural alterations related to inhibitory control can be detected in tinnitus even with intact SiN performance.

### *Behavioral Measures: SiN and Neuropsychological Tests*

The main outcome measure of SiN performance varied slightly in each study, aiming to differentiate individuals with tinnitus from those without by challenging one's SiN ability. The difficulty of the task increased from Study 1 to 3 gradually: 1) Study 1 focused on consonant recognition in noise, with more scoring items that potentially improve SiN performance than using word recognition, 2) Study 2 involved sentence recognition at 5-dB SNR following the presentation of an easier 10-dB SNR condition, and 3) Study 3 contained sentences presented at a fixed 5-dB SNR, tagging attention allocation to the target talker in a challenging listening condition. Surprisingly, SiN performance in individuals with tinnitus and normal or near-normal hearing did not significantly differ from that in hearing-matched controls in any study. Moreover, in Study 3, a between-group difference was not found in any neuropsychological task or the Go/Nogo task. Taken together, the finding not only underpins the assumption that behavioral measures alone may not reflect cognitive control or SiN deficits (Getzmann et al., 2015), especially in individuals with normal hearing but also indicates modified approaches of SiN tests that incorporate spatial or reverberation conditions are warranted for future studies (Brungart et al., 2014; Phatak et al., 2018).

### ***Objective Measures: Linking the Neuroanatomical and the Electrophysiological Studies***

Response inhibition to irrelevant stimuli such as environmental noise or tinnitus requires the activation of a common neural network, which includes the ACC, dorsolateral prefrontal gyrus, IFG, posterior parietal cortex, and pre-supplementary motor area (Aron, 2011; Lustig et al., 2007; Menon et al., 2001; Mostofsky & Simmonds, 2008; Nee et al., 2007; Rubia et al., 2001; Sylvester et al., 2003). In addition to being part of the core speech network for speech processing (Harris et al., 2009; Peelle, 2018; Peelle & Wingfield, 2016), bilateral IFG are important for a variety of high-level cognitive functions such as for the maintenance of stimuli in WM and error processing (Menon et al., 2001; Mostofsky & Simmonds, 2008). Several task-based fMRI studies have confirmed the activation of bilateral IFG during Go/Nogo tasks. For example, it has been found that the right IFG involves the inhibition of inappropriate response (Goghari & MacDonald, 2009; Nee et al., 2007) and the orientation of attention to task-relevant stimuli in Go/Nogo tasks (Aron, 2011; Simmonds et al., 2008), whereas the left IFG relates to response selection of task-relevant stimuli (Goghari & MacDonald, 2009). Accordingly, in individuals with tinnitus, if the reduced GM volume in bilateral IFG is indeed due to constant recruitment of IFG (Study 2), then it is conceivable that the inefficient usage of cognitive capacity results in alterations of cognitive control, manifested by prolonged latency and reduced amplitude of the N2 component (Study 3). Further studies that include fMRI and Go/Nogo tasks in a tinnitus cohort can be beneficial to verify the assumption.

### ***Confounding Factors***

In addition to the confounding factors such as age, hearing acuity, or emotional states (depression and anxiety) that are commonly reported to affect cognitive control abilities in tinnitus (Andersson & McKenna, 2006; Clarke et al., 2020), one should consider factors that can potentially moderate or mediate the relationship between cognitive control and SiN performance in the tinnitus population (Andersson & Westin, 2008). For example, sleep deprivation can cause fatigue, making a cognitive task more effortful, and reducing one's motivation to perform well (Massar et al., 2019). Among individuals with chronic tinnitus, up to 73% develop insomnia due to negative emotion to tinnitus and constantly worrying about the sleep quality (Cronlein et al., 2016; Crönlein et al., 2007). Additionally, insomnia was found to be more common among individuals with tinnitus than those without (Lasisi & Gureje, 2011). Thus, one might query that insomnia can mediate any between-group differences observed in a tinnitus study. A comprehensive evaluation of tinnitus and how tinnitus can impact daily activities may require considering the interaction between tinnitus and one's environment in an ecological framework (Searchfield, 2014). In other words, a better understanding of the relationship between cognitive control and SiN performance in tinnitus requires a multidisciplinary work.

## 5.2 Future Directions

Understanding the relationship between cognitive control and SiN performance in the tinnitus population has a potential significance in advancing cognitive control training for improving patients' quality of life. Clinically, psychological therapies focusing on cognitive control of emotion (e.g., Cognitive Behavioral Therapy and the Mindfulness-Based Cognitive Therapy) have been used to reduce one's emotional reaction to distressing tinnitus (McKenna et al., 2020). As a novel tinnitus treatment approach, cognitive training program for auditory or visual attention has been shown to increase functional connectivity of brain regions in cognitive control networks, to reduce the severity of tinnitus, and to improve the performance of memory or attentional tasks (Kallogjeri et al., 2017; Spiegel et al., 2015; Wise et al., 2016). Moreover, Krick et al. (2015, 2017) found that individuals with tinnitus who underwent a neuro-music therapy that comprises auditory attention control task had increased GM density in frontal and auditory cortices, and decreased omission errors of a visual Go/Nogo task, although the therapeutic effect is more pronounced in chronic than in recent-onset tinnitus. However, it should be noted that the improvement after a cognitive training might result from the reduction of psychological distress, as a successful cognitive training also requires proper support of fulfilling individuals' emotional and social needs (Diamond & Ling, 2016). Although training on both cognitive control of attention and emotion might improve one's everyday performance, the potential benefit of such training on SiN recognition in individuals with tinnitus remains to be explored.

In conclusion, the findings of this dissertation research confirmed the potential benefit of incorporating multimodal approaches to examine neuroanatomical or neural alterations before behavioral changes can be detected. Further, the findings serve as the baseline for future endeavors to explicitly investigate the effect of tinnitus and hearing loss on aging, while controlling for tinnitus duration and severity. Because tinnitus is a heterogeneous disorder regarding its etiology and effect, a better understanding of how tinnitus with varying hearing profiles impact cognitive control abilities and SiN performance can be invaluable in developing patient-specific treatment strategies.

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