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The sounds we are not measuring

How tinnitus and hearing thresholds above 8 kHz relate to cognitive performances

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The sounds we are not measuring

This thesis presents four studies examining cognitive performance in individuals with and without tinnitus. In total, 89 participants with tinnitus and 89 control participants without tinnitus (matched for age, sex and educational level) were variously assessed on measures of tinnitus severity, hearing, anxiety, depression, executive attention, working memory and performance and perceived exertion on an office-like task.

No significant relationships were observed between tinnitus and poorer cognitive performances, when controlling for hearing status, age, sex, educational level, anxiety and depression. However, all three studies including measures of hearing thresholds at frequencies currently not included in the standard clinical audiological test battery showed significant relationships between hearing ability at 10 to 16 kHz and cognitive performances. Specifically, better high frequency hearing is associated with better cognitive performances, regardless of presence of tinnitus. These findings have clinical implications for future management of individuals with (and without) tinnitus experiencing cognitive difficulties.

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Sebastian Waechter

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle
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How tinnitus and hearing thresholds above 8 kHz relate to cognitive performances

Abstract

Background

Tinnitus sufferers commonly report experiencing cognitive difficulties due to their tinnitus. In line with such reports, previous research has shown poorer performances on behavioural cognitive tests in tinnitus sufferers compared to control subjects without tinnitus. However, those studies have not ruled out the potentially confounding effects of hearing status on cognitive performance. As there are currently no evidence-based interventions available for tinnitus sufferers experiencing cognitive difficulties, it is important to distinguish the underlying cause for self-reported cognitive difficulties in adults with tinnitus in order to enable future interventions for this patient group.

Aim

To investigate whether tinnitus is associated with cognitive performance after controlling for hearing status.

Methods

In a series of two case control studies and two cross sectional studies, adults with tinnitus (tinnitus groups) and adults without tinnitus (control groups) with and without hearing impairment were matched for age-, sex- and education, and were assessed on measures of executive attention, working memory (WM), and performance and perceived exertion on an office-like task.

Results

Tinnitus per se was not associated with cognitive performance in executive attention, WM or performance or perceived exertion on an office-like task in adults with or without hearing impairment up to 8 kHz. Hearing thresholds at 10 to 16 kHz however, returned significant corrections in the analyses of WM and performance on an office-like task.

Conclusions

In contrast to previous research limited by lack of control for hearing status, the present project showed tinnitus was not associated with poorer cognitive performance. Instead, significant corrections for high frequency hearing thresholds identified in the analyses of WM and performance on an office-like task suggest cognitive performance was associated with hearing thresholds at 10 to 16 kHz in adults with and without tinnitus. These findings identify the need for clinicians and researchers to assess hearing thresholds above 8 kHz in adults reporting tinnitus as associated impairments in cognitive performances could be associated with high frequency hearing impairment and not with the tinnitus itself. These findings, if further corroborated, may also open up for new interventions among tinnitus sufferers with cognitive difficulties.

Key words
Tinnitus, Hearing, Normal Hearing, Hearing Impairment, Hearing Loss, Extended High-Frequency (EHF) Hearing, Cognitive Performance, Cognitive Function, Working Memory, Executive Attention

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MADE IN SWEDEN

In memory of all the hours I’ve spent on this project

may they rest in peace, and serve as soil for whatever comes next

TABLE OF CONTENTS

ABBREVIATIONS

ANCOVA – Analysis of Covariance

ANOVA – Analysis of Variance

BEHFPTA – Best Ear High Frequency Pure Tone Average (at 10, 12.5, 14 and 16 kHz)

BEPTA – Best Ear Pure Tone Average (at 0.5, 1, 2 and 4 kHz)

dB HL – Decibel Hearing Level

GBD – Global Burden of Disease

HADS – Hospital Anxiety and Depression scale

HADSA – HADS Anxiety subscale

HADSD – HADS Depression subscale

kHz – kilo Herz

MANCOVA - Multivariate Analysis of Covariance

PSQI – Pittsburg Sleep Quality Index

SD – Standard Deviation

THI – Tinnitus Handicap Inventory

TQ – Tinnitus Questionnaire

RCS – Rate Correct Score

RPE – Rating of Perceived Exertion

WHO – World Health Organization

WM – Working Memory

LIST OF PUBLICATIONS

Study I

Waechter, S., & Brännström, K. J. (2015). The impact of tinnitus on cognitive performance in normal-hearing individuals. Int J Audiol, 54(11), 845-851. doi:10.3109/14992027.2015.1055836

Study II

Waechter, S., Hallendorf, L., Malmstein, E., Olsson, A., & Brännström, K. J. (2019). The impact of tinnitus on n-back performance in normal hearing individuals. J Am Acad Audiol, 30(3), 169-177. doi:10.3766/jaaa.17048

Study III

Waechter, S., Wilson, W. J., & Brännström, K. J. (2020). The impact of tinnitus on working memory capacity. Int J Audiol, *accepted for publication*.

Study IV

Waechter, S., Wilson, W. J., Magnusson, M., & Brännström, K. J. (2020). The impact of tinnitus on performance and perceived exertion on an office-like task. *Submitted manuscript under review*.

THESIS AT A GLANCE

Table 1. Overview of aims, materials, sample sizes, designs, results and conclusions for each study of the present PhD project.

	Study I	Study II	Study III	Study IV
Aim	To determine if tinnitus was associated with executive attention in normal hearing adults.	To determine if tinnitus was associated with WM capacity in normal hearing adults.	To determine of tinnitus was associated with WM capacity in adults with normal hearing and adults with hearing impairment.	To determine if tinnitus was associated with performance and perceived exertion on an office-like task in adults with normal hearing and adults with hearing impairment.
Material	Visual Stroop test, HADS, TQ	N-back test, HADS, TQ	N-back test, HADS, THI	Sök 1, Borg CR10, HADS, THI
Sample size	40 normally hearing adults, 20 with and 20 without tinnitus.	62 normally hearing adults, 31 with and 31 without tinnitus.	76 adults, 38 normally hearing and 38 with hearing impairment, with each group including 19 adults with and 19 without tinnitus.	As per Study III.
Design	Case-control study. Groups matched for age, sex and educational level.	Case-control study. Groups matched for age, sex and educational level.	Two group cross-sectional research design. Groups matched for age, sex and educational level.	Two group cross-sectional research design. Groups matched for age, sex and educational level.
Results	Executive attention performance was similar for normally hearing adults with tinnitus versus those without tinnitus.	WM performance was similar for normally hearing adults with tinnitus versus those without tinnitus. WM was negatively associated with hearing thresholds at 10 to 16 kHz regardless of tinnitus.	WM performance was similar for normally hearing adults and adults with hearing impairment with tinnitus versus those without tinnitus. The analysis was significantly corrected for hearing thresholds at 10 to 16 kHz.	Performance and perceived exertion on an office-like task was similar for normally hearing adults and adults with hearing impairment with tinnitus versus those without tinnitus. The analysis for task performance was significantly corrected for hearing thresholds at 10 to 16 kHz.
Conclusion	Executive attention was not associated with tinnitus in normally hearing adults. The previously reported negative effect of tinnitus on executive attention may be caused by comorbid hearing impairments, rather than presence of tinnitus.	WM was not associated with tinnitus in normally hearing adults. The previously reported negative effect of tinnitus on WM may be caused by comorbid hearing impairments, rather than presence of tinnitus. Hearing thresholds at 10 to 16 kHz may play a critical role for WM capacity.	WM was not associated with tinnitus in normally hearing adults or adults with hearing impairment. Hearing thresholds at 10 to 16 kHz were associated with WM regardless of the presence of tinnitus.	Performance and perceived exertion on an office-like task was not associated with tinnitus in normally hearing adults or adults with hearing impairment. Hearing thresholds at 10 to 16 kHz were associated this performance regardless of the presence of tinnitus.

LAY SUMMARY

Tinnitus sufferers, clinicians and researchers have assumed that the presence of tinnitus impairs cognitive performances: tinnitus sufferers because they experience it, clinicians because their patients report it, and researchers because they have observed worse cognitive performance in tinnitus sufferers compared to individuals without tinnitus. All have come to the same conclusion that tinnitus can affect cognitive abilities, with the most popular hypothesis of the underlying mechanism seeming intuitive – constantly having to suppress tinnitus taxes our finite amount of cognitive resources.

However, the majority of tinnitus sufferers also have some degree of hearing impairment, and hearing impairment also seems to negatively affect cognitive performance. Therefore, in order to fully explore the potentially negative effects of tinnitus on cognitive performance, we have to carefully control for hearing status. The realization that previous studies investigating the link between tinnitus and cognitive performance have failed to carefully control for hearing status is what motivated the present PhD project.

In my PhD project, I conducted two studies on adults with normal hearing thresholds up to 8 kHz with and without tinnitus to investigate the possible effects of tinnitus on executive attention and working memory. I then conducted two studies on adults with normal hearing thresholds up to 8 kHz and adults with hearing impairment with and without tinnitus to investigate the possible effects of tinnitus on working memory and performance and perceived exertion on an office-like task. In all of these studies, I carefully matched the participants for age, sex and educational level.

When measuring cognitive performances in tinnitus sufferers and individuals without tinnitus, and controlling carefully for hearing status, anxiety, depression, age, sex and educational background, the trend was clear: the presence or absence of tinnitus could not be shown to be associated with cognitive performance. What was associated with cognitive performance was something commonly disregarded by tinnitus sufferers, clinicians and researchers: hearing thresholds above 8 kHz. Hearing status in this specific frequency region was strongly associated with cognitive performance regardless of tinnitus, yet such high frequencies are rarely measured clinically or in research. The findings of my PhD project argue that all clinicians and researchers should assess hearing above 8 kHz in adults reporting tinnitus as any associated impairments in cognitive performance could be associated with high frequency hearing impairment rather than with the tinnitus itself.

PREFACE

Imagine being at a concert with your friends. When enjoying the company, the music, and the energy in the air at this specific venue, you might not act your wisest. You might be at the front, making sure not to miss anything of what is going on at the stage, not caring about the sound level or the fact that you forgot to bring your hearing protection. After the last song, the sound environment gets gradually calmer – conversations among your friends go from ecstatic to content, the traffic sounds from the city fade out as you get closer to your home. You shut the outer world out when closing the door to your home, but it never gets entirely quiet. As external sounds gradually become less intense, you start noticing a tone that keeps ringing in your ears. You have experienced this before, and are admitting to yourself that you might have been a hair too close to the loudspeakers at the concert, but you stay calm as it usually goes away over the next couple of days. However, this time, the sound keeps ringing, and as days turn into weeks, the absence of silence is slowly starting to eat you from the inside.

This is one of many ways you can get tinnitus, a hearing related condition suspected to affect more than 1 in 10 adults. For most people it is manageable to live with a constant sound in their head, for others the sound experience has clear negative effects on every-day life and well-being. One of the most common complaints among tinnitus sufferers is the experience of cognitive difficulties; that it gets harder to concentrate at work when having to deal with a source of noise you cannot turn down or shut out. Currently there are no evidence-based interventions for this specific problem among tinnitus sufferers, and previous research on the link between tinnitus and cognitive difficulties have several shortcomings hindering establishment of such interventions at the time of writing.

The present PhD project aims to take us one-step closer to understanding the isolated effect presence of tinnitus has on cognitive performance. This was done in a series of four studies, where I compared a range of cognitive aspects in tinnitus sufferers and well matched control participants, controlling carefully for age, educational background, anxiety, depression and hearing status, as these are factors known to impact cognitive performance and differ in tinnitus sufferers compared to the general population.

BACKGROUND

Prevalence and physiology of tinnitus

Tinnitus is defined as the experience of an internal sound in absence of external acoustic source (i.e. a phantom sound experience), often described by the sufferer as ringing or buzzing sounds perceived in one or both ears or inside the head. This is believed to be one of the world's most common known hearing related conditions in adults, suspected to affect about 15% of all adults (Andersson, Baguley, McKenna, & McFerran, 2005). However, prevalence figures vary between 5 and 43% depending on how tinnitus is defined and diagnosed (McCormack, Edmondson-Jones, Somerset, & Hall, 2016). In addition, some members of society are more likely than others to experience tinnitus. The most pronounced difference across society seems to be related to excessive sound exposure, as there is a 12 to 70% prevalence of tinnitus among individuals working in environments with high sound pressure levels compared to the 2 to 14% prevalence among individuals working in quieter environments (Axelsson & Prasher, 2000; Poole, 2010). Apart from this, smokers, individuals with diabetes mellitus, dyslipidaemia, hypertension or a BMI > 30 also seem to be significantly more likely than others to experience tinnitus (Shargorodsky, Curhan, & Farwell, 2010).

While tinnitus is often referred to as a disease, it is more accurate to describe it as a symptom which can occur due to several different underlying causes. As previously mentioned, excessive sound exposure is a primary risk factor for tinnitus, which has drawn attention to the link between hearing impairment and tinnitus. The exact aetiology of tinnitus due to cochlear damage is still debated, but there are indications regarding what underlying causes might result in tinnitus and why. The most popular hypothesis seems to be that malfunctioning neural plasticity after cochlear damage results in increased neural synchrony and spontaneous firing rates of auditory neurons, which could generate a phantom sound experience (see Shore, Roberts, & Langguth, 2016 for review).

Even though cochlear damage seems to be the most common underlying cause for tinnitus, phantom sound experiences may also be experienced due to a range of different causes (see *figure 1* for visualization) such as;

a) *other otological conditions* (e.g. otosclerosis [Deggouj, Castelein, Gerard, Decat, & Gersdorff, 2009], chronic otitis media [Acikalin, Haci, Altin, & Alimoglu, 2019; Guo, Sun, & Wang, 2018; Kim et al., 2011], superior canal dehiscence [Ward, Carey, & Minor, 2017], Ménière’s disease [Herraiz, Tapia, & Plaza, 2006; Lopez-Escamez et al., 2015]),

b) *cardiovascular and cerebrovascular conditions* (e.g. fibromuscular dysplasia [Foyt, Carfrae, & Rapoport, 2006; Raj, Gandhi, & Katzen, 2012], carotid stenosis [Carlin, McGraw, & Anderson, 1997; Emery, Ferguson, & Williams, 1998; Kirkby-Bott & Gibbs, 2004], aneurysm [Cuellar et al., 2018; Depauw, Caekebeke, & Vanhoenacker, 2001; Kim, Kim, & Lee, 2018], sinus thrombosis [Schütt, Jansen, Fehrmann, & Holz, 1998; Sigari, Blair, & Redleaf, 2006], high jugular bulb [Sayit, Gunbey, Fethallah, Gunbey, & Karabulut, 2016; Weiss, Zahtz, Goldofsky, Parnes, & Shikowitz, 1997], arteriovenous malformations [Önerci, 2009], microvascular compression [De Ridder et al., 2012], benign intracranial hypertension [Meador & Swift, 1984]),

c) *tumours* (e.g. vestibular schwannoma [Baguley, Humphriss, Axon, & Moffat, 2006; May, Ramachandran, & Cacace, 2011], glomus jugulare tumour [Fayad, Keles, & Brackmann, 2010; Gerosa et al., 2006; Hafez, Morgan, Fahmy, & Hassan, 2018; Liscak et al., 2014], glomus tympanicum [Devuyst, Defreyne, Praet, Geukens, & Dhooge, 2016; Misale, Lepcha, & Tyagi, 2018]),

d) *head trauma* (Vernon & Press, 1994),

e) *temporomandibular joint disorders* (Ralli et al., 2018),

f) *medication including ototoxic substances* (e.g. acetylsalicylic acids and loop diuretics [Koegel, 1985], cisplatin [Frisina et al., 2016], amikacin [Black, Lau, Weinstein, Young, & Hewitt, 1976; Melchionda et al., 2013], kanamycin [Frost, Hawkins, & Daly, 1960], erythromycin [Swanson et al., 1992], quinine [Roche et al., 1990]),

g) *muscular tension in neck and jaw* (Sanchez & Rocha, 2011), and

h) *cervical spine dysfunction* (Michiels, van de Heyning, Truijen & de Hertogh, 2015).

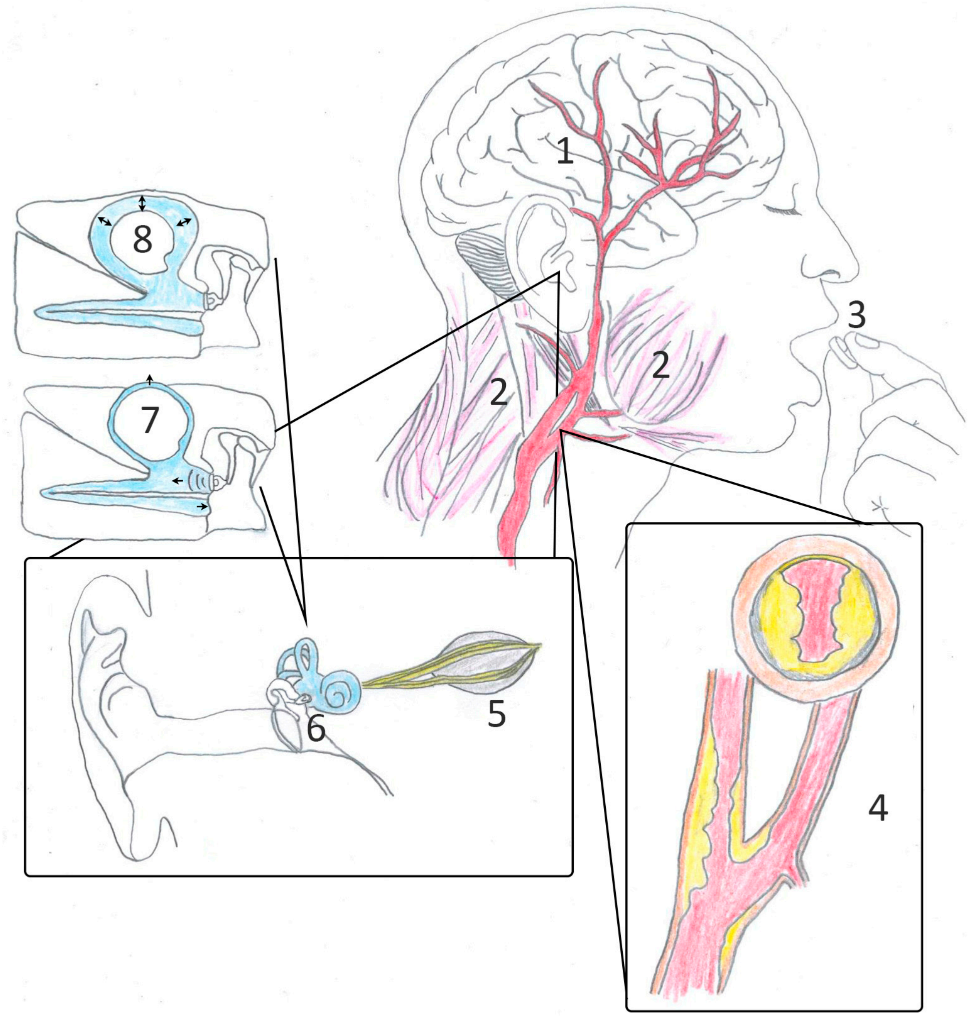

Figure 1. Examples of underlying causes to tinnitus. 1) malfunctioning neural plasticity after cochlear damage, 2) tension in neck and jaw muscles, 3) medication, 4) carotid stenosis, 5) vestibular schwannoma, 6) otosclerosis, 7) superior canal dehiscence, 8) Ménières disease. Illustration: S. Waechter.

Consequences of tinnitus

Consequences for the individual tinnitus sufferer

Tinnitus affects people differently, both in terms of tinnitus severity (i.e. how distressing, annoying or disabling tinnitus is for the individual tinnitus sufferer, see McCormack et al., 2016 for review) and what kind of problems the tinnitus sufferer experiences (see Hall et al., 2018 for review). Many individuals with tinnitus are not bothered at all, while 3 to 31% of individuals with tinnitus experience clear negative impact on their every-day life (McCormack et al., 2016), some even to a suicidal extent (Aazh & Moore, 2018).

The most commonly reported difficulties due to tinnitus are anxiety, depression, sleeping difficulties, and cognitive difficulties (Hall et al., 2018). Several research groups have been trying to investigate if and how tinnitus affects cognitive performance in particular, which identifies many questions that need to be answered in order to enable establishment of evidence based interventions for tinnitus sufferers experiencing cognitive difficulties.

Monetary societal cost

Tinnitus can be a personal tragedy for the individual tinnitus sufferer, but the prevalence of tinnitus, and shortcomings in strategies of treatment thereof, affect us all. To date, the only research article covering the overall societal cost of tinnitus was reported by Maes, Cima, Vlaeyen, Anteunis and Joore (2013). These researchers estimated that tinnitus burdens the economy of the Netherlands with about 6.8 billion € yearly, of which only about 1.9 billion € are attributed to health care costs. That is equivalent to approximately 1% of the Netherlands Gross Domestic Product (GDP) at the year of investigation. To put the findings into context, the Netherlands is assumed to have a tinnitus prevalence comparable to most western countries and has no clear deviations in terms of strategies for tinnitus care. Hence, while the evidence for overall societal cost due to tinnitus is so far scarce (relying on one study only), the findings could be applicable for many western nations.

Current clinical management

There are several clinical guidelines for tinnitus management available (e.g. Cima et al., 2019; Ogawa et al., 2020; Tunkel et al., 2014). Generally, they are recommending to:

a) perform a physical examination to detect the underlying cause of tinnitus,

b) perform audiological assessment, if the patient reports hearing difficulties,

c) screen for bothersome tinnitus, typically done with a questionnaire targeting tinnitus related distress such as the Tinnitus Handicap Inventory (THI; Newman, Jacobson, & Spitzer, 1996) or the Tinnitus Functional Index (TFI; Henry et al., 2014),

d) provide information about tinnitus and treatment options, typically the Tinnitus Retraining Therapy (TRT; Jastreboff & Hazell, 2004),

e) fit the patient with hearing aids if they have a hearing impairment, and

f) let the patient undergo tinnitus adapted cognitive behavioural therapy (CBT) in order to cope with the phantom sound experience.

Worth noting is that the recommended treatments tend to be symptomatically oriented rather than causally oriented. The reason for this is there is no universal treatment that alleviates or cures tinnitus in all cases (McFerran, Stockdale, Holme, Large, & Baguley, 2019). One of the contributing causes to this is that the patients, as previously mentioned, are actually suffering from different conditions that have in common the symptom of tinnitus (a phantom sound experience). Tinnitus patients are falsely regarded as a homogenous group not only in society generally, but also often in the clinic and research settings specifically. A considerable part of tinnitus treatment trials seems to disregard tinnitus aetiology when evaluating the efficacy of a tinnitus treatment. This leads to potentially highly effective treatments for specific subtypes of tinnitus being discarded if they show modest results for the entire tinnitus population. Despite there being many known possible underlying causes for tinnitus (see examples under *Prevalence and physiology of tinnitus*, and in *figure 1*), a majority of tinnitus patients seem to be told that there is nothing one can do to help their tinnitus, and the underlying cause of their tinnitus is not fully examined (Husain, Gander, Jansen, & Shen, 2018).

Another problem is that the outcome measure of tinnitus treatments both in clinic and research is typically a questionnaire targeting general subjective experiences of tinnitus distress, or possibly an additional measure of subjective tinnitus loudness as measured by a visual analogue scale (Cima et al., 2020). This is problematic as tinnitus sufferers experience different difficulties due to their tinnitus, such as sleeping difficulties or cognitive difficulties. Actual measurements of sleep quality or cognitive performance pre and post intervention are rarely made, instead treatments are evaluated only based on their ability to lower the scores on a questionnaire indicative of subjective tinnitus distress. Thus, we will not be able to determine what intervention is suitable for the different, specific tinnitus related difficulties. It is also problematic to mainly rely on tinnitus questionnaires targeting general tinnitus distress when determining which patients to prioritize for management. Tinnitus patients experiencing major difficulties in only a single domain are at risk of being deprioritized in the clinic if the single domain (no matter how severely it affects them) makes up a too small a proportion of the topics covered in the questionnaire. In addition, different topics make up different proportions of different tinnitus questionnaires (Kennedy, Wilson, & Stephens, 2004), which in reality means that the individual tinnitus sufferer's chances of being prioritized is also dependent on what questionnaire their local clinic has chosen to use for grading their level of tinnitus severity.

As a result of the problems discussed above, clinics are left with limited tools to manage the individual tinnitus sufferer. With a few exceptions (e.g., tinnitus due microvascular compression of the cochlear nerve, characterized by its clicking typewriter-like sound experience, which seems to be curable by carbamazepine; [Mardini, 1987]), clinicians simply do not know what tinnitus characteristics motivate a certain treatment over another, and they rarely know what treatment will yield the best results for a specific tinnitus related difficulty. Due to this, clinics do not seem to rigorously follow a given guideline, but rather over time establish their own local strategy for tinnitus care based on local tradition, economic conditions and medical knowledge. Cima et al. (2020) reported findings in line with this, as their survey showed considerable differences among tinnitus healthcare professionals ("clinical experts, researchers and policy-makers involved in national tinnitus healthcare and decision-making") in northern, southern and eastern Europe in terms of opinions regarding what tinnitus is, how it is diagnosed and treated. The mean time between medical discovery and broad clinical implementation is estimated to be about 17 years (Morris, Wooding, & Grant, 2011), and tinnitus care does not seem to be an exception. Taken together, even though tinnitus research admittedly has a long way to go before solving some of the fundamental issues with tinnitus, there is a lot of generated knowledge which could benefit the patient group that is yet to be implemented at the clinic level.

Previous research on the link between tinnitus and cognitive performance

Previous findings

The general strategy adopted in previous studies assessing the effect of tinnitus on cognitive performance has been to compare individuals with tinnitus and control subjects without tinnitus on behavioural cognitive tests. Examination of cognitive performance have been done using tasks targeting the following abilities:

a) regulating one's responses in situations with conflicting information i.e. *executive attention* (Rueda, Posner, & Rothbart, 2005) (measured in tinnitus sufferers by Andersson, Eriksson, Lundh, & Lyttkens, 2000; Jackson, Coyne, & Clough, 2014; Leong et al., 2020; Stevens, Walker, Boyer, & Gallagher, 2007),

b) maintaining task-relevant information available for processing i.e. *working memory* (WM; Miyake & Shah, 1999) (measured in tinnitus sufferers by Rossiter, Stevens, & Walker, 2006),

c) "readiness to detect rarely and unpredictably occurring signals over prolonged periods of time" i.e. *sustained attention* (Sarter, Givens, & Bruno, 2001) (measured in tinnitus sufferers by Dornhoffer, Danner, Mennemeier, Blake, & Garcia-Rill, 2006; Hallam, McKenna, & Shurlock, 2004; Leong et al., 2020),

d) "capacity to maintain a state of alert arousal" i.e. *alerting attention* (Mezzacappa, 2004) (measured in tinnitus sufferers by Cuny, Norena, El Massioui, & Chery-Croze, 2004; Heeren et al., 2014), and

e) "orienting attention towards a specific set of entities or representations while ignoring others" i.e. *selective attention* (Vandierendonck, 2014) (measured in tinnitus sufferers by Hallam et al., 2004; Leong et al., 2020; Stevens et al., 2007).

The tendency seen in these studies is that tinnitus sufferers achieve similar scores as individuals without tinnitus across cognitive domains, but need slightly longer times to do so (Andersson et al., 2000; Dornhoffer et al., 2006; Hallam et al., 2004; Heeren et al., 2014; Jackson et al., 2014; Leong et al., 2020; Rossiter et al., 2006; Stevens et al., 2007). The most popular explanation for this is based on the habituation model of tinnitus by Hallam, Rachman and Hinchcliffe (1984). This model implies that tinnitus sufferers who do not manage to habituate the tinnitus sounds use cognitive resources to suppress tinnitus, which leaves them with less cognitive resources to spend on the actual cognitive task. See *figure 2* for visualisation of presumed relationship between tinnitus and cognitive difficulties, including possible confounding factors.

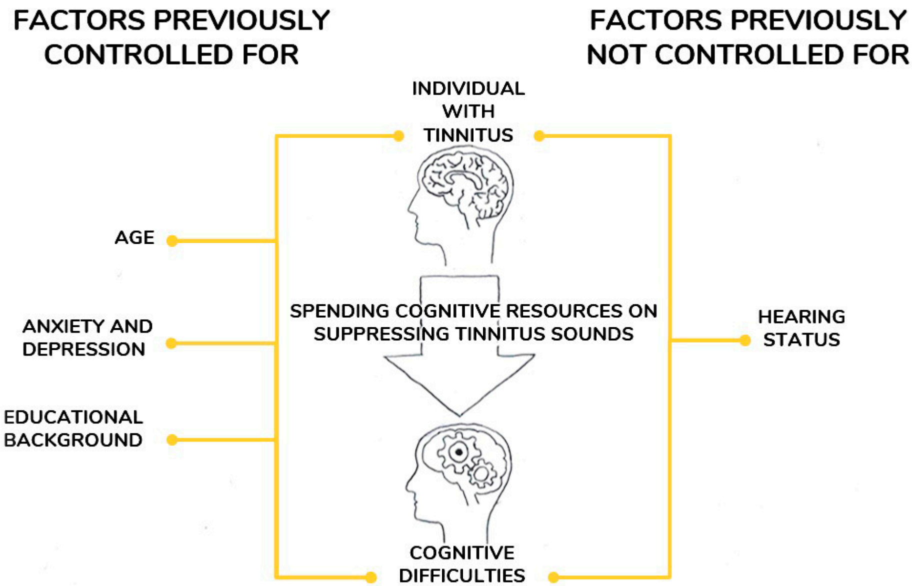

Figure 2. Presumed relationship between tinnitus and cognitive difficulties, including possible confounding factors. Illustration: S. Waechter.

Previously controlled possible confounders

The studies investigating the link between tinnitus and cognitive performance have identified, and controlled for, several possible confounders (see *figure 2*). Examples include age, anxiety and depression as well as educational background. Age has been identified as a possible confounder as tinnitus is more common in older individuals (Martinez, Wallenhorst, McFerran, & Hall, 2015; Shargorodsky, Curhan, Curhan, & Eavey, 2010), and ageing is associated with cognitive deterioration (i.e. decline in cognitive domains such as executive functions, processing speed, visospatial-, memory-, and language abilities [Bialystok & Craik, 2006; Harada, Natelson Love, & Triebel, 2013]). Anxiety and depression has been identified as possible confounders as those are psychological conditions which are often present in tinnitus sufferers and have been shown to be associated with worse performances on cognitive tests (Andersson, 2009; Cisler & Koster, 2010; Kaiser et al., 2003; Peckham, McHugh, & Otto, 2010; Rizzardo, Savastano, Maron, Mangialaio, & Salvadori, 1998). Education has been identified as a possible confounder as poorer education is a risk-factor for tinnitus (as individuals with lower levels of education on average work in noisier environments and are more often exposed to excessive noise levels [Axelsson & Prasher, 2000; Casey et al., 2017; Poole, 2010]), and longer education seems to be positively correlated with cognitive ability (i.e. longer education being associated with greater cognitive abilities [Falch & Massih, 2011; Hansen, Heckman, & Mullen, 2004; Winship, 1997]).

The neglected role of hearing impairment

About 90% of adult tinnitus sufferers are assumed to also have some sort of hearing impairment (Barnea, Attias, Gold, & Shahar, 1990; Sanchez, Medeiros, Levy, Ramalho Jda, & Bento, 2005). This association is well known and should not be a surprise as tinnitus often arises due to cochlear damage. Despite this, previous studies investigating link between tinnitus and cognitive performance have fully or partly disregarded hearing impairment as a variable (see Mohamad, Hoare, & Hall, 2016 for review). This may be a critical limitation as there is growing evidence suggesting hearing impairment is negatively associated with cognitive performance (see Uchida et al., 2019 for review).

The most common explanation for the choice not to include hearing as a parameter of interest when investigating the link between tinnitus and cognitive performance has focused on task modality. Researchers have argued that potential hearing impairments among participants would have minimal effect on task performance as the cognitive tasks have typically been presented visually (e.g. Heeren et al., 2014; Rossiter et al., 2006). While this may intuitively sound like an acceptable argument, Lin, Ferrucci, Metter, An, Zonderman and Resnick (2011) showed that hearing impairments are independently associated with poorer performance on the Stroop test (Stroop, 1935), which is the most commonly used cognitive test in the previous research on the link between tinnitus and cognitive performance. In the classic version of the Stroop test, the participant is presented with words describing colours with each word printed in a colour other than that described by the word (e.g. the word "green" printed in the colour red). For each presentation, the participant must report the text colour and not the text word.

Not only is hearing impairment associated with poorer task performance in cognitive tests, it has also been identified as the number one potentially modifiable risk factor for developing dementia (Livingston et al., 2017). This highlights the importance of healthy hearing status for maintaining cognitive capability.

Taken together, evidence suggests hearing impairments have long-term negative effects on cognitive performance regardless of task modality, and most tinnitus sufferers have some kind of hearing impairment. Hearing impairment should therefore be seen as a factor of particular interest when assessing cognitive performance in tinnitus sufferers, given the high comorbidity of tinnitus and hearing impairment.

Previous studies investigating the link between tinnitus and cognitive performance have either examined a tinnitus group with poorer hearing thresholds than their control group (either confirmed [Stevens et al., 2007], or highly suspected due to participant sampling [Andersson et al., 2000]), not measured their participants' hearing at all (Heeren et al., 2014; Jackson et al., 2014; Rossiter et al., 2006), or obtained audiograms from some or all of their participants but not used that data as a co-variate in their main data analysis (Cuny et al., 2004; Hallam et al., 2004; Leong et al., 2020). This has led to researchers raising awareness of the high risk of hearing status being a confounder in previous studies investigating the link between tinnitus and cognitive difficulties (Mohamad et al., 2016). While it is easy to argue that the approaches of previous studies to controlling for hearing status have been insufficient, solving this problem raises the challenge of determining how best to evaluate participant hearing. A first step towards better understanding the link between tinnitus and cognitive difficulties could be to investigate whether previous findings would be applicable for normal hearing individuals with and without tinnitus. In order to test if this is the case, we first have to answer the question: "what is normal hearing?".

According to the World Health Organization's (WHO) current classification, normal hearing is defined as having a mean hearing threshold of 25 dB HL or better (in the best ear) at frequencies 0.5, 1 and 2 kHz (WHO, 1991). However, this is based on opinions from a WHO expert group, not on physiological evidence. The expert group also added a slight reservation to their classification, stating that the cut-off level could also be recommended to be 20 dB HL and that individuals with mean hearing thresholds of 15-20 dB HL (in best ear) at frequencies 0.5, 1 and 2 kHz may experience hearing difficulties. Recently, Humes (2019a, 2019b) proposed the WHO should change their hearing impairment classification system to define normal hearing as having a mean hearing threshold better than 20 dB HL in the better ear. This was partly inspired by an analysis by the Global Burden of Disease (GBD) project's hearing loss expert group (Stevens et al. 2013), which based their classification not solely based on expert opinion, but on an analysis of 42 studies covering hearing impairment prevalence in different countries. In line with the GBD expert group, Humes (2019a, 2019b) also suggested mean hearing threshold should be calculated from 4 frequencies (0.5, 1, 2 and 4 kHz) instead of 3 (0.5, 1 and 2 kHz). This is supposed to give a better representation of the individuals hearing, as individuals can have perfect hearing thresholds between 0.5 and 2 kHz but still experience severe hearing difficulties due to hearing impairment above 2 kHz. Calculating a mean from 4 frequencies instead of 3 may be better, but the main problem of averaging persists – you end up with reduced detail and are led to believe that poor hearing at some frequencies can be compensated by better hearing at others. This is problematic as 5-15% of individuals seeking healthcare due to hearing difficulties are classified as normal hearing based on their hearing threshold means (Cooper & Gates, 1991; Hind et al., 2011; Kumar, Ahuja, Khandelwal, & Bakshi, 2012), and are thereby at risk of not receiving adequate healthcare due to our arbitrary way of classifying hearing impairments. While obtaining a mean hearing threshold has the advantage of giving a rough idea of degree of hearing impairment condensed into a number, it might not be the best way to analyse hearing status when trying to rule out potential confounding effects of hearing status, as in the case with the present PhD project. Therefore, within the present PhD project, I chose not to classify participant hearing based on mean hearing thresholds calculated from few of the measured frequencies, but based on all standard audiometric frequencies (0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz). As 20 dB HL seems to be the most frequently used cut-off for hearing impairment, I chose to regard individuals with hearing thresholds ≤ 20 dB HL at each standard audiometric frequency in the worst ear as having "normal hearing".

It should be noted, that while pure tone audiometry is by far the most common hearing test for adults, it does not reveal everything about your hearing. For example, the test tells us little about the listener's speech intelligibility, frequency discrimination, time coding, sound localization ability, listening effort, dichotic listening, outer hair cell activity, binaural integration and many other aspects of hearing that have major impact for the listener in every-day life. While broader aspects of hearing would have been valuable to examine, I chose to only test hearing thresholds obtained by pure tone audiometry. This decision was made as pure tone audiometry allows comparability with majority of other studies, and is easily relatable for clinics. As it is difficult to motivate volunteers to participate for long time in experiments, and as my test batteries already included time consuming and fatiguing activities for the participants, I decided not to add additional evaluation of the hearing system.

The possible role of high frequency hearing

While a fully functioning human auditory system can detect sounds at frequencies ranging from approximately 0.02 to 20 kHz (Rosen & Howell, 2011), audiologists have traditionally measured audiograms at frequencies ranging from 0.125 to 8 kHz thus disregarding most of the human auditory range. Hence, the above mentioned negative effect of hearing impairments on cognitive performance refer to hearing impairments at 0.125 to 8 kHz. The effect of hearing impairments above 8 kHz is not nearly as well-documented.

Paralleling the research focusing on the impact of tinnitus on cognitive performance has been research studying the effect of tinnitus on neurological changes in brain structure. One finding from such studies has been that tinnitus sufferers have less grey matter in the subcallosal region of the brain (Leaver et al., 2011; Mühlau et al., 2006). This is a brain region which activity correlates with perception of unpleasant sounds (e.g. Blood, Zatorre, Bermudez, & Evans, 1999), and is believed to be involved in depression (e.g. Hamani et al., 2010). In addition, more recent research has shown that atrophy in the subcallosal region is also significantly associated with behavioural symptoms of neurodegenerative diseases such as mild cognitive impairment, behavioural variant frontotemporal dementia irrespective of disease aetiology and Alzheimer's disease (Cajanus et al., 2019). This indicates that the subcallosal region could also play a role for cognitive processes. The previous studies claiming tinnitus sufferers to have less grey matter in the subcallosal area (Leaver et al., 2011; Mühlau et al., 2006) could therefore be interpreted as being in line with the common complaint about cognitive difficulties among tinnitus sufferers. However, the studies exploring the association between tinnitus and neurological changes in brain structure have also commonly disregarded the importance of controlling for hearing status. An exception to this is Melcher, Knudson, and Levine (2013) who showed that the above mentioned differences in grey matter in the subcallosal region were associated not with tinnitus, but with impaired hearing thresholds above 8 kHz. This unexpected finding has sparked interest in the present PhD project to control not only for hearing thresholds at 0.125 to 8 kHz, but also for hearing thresholds at higher frequencies.

The possible neglecting of other aspects of cognition

Previous studies investigating the link between tinnitus and cognitive performance have all used short-duration, intensive cognitive tests targeting specific cognitive domains as outcome measures. This is a good strategy when trying to determine whether tinnitus has significant effect on, say, WM capacity. However, at the group level tinnitus sufferers' complaints regarding cognitive difficulties seem to be heterogeneous and lacking enough distinction to indicate which exact cognitive domain to test. An alternative way to explore the possible link between tinnitus and cognitive abilities while increasing ecological validity (i.e. the generalizability to real life settings) could be to measure performances on tasks reminding more of the every-day life causing tinnitus sufferers to complain about cognitive difficulties. One way to do so would be to adopt the cognitive office-like tasks presented by Hua et al. (2014), which are more relatable to every-day life than the tests used in previous studies yet still allowing quantification of performances.

Furthermore, the previous studies investigating the link between tinnitus and cognitive performance have all focused on *performances* on different cognitive tests (see Mohamad et al., 2016 for review), assuming that the negative effect on cognitive abilities experienced by tinnitus sufferers would manifest in the form of poorer test scores. It is, however, also possible that the presence of tinnitus has a fatiguing effect on the individual, which is an aspect not easily detectable using previous studies' strategies. Two individuals may achieve the same result on a cognitive test with different levels of cognitive effort (i.e. "different degrees of engagement in demanding tasks" [Westbrook & Braver, 2015]). In hearing research, the Borg CR10 scale (Borg, 1990; originally developed as a measure of subjective physical exertion) has commonly been adopted to measure participants' subjective ratings of perceived cognitive effort, normal sound level and listening effort (Brännström, Karlsson, Waechter, & Kastberg, 2018; Hua et al., 2014; Kähäri, Eklöf, Sandsjö, Zachau, & Möller, 2003; Larsby, Hällgren, Lyxell, & Arlinger, 2005). As Borg (1990) used the term exertion instead of effort when describing the Borg CR10 scale, I will hereinafter refer to cognitive effort as *exertion*.

Summary

Taken together, tinnitus is a common phenomenon that can arise due to several different underlying causes. Tinnitus can be a personal tragedy and comes with a great monetary cost to society. Tinnitus sufferers often experience many difficulties including cognitive difficulties. Previous studies investigating the link between tinnitus and cognitive performance have a common consistent limitation in the lack of control for hearing status. This is problematic as hearing impairment has been associated with cognitive decline, and there is a high comorbidity of tinnitus and hearing impairment. Modern tinnitus care focuses mainly on enabling the patient to cope with their tinnitus, and there is currently no evidence-based intervention for tinnitus sufferers experiencing cognitive difficulties. In order to develop such interventions, we first need to distinguish the effects of tinnitus versus hearing status on cognitive performance, something previous studies focusing on the impact of tinnitus on cognitive performances have failed to do.

AIMS

Overall aim of the PhD project

The overall aim of the present PhD project was to investigate if tinnitus was associated with cognitive performance when controlling for hearing status. Filling that knowledge gap is an important step towards understanding the complexity of tinnitus and enabling future development of evidence based interventions.

Specific aims for each study

Study I

To determine if tinnitus was associated with executive attention in adults with normal hearing.

Study II

To determine if tinnitus was associated with WM capacity in adults with normal hearing.

Study III

To determine if tinnitus was associated with WM capacity in adults with normal hearing and adults with hearing impairment.

Study IV

To determine if tinnitus was associated with performance and perceived exertion on an office-like task in adults with normal hearing and adults with hearing impairment.

MATERIAL AND METHODS

Facilities and equipment

All studies described in the present thesis were conducted at Skåne University Hospital, Lund, Sweden. All testing was performed in a sound treated room, complying with international standard for hearing threshold measurements (ISO 8253-1:2010). A Madsen Astera[2] (GN Otometrics, Taastrup, Denmark) audiometer was used for measurements of hearing thresholds. Auditory stimuli were presented via HDA 200 earphones (Sennheiser, Wedemark, Germany) in all studies except for Study I, where TDH-39 earphones (Telephonics, Farmingdale, USA) were used. Earphones were calibrated in accordance to international standard for audiometric equipment (ISO 389-5:2006; ISO 389-8:2004), using a type 2209 sound level meter and type 4153 artificial ear (Brüel & Kjær Sound & Vibration Measurement, Nærum, Denmark). Cognitive tasks were visually presented on a ThinkPad T410 computer (Lenovo, Morrisville, USA). For Study I, statistical analyses were performed in IBM SPSS Statistics, Version 22.0.0.0 64-bit edition for Macintosh (IBM, New York, USA). For Studies II to IV statistical analyses were performed in IBM SPSS Statistics version 24.0.0.0, 64-bit edition for Windows. All questionnaires were printed on paper and completed by hand, with the exception of the TQ in Study I which was electronically distributed and completed.

Audiometry

Audiometry is a method to obtain an individual's audiogram, and pure tone audiometry using the modified Hughson-Westlake method (Carhart & Jerger, 1959) is the current golden standard test for measuring hearing thresholds. The test is very simple; the test person sits on a chair in a sound treated room (complying with international standard for audiometric testing, [ISO 8253-1:2010]) with earphones on and a response button to indicate whenever a tone is heard. Auditory stimuli can also be presented via a bone conductor. Using both ways of presenting stimuli makes it possible to distinguish whether a hearing impairment is due to sensorineural or conductive causes. Using an audiometer, an audiologist will follow a specific test protocol presenting sine tones at given frequencies, with standard frequencies being 0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz. Standard frequencies were measured in all studies of the present project, while Studies II to IV also measured hearing thresholds at the additional frequencies of 10, 12.5, 14 and 16 kHz. Depending on the test person's responses, the amplitude of the tone is either increased (5 dB; if no response was received) or decreased (10 dB; if reliable response was received) until a hearing threshold (i.e. the weakest audible tone at a given frequency) can be determined. When reported graphically, the hearing thresholds form a curve called an audiogram that shows how the test person's hearing thresholds vary by frequency. Before audiometry, the audiologist performs otoscopy in order to check for abnormalities in the outer ear canal and tympanic membrane that could have impact on the test results.

Cognitive measures

All cognitive tests used in the present project were presented visually. This was done to maximize comparability with previous studies investigating the link between tinnitus and cognitive performance, as all such studies had used visual behavioural tests to assess cognitive performances. Another reason for presenting the cognitive tests visually was to avoid any effects of audibility on the cognitive testing had it been presented auditorily. For all behavioural cognitive tests, outcomes were measured as accuracy (i.e. the ratio of correct to total responses), response time (how quickly the test person responded), a combination of the accuracy and response time, or self-rated exertion due to performing the test.

Stroop test

The Stroop test is a way to measure the test person's executive attention, specifically by examining the ability to suppress irrelevant stimuli in order to focus on a task-relevant stimulus to achieve a given goal. The original and most well-known version was developed by Stroop (1935) and could be described as a visual word/colour-test, where the test person is presented with one word at the time. The words are describing a colour while the colour of the text is a different colour (e.g. the word "green" written in red letters). The task for the test person is to suppress the urge to say the written word, but instead as quickly as possible name in what colour the text is written.

The Stroop test was chosen as it was the most commonly used test in previous studies examining cognitive performances in tinnitus sufferers compared to control participants without tinnitus. However, there were a range of versions of the Stroop test used in previous studies (e.g. colour words, words associated with tinnitus, words associated with physical threat), and none of the previous studies had used the exact same version. Therefore, I also decided to use an altered version of the Stroop test, specifically a computer based number version where the test person was seated in front of a computer screen upon which digits were presented one to three digits at a time (e.g. “222” or “33”). The task was to report (with a keypad) how many digits where presented and suppressing the urge to report the name of the digits shown. A new stimulus was presented as soon as the test person had responded. The number based version was chosen in order to minimize the effect of language ability. In order to make the test harder, I also included a switched task condition (i.e. where task was switched from being “report how many digits you see, not what digits” to “report what digits you see, not how many”). The switched task condition was indicated by a change in background colour, where digits presented on white background indicated original task and digits presented on a yellow background indicated switched task. For these tests, I measured the outcomes as accuracy and response times separately in order to maximize comparability with previous studies.

N-back test

The n-back test is a visual test of WM developed by Kirchner (1958) that has since been widely used in psychological research. It consists of several subtests, where N equals a non-negative integer (e.g. 0-back, 1-back, 2-back and so on). In each subtest, the test person is presented with one symbol at a time (typically letters) and the fundamental task is to report whether the current symbol is identical to the symbol seen N presentations ago. This means that the test person tries to remember and report whether the current symbol is identical to the previous symbol in the 1-back condition, whether the current symbol is identical to the symbol presented before the previous in the 2-back condition and so on. The 0-back condition is an exception as the current symbol will always be identical to the symbol presented zero presentations ago. In the 0-back condition, the test person’s task is to report whenever they see a specific symbol (e.g. press the button every time you see “X”, do not press the button if you see a letter that is not “X”). With each increase of N, the task constitutes an increased load on the test person’s WM.

I used a computer based letter version of the n-back test, where the test person was seated in front of a computer screen upon which letters were presented one at the time. Letters were shown for half a second in the middle of the screen, followed by a blank white screen for three seconds until the next letter was presented. 0-back, 1-back, and 2-back were used as subtests. A key pad was used for participants to respond.

The n-back test was chosen in order to address the uncertainties regarding influence of hearing status on the results seen in previous research suggesting tinnitus negatively affected WM capacity. The previous study on the link between tinnitus and cognitive performance that most clearly targeted WM used another test to assess WM; a reading span test (Rossiter et al., 2006). A way to maximize comparability would have been to use the exact same test. However, reading span tests have received criticism for being influenced by the test person’s linguistic abilities

(Daneman & Hannon, 2007). This lead to the decision to trade the benefit of optimal comparability for a better measure of the cognitive domain of interest.

Sök 1

Sök 1 is a novel visual computer-based test that uses an office-like task to test a person's ability to extract information from written documents. The test was developed by Hua et al (2014), who gave the present author permission to use their test and provided the necessary computer files to do so. In their article (Hua et al., 2014), the test is mentioned as a single unnamed work-related test. However, the received computer files provided several slightly different versions of the test as described in the article. The version used in the present project was called Sök 1. The Sök 1 test consists of a series of information tables and accompanying questions. The tables have 15 rows and six to seven columns, with a new table appearing as soon as the test person has indicated its response with a keypad. The answer to each question accompanying a table can either demand information from two columns (e.g. "which car has driven the longest distance?") or four columns (e.g. "Which state ruled by CDU, and accounting for 1.96% or less of Germanys BNP, has the most workers within the construction sector?"). Hereafter, questions requiring information from two columns will be referred to as representing a simple office-like task condition, questions requiring information from two columns will be referred to as representing a complex office-like task condition, and all questions will be referred to as total office-like task condition. The participant responds by typing the number of the row that provides the answer corresponding to the question. The maximum time for each question is 60 seconds. If the participant does not manage to answer within this time frame, then the next table and question is presented.

Sök 1 was chosen as it enables assessment of both if and how different parameters (e.g. tinnitus) are associated with behavioural measures of generic work performance. This is something tinnitus sufferers experiencing cognitive difficulties typically complain about, yet an aspect previous tinnitus research has completely disregarded.

Questionnaires and scales

TQ

The Tinnitus Questionnaire (TQ) was developed by Hallam et al. (1988) in order to assess the degree of annoyance perceived due to tinnitus by the individual tinnitus sufferer. The TQ is rarely used in clinic, but was chosen as a measure of tinnitus severity in Studies I and II as it was one of the most commonly used questionnaire in previous studies investigating the link between tinnitus and cognitive performance. The TQ consists of 52 statements regarding how the respondent perceives their tinnitus (e.g. “I can sometimes ignore the noises even when they are there”), for each statement the respondent indicates the statements applicability to their own situation by ticking “True”, “Partly true” or “Not true”. 41 of the statements are scored 2, 1 or 0 points depending on response (remaining 11 statements are included in the questionnaire as they, despite not being scored, may individually “provide clinically useful information” [Hallam, 2008]), resulting in scores ranging from 0 to 82, where greater score indicates greater tinnitus distress. There is no grading system for the TQ, indicating cut off for clinical significant degree of distress.

THI

The Tinnitus Handicap Inventory (THI) was developed by Newman et al. (1996) as a measure of the degree of handicap due to tinnitus (also commonly referred to as tinnitus severity). The THI was chosen as a measure of tinnitus severity in Studies III and IV as it is widely used in both clinic and research. The questionnaire consists of 25 questions (e.g. “Do you feel like you can no longer cope with your tinnitus?”), and the respondent is asked to answer each question by ticking “Yes”, “Sometimes” or “No” with each answer scored 4, 2 and 0 points, respectively. This results in a score range of 0 to 100, where 0-16 is deemed to indicate no handicap, 18-36 a mild handicap, 38-56 a moderate handicap, and 58-100 a severe handicap. In order to minimize effects of language, a Swedish translation of the THI was used.

HADS

The Hospital Anxiety Depression Scale (HADS) was developed by Zigmond and Snaith (1983) in order to assess symptoms of anxiety and depression in patients. The HADS was used to control for anxiety and depression in all studies of the present project as it has been commonly used among previous studies investigating the link between tinnitus and cognitive performance, as well as being widely used in both clinic and in research in general. The HADS consists of 14 statements, half covering symptoms of anxiety (e.g. “I get sudden feelings of panic”) and half covering symptoms of depression (e.g. “I have lost interest in my appearance”). This results in two subscales: anxiety (HADSA) and depression (HADSD). Each statement is followed by four response options. The respondent is asked to tick the one that the best indicates the statements applicability to how they have been feeling during the past week. Each answer is scored 0-3 depending on which degree of anxiety/depression it indicated. This results in a score range of 0-21 points for each subscale, with scores below 8 categorized as no clinical symptom of anxiety/depression, scores from 8-10 categorized as borderline cases, and scores of 11 points or more categorized as clinical symptoms of anxiety/depression.

Borg CR10

The Borg CR10 scale was developed by Borg (1990) as a measurement of perceived exertion due to physical tasks. The scale is a combination of a category and ratio scale, simultaneously ranging from 0 to 10 and "Nothing at all" to "Extremely strong". The respondent fills out the scale by marking level of perceived exertion. The scale was first developed for the field of sports medicine, but has been adopted for countless contexts with examples including breathlessness during exercise (Mahler, Mejia-Alfaro, Ward, & Baird, 2001), intensity of headache (Sjögren et al., 2005), intensity of taste (Garriga-Trillo, Muro, & Merino, 2002; Neely & Borg, 1999), and satiety in anorexia patients (Bergh, Brodin, Lindberg, & Södersten, 2002). This scale was chosen as a measure of perceived exertion due to an office-like task in Study IV as it has recently been adopted for measures of perceived cognitive effort, normal sound level and listening effort in hearing research (Brännström et al., 2018; Hua et al., 2014; Kähäri et al., 2003; Larsby et al., 2005).

Participants

All participants were adult volunteers recruited through audiology clinics, public advertisement and word of mouth in southern Sweden. Each tinnitus participant was matched with a control participant, both meeting a strict set of inclusion criteria including: maximum deviation in age (12 months for Study I, 18 months for Study II and 24 months for Studies III and IV; age matching criteria was expanded in later studies due to difficulties of finding matching co-participants), same sex, same hearing status (normal hearing or hearing impairment), and comparable level of educational background. See *table 2* for descriptive data of sex, age, and educational level for each study and group. All included participants had normal vision or corrected to normal vision.

Table 2. Sex, age, and educational background for each study and group.

	Study I (n = 40)		Study II (n = 62)		Studies III and IV (n = 76)	
	Tinnitus group	*Control group*	*Tinnitus group*	*Control group*	*Tinnitus group*	*Control group*
Sex (female/male)	11/9	11/9	19/12	19/12	22/16	22/16
Age (span, mean ±*SD*)	21.8-55.0, 30.3 ±*9.0*	20.9-55.2, 30.3 ±*9.1*	20.9-44.3, 26.9 ±*5.7*	21.1-43.8, 27.1 ±*5.6*	23.3-65.2, 36.9 ±*12.4*	23.7-66.3, 36.8 ±*12.4*
Educational background (high school level/university level)	3/17	2/18	4/27	8/23	0/38	0/38

The inclusion criterion for tinnitus participants was to have experienced tinnitus for 6 months or longer (in order to maximize comparability with previous studies), while the inclusion criterion for control participants was to report no tinnitus. Normal hearing was defined as having no hearing thresholds worse than 20 dB HL at frequencies 0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz in either ear. Hearing impairment was defined as not meeting the criteria for normal hearing. These hearing criteria could hypothetically result in very mild impairments in the hearing impaired group as an individual with only one hearing threshold worse than 20 dB HL would technically fall under the hearing impaired category. However, as seen in *figure 3*, while the individuals with hearing impairment on group level had quite mild impairments, there were clear differences in terms of hearing thresholds between the hearing impaired and normal hearing individuals.

There were no inclusion or exclusion criteria regarding tinnitus severity. Tinnitus severity was examined using the TQ (range: 0-82, median point: 43) in Study I and II, and the THI (range: 0-100, median point: 36) in Studies III and IV. In each study of the present project, participants' tinnitus severity ranged from mild to severe (Study I: 16-61 (TQ); Study II: 15-72 (TQ); Studies III and IV: 6-84 (THI) and averaged slightly below the scales' median points (Study I: 40; Study II: 35; Studies III and IV: 35).

Study I

In Study I, only individuals with normal hearing were included. Initially 46 participants were recruited but six participants (five with tinnitus, one without tinnitus) were excluded due to not meeting hearing criteria. This resulted in 40 individuals included in the study (see *table 2* for descriptive data of sex, age, and educational background) forming a tinnitus group (n=20) and a control group (n=20).

Study II

In Study II, only individuals with normal hearing were included. Initially 63 participants were recruited, but one participant (with tinnitus) was excluded from the study due to difficulties finding a normal hearing control participant matching in age and sex. This resulted in the 62 individuals included in the study (see *table 2* for descriptive data of sex, age, and educational background) forming a tinnitus group (n=31) and a control group (n=31).

Studies III and IV

The same 76 participants were examined in Studies III and IV. In these studies, both individuals with normal hearing and hearing impairment were studied. Initially 82 participants were recruited, but six participants (four with tinnitus, two without tinnitus) were excluded from the study due to difficulties finding age matched co-participants (in three of the cases) or an education matched co-participant (in one case), due to neurological comorbidity assumed to affect the results (in one case), or due to withdrawal from the study after reporting unmanageable fatigue during the studies' cognitive tasks (in one case). This resulted in the 76 individuals included in the studies (see *table 2* for descriptive data of sex, age, and educational background), forming a tinnitus group (n=38) and a control group (n=38), each consisting half of normally hearing individuals (n=19) and half of individuals with hearing impairment (n=19) (see *figure 3* for visualization of hearing status).

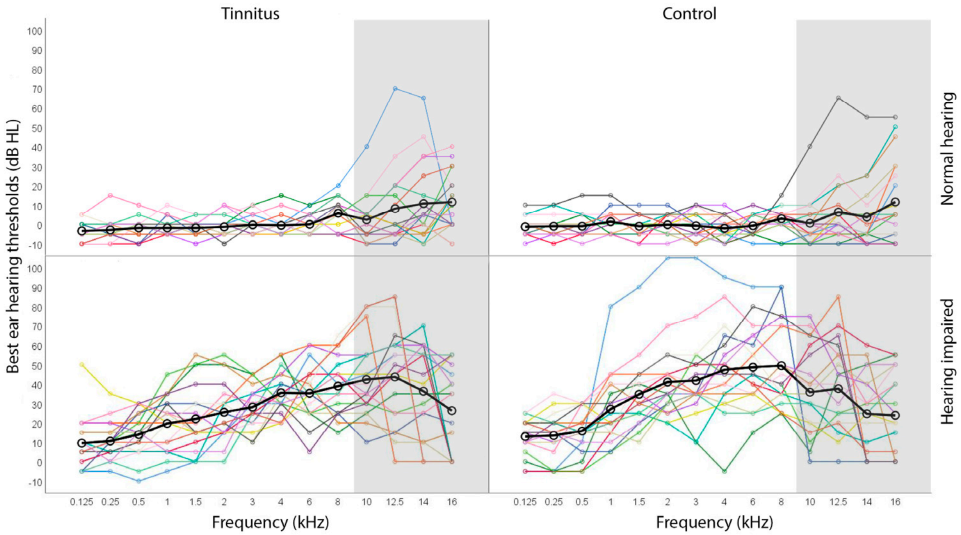

Figure 3. Best ear audiograms in Studies III and IV, divided by hearing status (normal hearing vs hearing impaired) and tinnitus (yes or no). Coloured thin lines show individual data, thick black lines show group mean, gray area shows frequency region that is currently not measured at the clinic.

Data analysis

For the Stroop test (Study I), outcomes were measured as accuracy and response times separately in order to maximize comparability with previous studies.

For the n-back test (Studies II and III), outcomes were measured as a combination of accuracy and response time as analysing accuracy and response time separately may lead to incorrect conclusions about WM capacity (Vandierendonck, 2017). In Study II accuracy and response time was arbitrarily combined into a single figure by dividing percentage of correct responses by mean response time. In Study III, accuracy and response time was combined into a single figure by using the Rate Correct Score (RCS), first presented by Woltz and Was (2006) as:

$$RCS = \frac{c}{\sum RT}$$

where c stands for number of correct responses, and RT stands for response times. Practically, this way of combining accuracy and response time data into a single figure renders the exact scores as with our initial arbitrary method used in Study II, but divided by 100.

For Sök 1 (Study IV), performance outcomes were measured as accuracy and response time combined into a single figure by using the RCS as described above. For Sök 1, exertion outcomes were measured by subtracting the baseline self-reported exertion from the self-reported exertion due to performing the office-like task, resulting in a measure of added exertion due to the office-like task. Levels of exertion were rated using the Borg CR10 scale.

In Study II high frequency hearing was measured as best ear mean pure tone hearing threshold at 10, 12.5, 14 and 16 kHz. In Studies III and IV, hearing status was measured as best ear mean pure tone hearing threshold at 0.5, 1, 2 and 4 kHz (BEPTA), as well as best ear mean pure tone hearing threshold at 10, 12.5, 14 and 16 kHz (BEHFPTA).

In all studies (I to IV), outcomes data were analysed descriptively by inspection of frequency histograms, Q-Q plots, calculation of skewness, and kurtosis z-values, in order to evaluate the distribution of the data.

In Study I, Mann-Whitney U test was used to determine whether groups differed in terms of mean accuracy. The use of a non-parametric test was motivated by the initial descriptive analysis, which had indicated significant deviations from normal distribution for accuracy. As the initial analysis of response times indicated no significant deviations from normal distribution, an ANOVA was used to determine whether groups differed in terms of response time.

In Study II, Mann-Whitney U test was used to determine whether groups differed in n-back score. The use of a non-parametric test was motivated by the initial descriptive analysis, which had indicated significant deviations from normal distribution for accuracy. Thereafter, the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995) was used to adjust p-values for false discovery rate, as I analysed three different n-back conditions, which implies a risk of finding falsely positive significant differences. Furthermore, the relationship between high frequency hearing and n-back score was explored using a partial correlation analysis with correction for participants' age. Again, the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995) was applied in order to adjust p-values for false discovery rate.

In Study III, a one-way MANCOVA was used to determine whether tinnitus was associated with WM capacity. In that analysis, the dependent variables were n-back performance in the 0-back, 1-back and 2-back conditions, the independent variable was presence of tinnitus, and the co-variables were symptoms of anxiety and depression (measured as scores on the HADS), and hearing status (in the form of BEPTA and BEHFPTA). Additionally, n-back scores were analysed in participants with tinnitus in order to explore what parameters may predict WM capacity in tinnitus sufferers. This was done using a multivariate multiple regression analysis. In that analysis, the dependent variables were n-back performance in the 0-back, 1-back and 2-back conditions, the independent variables (predictors) were tinnitus distress (measured as THI score), anxiety and depression (as scores on HADS), and hearing status (measured as BEPTA, and BEHFPTA).

In Study IV, a one-way MANCOVA was used to determine whether tinnitus was associated with performance an office-like task. In that analysis, the dependent variables were simple task-, complex task-, and total task-performance in Sök 1, the independent variable was presence of tinnitus, and the co-variables were symptoms of anxiety and depression (measured as scores on the HADS), and hearing status (in the form of BEPTA and BEHFPTA). Furthermore, a one-way ANCOVA was used to determine whether there was an effect of tinnitus on perceived exertion due to performing the office-like task. In that analysis, the dependent variable was added RPE due to Sök 1 (i.e. absolute RPE due to Sök 1 minus baseline RPE), the independent variable was presence of tinnitus, and the co-variables were symptoms of anxiety and depression (measured as scores on the HADS), and hearing status (in the form of BEPTA and BEHFPTA).

Ethical approval

The design and conduct of the studies of the present PhD project adhered to the Helsinki declaration of ethical principles for medical research involving human subjects (World Medical Association, 2013). All participants were informed in text and verbally regarding the studies' purposes and designs before participating. It was emphasized that participants may abort their participation at any time with no questions asked.

Data was pseudonymized, i.e. data was de-identified so that it could only be linked to the corresponding individual using a separately stored encrypted code key. As the studies of the present PhD project included collecting sensitive personal data (specifically information regarding the participants' health status), the studies were subject to a permit in accordance with paragraph 3 (2003:460) of Swedish law on ethical review of research involving human individuals. The application for ethical review was submitted to the Regional Ethical Review Board in Lund, Sweden, which approved the studies with special conditions (approval number 2014/95).

FINDINGS

Study I

Study I indicated no significant differences in terms of Stroop performance for accuracy or response time between the tinnitus group and the control group. See *figure 4* for visualisation of the main findings of Study I. The results indicate that presence of tinnitus itself does not imply poorer executive attention in normal hearing individuals.

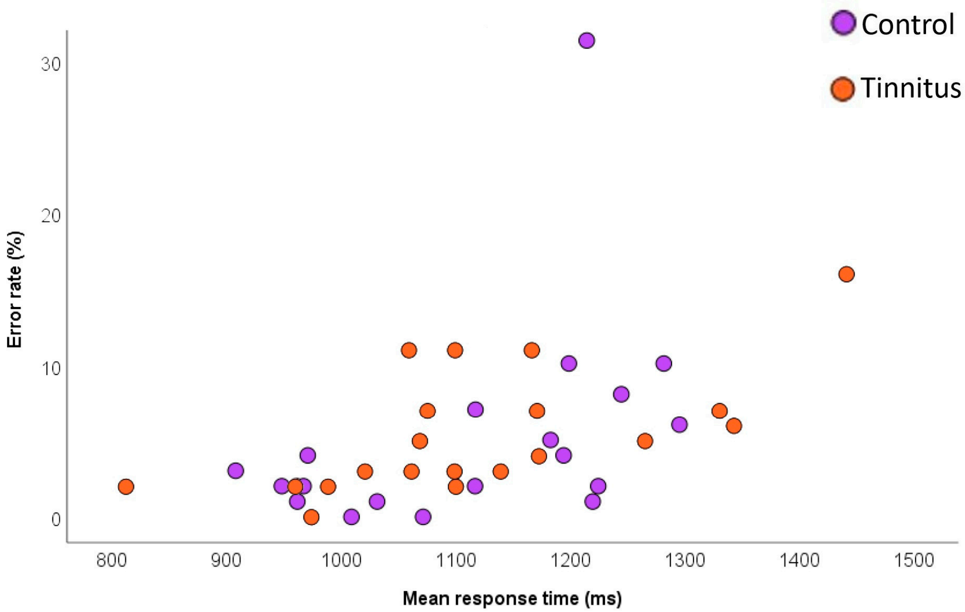

Figure 4. Performances on visual Stroop test for normally hearing individuals with and without tinnitus.

Study II

Study II indicated no significant differences in terms of n-back performance between the tinnitus group and the control group, with the exception of the 2-back condition where the tinnitus group performed significantly better than the control group. In addition, a significant negative correlation was found between n-back performance (in the 1-back and 2-back conditions) and BEHFPTA (i.e. poorer high frequency hearing being associated with poorer WM capacity), when controlling for age. See *figure 5* for visualisation of the main findings of Studies II and III. The results indicate that the presence of tinnitus itself does not imply poorer WM capacity in normal hearing individuals, but that there is a significant association between poorer high frequency hearing thresholds and poorer WM capacity.

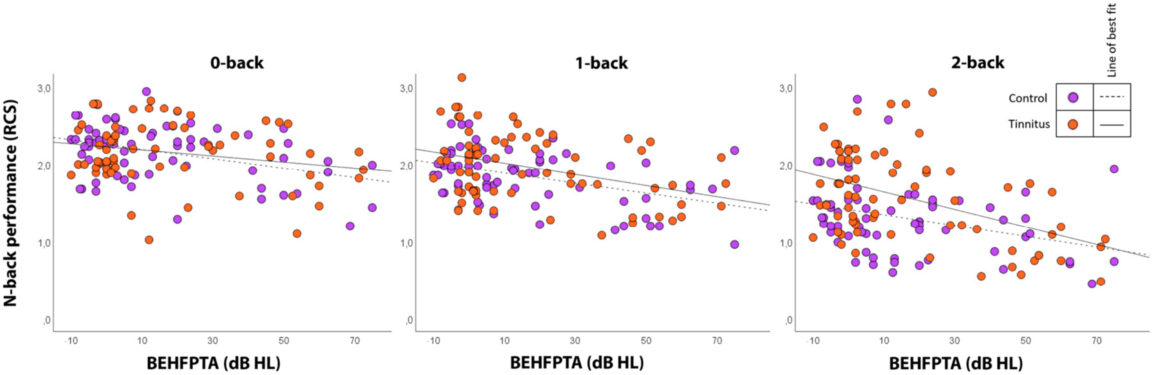

Figure 5. Association of n-back performance for each task condition and best ear high frequency hearing thresholds (at frequencies of 10 to 16 kHz) in individuals with and without tinnitus, from Studies II and III together.

Study III

Study III indicated no significant effect of tinnitus on n-back performance (regardless of n-back condition), when controlling for HADSA score, HADSD score, BEPTA and BEHFPTA. Corrections for BEHFPTA were significant in each n-back condition. In tinnitus sufferers, THI score and BEHFPTA significantly predicted variation in the 0-back condition, and BEHFPTA significantly predicted variation in the 2-back condition. See *figure 5* for visualisation of the main findings of Studies II and III. The results indicate that presence of tinnitus itself does not imply poorer WM capacity when controlling for hearing status, but that poorer high frequency hearing thresholds (at 10 to 16 kHz) seems to be negatively associated with WM capacity.

Study IV

Study IV indicated no significant effect of tinnitus on performance on Sök 1 or perceived exertion due to performing Sök 1, when controlling for HADSA score, HADSD score, BEPTA and BEHFPTA. In the analysis of Sök 1 performance, corrections for BEHFPTA were significant in each Sök 1 condition. See *figure 6* for visualisation of the main findings of Study IV. The results indicate that presence of tinnitus itself does not imply poorer performances or greater levels of exertion at office-like tasks, but that there is a significant association between poorer high frequency hearing thresholds and poorer performances at the office-like tasks.

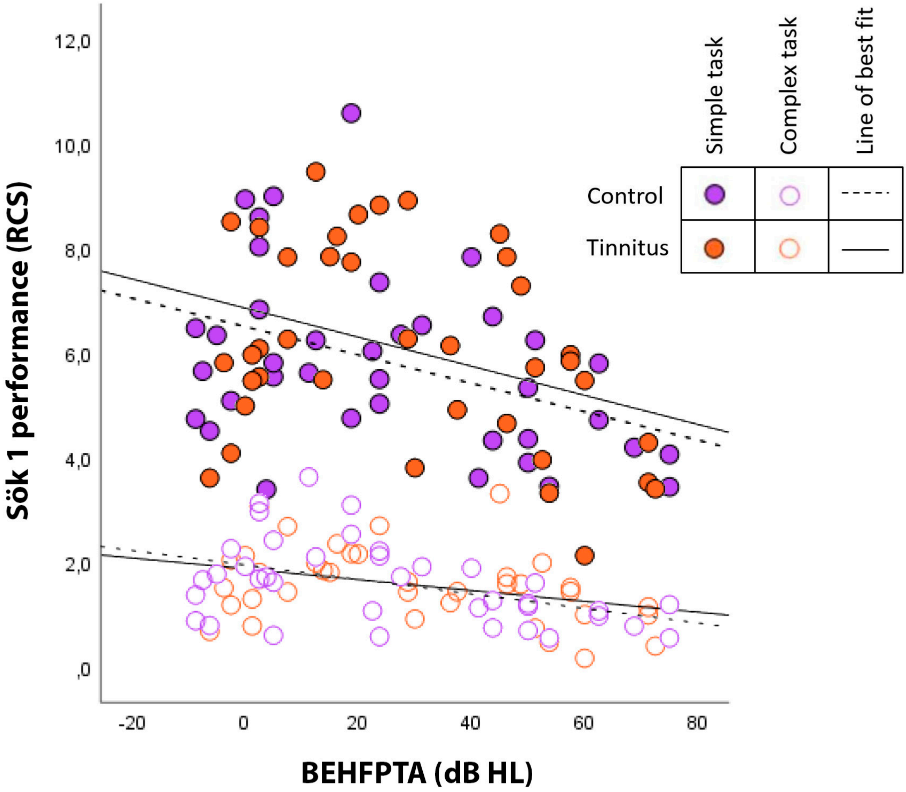

Figure 6. Association between office-like task performances (for simple and complex task conditions) and best ear high frequency hearing thresholds (at frequencies of 10 to 16 kHz) in tinnitus sufferers and individuals without tinnitus.

DISCUSSION

Discussion of findings

Main findings

Tinnitus was not associated with executive attention, WM, performances on office-like task or perceived exertion on office-like task in the adults who participated in the present PhD project. Instead, WM and performances on office-like task were associated with participants' hearing status. For WM and ability to solve office-like tasks, Studies II to IV showed that the performances were specifically associated with hearing thresholds at 10 to 16 kHz.

An interesting aspect of present project's findings is that the participants either had hearing that would be defined as normal hearing with today's standards (participants in Studies I to IV), or mild to moderate hearing impairments on group level (in half of the participants in Studies III and IV). Therefore, our data does not allow us to draw conclusions about how more severe hearing impairments may be associated with cognitive performances. Hypothetically, greater hearing impairment would imply greater negative association although this need not be linear (especially not if hearing aids are used, which would be more likely in people with poorer hearing). On the other hand, this also means that hearing status seems to have significant impact on cognitive performance at mild to moderate hearing impairments, or even at hearing thresholds that are currently defined as normal.

The consistent finding in this project, that tinnitus per se was not associated with cognitive performances, was inconsistent with the findings of previous studies investigating the impact of tinnitus on WM (Rossiter et al., 2006) and executive attention (Andersson et al., 2000; Jackson et al., 2014; Leong et al., 2020; Stevens et al., 2007). Common to those studies was the lack of thorough control for hearing status (see Mohamad et al., 2016 for review). This may have affected the results as hearing impairment is both common among tinnitus sufferers (Barnea et al., 1990; Sanchez et al., 2005) and associated with cognitive decline (see Uchida et al., 2019 for review). The absence of significant difference between tinnitus sufferers and well matched controls was also reported in Study IV, where participants performed an office-like task attempting to resemble a cognitive task which tinnitus sufferers may encounter in every-day life (which has not been attempted in previous studies). Worth noting is that I also conducted a study where immediate and delayed recall on a reading comprehension test was compared in normal hearing individuals with and without tinnitus (Brännström & Waechter, 2018). That study indicated no significant difference in performance between individuals with and without tinnitus, which strengthens the conclusion that tinnitus per se does not have negative impact on cognitive tasks found in every-day life.

The lack of evidence in the present project supporting the notion that tinnitus per se is negatively associated with cognitive performances does however not mean that tinnitus does not affect cognitive abilities in any way. Studies III and IV indicated that hearing impairment is not decisive for reporting cognitive difficulties due to tinnitus. Furthermore, the majority of tinnitus participants in Studies I to IV reported some degree of cognitive difficulties due to their tinnitus (see *figure 7*), whether they had normal hearing or not. This indicates that hearing status might not be the only parameter of importance in any potential relationship between tinnitus and cognitive abilities. While executive attention, WM, performance and perceived exertion on office-like task were not negatively associated with tinnitus per se, the studies of the present project do not allow us to draw any conclusions about other cognitive aspects such as sustained, alerting or selective attention, which have previously been suggested to be negatively associated with tinnitus.

Despite tinnitus sufferers showing comparable performances on measures of cognition to carefully matched control subjects without tinnitus, the present project highlights that there still is something we could do for tinnitus patients complaining about cognitive difficulties. Even though tinnitus sufferers did not perform worse on cognitive measures than individuals without tinnitus, data from Study III suggest there being parameters that seem to have significant impact on the tinnitus sufferers WM capacity. In simple WM tasks, self-reported tinnitus severity and hearing thresholds at 10 to 16 kHz significantly predicted task performance. Hearing thresholds at 10 to 16 kHz also significantly predicted task performance in more complex WM tasks. These findings could be clues for how to approach tinnitus sufferers reporting cognitive difficulties in the clinical setting, as they suggest that WM in tinnitus sufferers could in general be related to high frequency hearing (above 8 kHz), but be related to emotional responses to tinnitus in less demanding WM conditions. The relationship of increased emotional distress and poorer cognitive abilities in general is previously known from studies of individuals without tinnitus (e.g. Horvat & Tement, 2020; Llewellyn et al., 2008), and recent research has also reported emotional distress to be associated with poorer WM specifically (e.g. Choi et al., 2013; Coifman et al., 2019). This indicates that the relationship between tinnitus and WM may not be a direct effect of experiencing phantom sounds, but an indirect effect of emotional distress (potentially elicited by tinnitus). Whilst speculative, this could indicate a potential focal point for tinnitus management in the clinical setting. Addressing the emotional response to the phantom sound experience could be recommended for tinnitus patients reporting problems carrying out easy every-day life tasks, while a thorough hearing rehabilitation could be recommended for tinnitus patients experiencing cognitive decline. However, it should be emphasized that these are clues and not clinical recommendations, as the present project did not evaluate outcomes of any interventions.

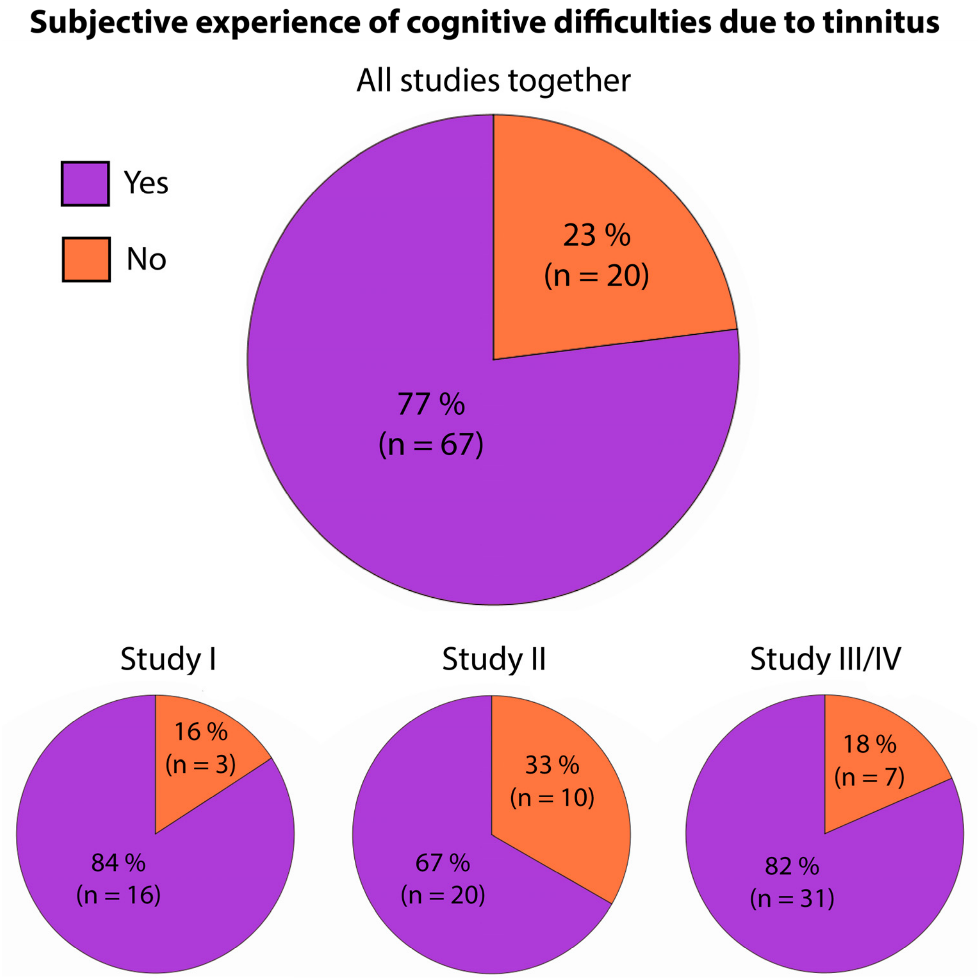

Figure 7. Proportion of tinnitus sufferers reporting cognitive difficulties due to their tinnitus, for each study and in total.

In hindsight, a question that has arisen is whether the studies of the present project (and other studies investigating the possible link between tinnitus and cognitive performance) might have benefitted from the inclusion of a measure of emotion. When trying to understand a tinnitus sufferer's situation, the emotional aspect of tinnitus should not be disregarded. It is possible that we as researchers have been focusing too much on "hard facts", searching for clear differences in task performance between tinnitus sufferers and individuals without tinnitus. It is common for tinnitus sufferers to feel like they are having problems performing optimally on cognitive tasks, but it is rare for tinnitus sufferers' colleagues complain about the tinnitus sufferer's work performance declining post tinnitus debut. This could indicate that the effect we are looking for might not be dramatic, or even noticeable for a bystander. There is a possibility that even very subtle changes in the cognitive capabilities of a person suffering from tinnitus, despite not actually obstructing their every-day life or performance on standardised clinical tests, may still lead to significant frustration when combined with a chronic phantom sound experience and the possible anxiety and/or depression often following tinnitus.

It is important to emphasize that the finding of hearing thresholds at 10 to 16 kHz being negatively associated with cognitive performance seemed to be true regardless of the presence or absence of tinnitus. In other words, a person may unknowingly have a hearing impairment possibly affecting their cognitive performance (explaining as much as 20% of variance in WM among individuals in working age with high educational background) regardless of whether or not they experience tinnitus. However, the presence of this hearing impairment at 10 to 16 kHz would often go undetected by an audiologist whose typical clinical assessment of hearing only extends to a highest frequency of 8 kHz (which is primarily a result of tradition rather than technical limitations). The consequences of only testing up to this frequency can be seen in *figure 8* showing the mean best ear audiogram in adults of different WM capacity who participated in the present PhD project.

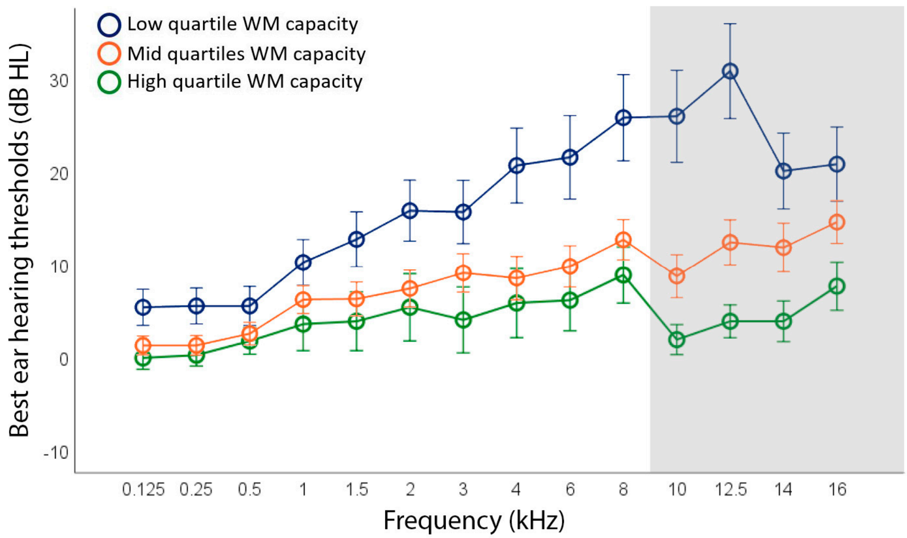

Figure 8. Mean best ear hearing thresholds for individuals with high (high quatile; Q3 to maximum), mid (mid quartiles; Q1 to Q3), and low (low quartile; minimum to Q1) WM capacity. Gray area shows frequency region that is currently not measured at the clinic. Error bars show 1 standard error.

Speculations regarding the role of hearing thresholds > 8 kHz

An important question arises from the studies of the current PhD project; why are poorer hearing thresholds at 10 to 16 kHz associated with poorer cognitive performance, and what could be the underlying cause for this relationship? There is currently no clear answer to this, but I will attempt to offer some possible hypotheses here for further consideration.

To put things into context, the studies of the present project are far from the first to indicate hearing impairment to have a negative impact on cognitive performance (see Uchida et al., 2019 for review). The underlying cause for this link is unclear, but there are four reoccurring main hypotheses:

a) *the cognitive load hypothesis*, which suggests that the increased effort of listening to speech that typically comes with hearing impairment leaves less cognitive resources available for cognitive operations (Sweller, Ayres, & Kalyuga, 2011),

b) *the common cause hypothesis*, suggesting that there might be an underlying cause contributing to both cognitive difficulties and hearing impairment (Lin & Albert, 2014; Stahl, 2017; Wayne & Johnsrude, 2015),

c) *the cascade hypothesis*, focusing on the possibility that the decreased sensory stimulation of the brain due to hearing impairment can lead to decreased total brain volume, and thereby affect the resources necessary for cognitive performances (Golub, 2017; Lin et al., 2014; Peelle, Troiani, Grossman, & Wingfield, 2011; Rigters et al., 2017), and

d) *the overdiagnosis hypothesis*, suggesting that hearing loss makes it difficult to follow orally presented cognitive test instructions, leading to clinicians overestimating the cognitive decline in individuals with hearing impairment (Dupuis et al., 2015; Jorgensen, Palmer, Pratt, Erickson, & Moncrieff, 2016).

The relationship between hearing and cognitive abilities seems to be complex, and it is possible that more than one of the above mentioned hypothesized relationships between hearing and cognitive abilities are true, and some or all of the described processes could be acting simultaneously. All of the above mentioned hypotheses are, however, based on reports of measures of cognitive abilities in relation to hearing thresholds at ≤ 8 kHz. In the present project an association was seen between cognitive performance and hearing thresholds > 8 kHz. While recent research has indicated that hearing thresholds above 8 kHz may affect speech intelligibility in noise (Motlagh Zadeh et al., 2019; Yeend, Beach, & Sharma, 2019), the American National Standard Methods for Calculation of the Speech Intelligibility Index ANSI S3.5 (1997) indicates frequencies of 0.8 to 4 kHz to be clearly more important for speech intelligibility compared to frequencies outside that range (note that there is cultural bias present, as ANSI S3.5 is applicable to non-tonal languages). This suggests poorer hearing thresholds at 10 to 16 kHz should have only a limited effect on one's ability to hear speech. This makes it unlikely that the main findings of the present project would be an effect of the cognitive load hypothesis, as hearing status above 8 kHz will probably only have implications for ability retrieve information from conversations in specific, very challenging conditions. Furthermore, the fact that most of the energy in the human speech signal is present far below 10 to 16 kHz also implies that the main findings of the present project are not an effect of the overdiagnosing hypothesis, as hearing impairments at such high frequencies would not be a disadvantage when trying to understand orally presented test instructions in a silent, sound treated room. Furthermore, in Studies I to IV, thorough task instructions that were easy to understand were given both orally, in pictures and in text, which would minimize the possible effect described in the overdiagnosing hypothesis.

On the other hand, the findings of the present project could be interpreted as being in line with both the common cause hypothesis and the cascade hypothesis. There are several factors that could act as a common cause driving both deterioration of cognitive performances and hearing thresholds. A commonly suggested common cause has been microvascular insufficiency (Uchida et al., 2019) as it can have negative effects for both hearing (e.g. Kocak et al., 2017; Trune & Nguyen-Huynh, 2012) and cognitive abilities (see De Silva & Faraci, 2016, for review). Another possible driving factor that has received little attention is lutein and zeaxanthin intake. These are two antioxidants found in high concentration in food sources as kale, spinach and parsley (Eisenhauer, Natoli, Liew, & Flood, 2017), a higher intake of which have been associated both with better hearing thresholds (Wong, Kaplan, & Hammond, 2017) and better cognitive performances (see Stringham, Johnson, & Hammond, 2019, for review). The interpretation that the findings of the present project are in line with the common cause hypothesis is reliant on inner hair cells responding to frequencies > 8 kHz being more sensitive than other inner hair cells to the potential driving factor. At the time of writing there are no published studies investigating such relationship. However, the general trend of sensorineural hearing impairments being worse at higher compared to lower frequencies is in line with the hypothesis.

The interpretation that the present findings are in line with the cascade hypothesis seems to be less conditional. The human auditory system is able to detect acoustic signals up to 20 kHz when fully functioning (Rosen & Howell, 2011), and hearing impairment has been shown to be associated with accelerated decrease in total brain volume when correcting for cardiovascular factors (Lin et al., 2014). Hence, decreased sensory stimulation of hearing thresholds > 8 kHz implies less electrical stimulation of the brain from a majority of the inner hair cells, which could have significant effect on total brain volume. In line with this hypothesis, other forms of sensory deprivations have shown similar effects. For example, there is a clear association between olfactory dysfunction and cognitive decline (e.g. Dintica et al., 2019) that could be explained with the same reasoning regarding sensory deprivation.

Clinical implications

The main clinical implication of the present project is that we should extend the basic (standard) audiological test battery to include measurements of hearing thresholds at frequencies > 8 kHz. This has also been argued by Yeend et al. (2019), who studied adult participants with normal or near-normal hearing at 0.25 to 6 kHz and reported hearing thresholds above 8 kHz and WM capacity to significantly predict speech intelligibility in noise. The studies of the present project indicate that impaired hearing thresholds within the range of 10 to 16 kHz were significantly and negatively associated with cognitive performance (specifically WM and performances on an office-like task), regardless of the presence or absence of tinnitus. Failure to measure hearing thresholds at those frequencies will impede our attempts to establish normal data, develop adequate interventions, and identify cases in need of intervention for patients with (or without) tinnitus who report cognitive difficulties. Measurements of hearing thresholds above 8 kHz are currently very rare in the clinical setting. There may be several reasons for this. As sounds with higher frequencies have shorter wave lengths, the transmission of high-frequency stimuli is more sensitive to obstacles, thus even minimal variations in headphone position may result in considerable changes in sound pressure at the tympanic membrane (Crepaldi de Almeida & Nishimori, 2006). Also, measuring hearing thresholds for more frequencies results in increased test duration. This is important as there are far more people with hearing impairment in the world than there are audiologists available to help them. Furthermore, most audiological patients seek medical care due to difficulties in communication and understanding speech, and 0.8-4 kHz seems to be the most critical frequency range for speech intelligibility (ANSI S3.5, 1997). Taken together, this has made it pragmatic to only measure hearing thresholds up to 8 kHz in the clinical setting. However, the human hearing system is able to detect acoustic signals at frequencies up to 20 kHz when fully healthy, modern equipment allows for the easy measurement of high frequency hearing thresholds, and there is growing evidence suggesting hearing thresholds at frequencies >8 kHz are of particular interest in a range of conditions. It would appear that the current reason for not measuring hearing thresholds at those frequencies is mainly one of tradition.

Furthermore, the project suggests several implications for management of tinnitus patients. First, hearing evaluation should be a routine assessment for patients complaining about tinnitus, whether they report hearing difficulties or not. About 90% of adults with tinnitus seem to have some kind of hearing impairment (Barnea et al., 1990; Sanchez et al., 2005) and the onset of tinnitus is often clear and sudden, while onset of hearing impairment is typically subtle and gradual. This could make patients focus on their tinnitus, rather than a potential hearing impairment. This is a concern that has also been raised by Henry et al. (2015) and Zaugg, Schechter, Fausti, & Henry (2002), who illuminated the tendency among tinnitus sufferers to associate hearing related issues with their tinnitus instead of their hearing impairment. Moreover, it usually takes considerable time for patients to seek help for hearing impairment despite early identification being associated with greater hearing aid benefit (Davis, Smith, Ferguson, Stephens, & Gianopoulos, 2007). Hence, the complaint about tinnitus could be seen as an opportunity to identify the need of hearing rehabilitation at an earlier stage than otherwise possible. This could improve the outcome of hearing related interventions. The present project also highlights the role of hearing status in one of the most common problems reported by tinnitus sufferers: reduced cognitive abilities. While the need for audiological evaluation for tinnitus sufferers might seem obvious, at the time of writing this is not always argued in clinical guidelines for tinnitus. For example, in one of the most cited clinical guidelines for tinnitus (Tunkel et al., 2014) the authors argue that examination of hearing should always be done if the patient has unilateral tinnitus or is showing other typical indications for tumour on the auditory nerve, but that hearing examination is optional for tinnitus patients in general. The present project indicates that hearing status might be of importance even in the absence of these extra indicators.

Second, tinnitus sufferers reporting cognitive difficulties should receive hearing rehabilitation. Impaired hearing thresholds are common among tinnitus sufferers and this project has shown that impaired hearing is associated with cognitive difficulties, which is in line with previous research on the effect of hearing impairment on cognitive abilities (see Uchida et al., 2019 for review). Previous studies have shown that cognitive deterioration due to impaired hearing at frequencies $\leq$ 8 kHz can be significantly slowed by using hearing aids (e.g. Dawes et al., 2015; Lin et al., 2011). Furthermore, previous research has also demonstrated adequate increase of neural electric activity via transcranial electric stimulation to result in enhanced cognitive performance (Fregni et al., 2005; Richmond, Wolk, Chein, & Olson, 2014). As enhanced hearing at $>$ 8 kHz implies increased neural stimulation, this is a promising indication that some sort of hearing rehabilitation could also slow the onset of cognitive difficulties caused by hearing impairments $>$ 8 kHz. However, today's hearing aids only deliver gain up to 10 kHz at best. Hearing aids with greater bandwidth will need to be developed or alternative audiological interventions will need to be considered that could reliably deliver such high frequency sounds to the human ear. Third, tinnitus interventions should be evaluated not only with questionnaires targeting tinnitus severity, but also behavioural measures targeting the specific difficulties reported by the individual tinnitus sufferer. This is currently rarely done neither in clinic nor research. The advantage of starting doing so would be to gather more detailed information of the impact of currently administrated interventions for tinnitus sufferers on cognitive performance. Currently there is no data to rely on when choosing the optimal intervention for a tinnitus patient experiencing cognitive difficulties, which leaves clinicians to rely solely on personal experience or local tradition.

Future research

The present project has provided new clues about how tinnitus and high frequency hearing might be associated with cognitive performance, but much is left to explore in order to fully understand such associations and to establish adequate interventions for the patient group in question. First, future research should continue to strive towards finding an objective measure of the cognitive difficulties experienced by tinnitus sufferers. If we cannot measure these difficulties, we can neither design interventions targeting the specific affected cognitive domain nor evaluate the cognitive outcomes of any tinnitus intervention. None of the previously suggested cognitive domains have been affected by tinnitus when controlling carefully for hearing status, but there are yet several cognitive domains suggested to be affected by tinnitus where the role of hearing status has not been fully explored. Examples include sustained attention, alerting attention, and selective attention.

Future studies investigating the possible link between tinnitus and cognitive performance could also consider including controls for sleep quality. Sleep disturbance is another common complaint among tinnitus sufferers (Hall et al., 2018), and poor sleep quality has been shown to be negatively associated with a range of cognitive measures (Jackson et al., 2013; Kaliyaperumal, Elango, Alagesan, & Santhanakrishanan, 2017; Lim & Dinges, 2010; Pilcher & Huffcutt, 1996). Thus, if future studies were to find negative associations between cognitive performances and tinnitus without controlling for sleep quality, it would be difficult to determine whether the negative association was due to tinnitus, to sleep, or both tinnitus and sleep. Determining these associations would be important as the choice of interventions could differ substantially across these different scenarios. It is worth noting is that the recently published study by Leong et al. (2020) (which reported poorer performances in tinnitus sufferers compared to control participants without tinnitus on cognitive tests targeting selective attention, sustained attention and executive attention) included the Pittsburg Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), a questionnaire designed to assess sleep quality over the past month, in their test battery. Leong et al. (2020) reported slightly, but not significantly, poorer PSQI scores in the tinnitus group compared to the control group without tinnitus, but did not use PSQI scores as a covariate in their main analysis. This makes it difficult to draw clear conclusions regarding the potential effect of sleep deprivation on the participants' cognitive performances in that study.

As mentioned in the introduction to this thesis, the current approach for evaluating tinnitus interventions at the clinic is to let the patient fill out questionnaires of general tinnitus distress pre and post intervention. This may render valuable information regarding the overall effect of the intervention, but the evaluation of tinnitus interventions should not be limited to questionnaires of general tinnitus distress. There is a growing body of literature on how interventions such as psychological treatments (see Hesser, Weise, Westin, & Andersson, 2011, for review), hearing aid use (see Hoare, Edmondson-Jones, Sereda, Akeroyd, & Hall, 2014, for review), neuromodulation (see Peter & Kleinjung, 2019, for review), and other treatments affect tinnitus distress and loudness. Despite this, we remain unable to determine which of these options (if any) might be best for the tinnitus sufferer seeking to improve their cognitive performances and/or perceived exertion when performing cognitive tasks. Future research should start evaluating the interventions currently used for tinnitus patients at the clinic not only by their effect on tinnitus questionnaires but also on behavioural measures. It would also be interesting to examine the value of educating tinnitus patients with cognitive difficulties about the association between hearing impairment and cognitive abilities in addition to, or perhaps rather than, educating them about the possible association between tinnitus and cognitive abilities. The value of this approach could be increased if it was coupled with adequate hearing rehabilitation such as the fitting of hearing aids. Tinnitus sufferers tend to associate hearing related problems with their tinnitus rather than their hearing impairment (Henry et al., 2015; Zaugg et al., 2002), and it is possible that their annoyance due to the phantom sound experience could be mildly mitigated by knowing more about what it does and what it does not cause.

Another challenge remaining for future research investigating the potential effect of tinnitus on cognitive performance is to explore if different types of tinnitus have different implications for cognitive performances. As mentioned previously, tinnitus should be seen as a symptom that could arise from a range of causes rather than a condition on its own. There has been attempts to start dividing tinnitus into subtypes (e.g. Landgrebe et al., 2010), but there is currently no consensus regarding how such sectioning should be formed or what degree aetiology should play compared to tinnitus characteristics (e.g. laterality, pitch, patterns of neurological activity etc.). Nevertheless, it is plausible that different types of tinnitus could affect cognitive abilities differently, and the current strategy for investigating the effect of tinnitus on cognitive performance (where all tinnitus sufferers are typically grouped together regardless of aetiology or characteristics) may blur the ability to identify the true impact of tinnitus in an individual person.

There is growing evidence suggesting that the use of hearing aids could slow down cognitive aging in individuals with hearing impairment (e.g. Dawes et al., 2015; Lin et al., 2011). However, until recently hearing aids rarely provided gain above 8 kHz, and at the time of writing, the very latest modern hearing aids do not provide gain above 10 kHz. Therefore, the effect of using todays' hearing aids on the cognitive difficulties associated with hearing impairment above 8 kHz is assumed to be minimal. However, the fact that amplification of sounds achieved with todays' hearing aids could have positive impact on cognitive measures in individuals with hearing impairment at 0.25 to 8 kHz is certainly a promising sign suggesting that it might be worth exploring the possibilities of amplification above 8 kHz as a treatment for individuals with (or without) tinnitus experiencing cognitive difficulties.

Finally, the findings of this thesis call for further investigation of what specific neurological structures are associated with hearing impairments at frequencies above 8 kHz. The relationships observed in Studies II to IV indicate that hearing impairments above 8 kHz may be negatively associated with several cognitive domains. This suggests that a neurological approach could be suitable to better understand the mechanisms underlying any associations between high frequency hearing and cognitive abilities. A first attempt to explore these aspects was made by Melcher et al. (2013), who reported poorer hearing thresholds above 8 kHz to be significantly associated with less grey matter in the subcallosal region of the brain. More research of this nature is warranted.

Methodological considerations

Sampling bias

When interpreting the results of the present project, it is important to understand that sampling bias was present. Tinnitus participants were mainly recruited through audiology clinics and public advertisement in southern Sweden. The tinnitus sufferers examined and included in the studies were young adults (typically 20 to 45 years old, never older than 67 years) with high educational background. They reported tinnitus severity quite evenly spread over the spectrum (i.e. from barely bothered by their tinnitus to the most severe cases of tinnitus). In Studies I and II all tinnitus sufferers had normal hearing (defined as having no hearing threshold worse than 20 dB HL at standard frequencies 0.125 to 8 kHz), and in Studies III and IV half of the tinnitus sufferers had normal hearing while half had hearing impairments (see *figure 3* for details regarding the participants hearing status). Every included control subject was matched to a tinnitus sufferer in terms of hearing status (normal hearing/hearing impairment), sex, age (maximum deviation of 12 months of age in Studies I and II, and 24 months in Studies III and IV) and educational background (comparable education on group level). This sampling serves a purpose, as the stratification minimizes the effect of the mentioned matched parameters, allowing us to focus on the possible impact of tinnitus on the outcomes. However, it should be emphasized that the individuals studied are not representative of the total tinnitus population (as it is typically older, more male dominated, has greater degrees of hearing impairment and poorer educational background compared to the individuals studied in the present project). Taken together, the individuals studied form an expedient dataset for investigating the isolated effect of tinnitus on cognitive performances, but not for investigating the experiences of the *typical* tinnitus sufferer.

Levels of tinnitus severity

As degree of tinnitus severity is commonly mentioned as a possible key factor for the suspected negative impact of tinnitus on cognitive performances (suggesting that tinnitus impairs cognitive performances more in cases with more severe tinnitus [e.g. Jackson et al., 2014; Rossiter et al., 2006; Stevens et al., 2007]), it is important to compare the levels of tinnitus severity in the present project with previous studies. However, the evidence for this assumption has been mixed, as some studies have reported significant correlations between self-reported tinnitus severity and measured cognitive performances (Cuny et al., 2004; Jackson et al., 2014; Leong et al., 2020; Stevens et al., 2007), some have reported absence of significant correlations between self-reported tinnitus severity and measured cognitive performances (Dornhoffer et al., 2006; Heeren et al., 2014), and others have not reported any attempts of calculating possible correlations between self-reported tinnitus severity and measured cognitive performances (Andersson et al., 2000; Rossiter et al., 2006). Caution should be paid to the possible risk of circle reasoning when claiming that a correlation between self-reported tinnitus severity and measured cognitive performance indicates that greater degree of tinnitus severity implies greater cognitive difficulties, since you are partly examining the same aspects with two different measurements as tinnitus questionnaires typically cover experiences of cognitive difficulties among other tinnitus related difficulties.

A majority of previous studies investigating the link between tinnitus and cognitive performance have examined the level of tinnitus severity among their participants, however, most have done so using different questionnaires:

a) Tinnitus Reaction Questionnaire (TRQ; Wilson, Henry, Bowen, & Haralambous, 1991), was used by Rossiter et al. (2006);

b) Tinnitus Psychological Impact Questionnaire (QIPA; unpublished), was used by Heeren et al. (2014);

c) Subjective Tinnitus Severity Scale (STSS; Halford & Anderson, 1991), was used by Cuny et al. (2004), Jackson et al. (2014);

d) Tinnitus Questionnaire (TQ; Hallam et al., 1988), was used by Stevens et al. (2007), Leong et al. (2020);

e) short version of the Tinnitus Questionnaire (S-TQ; Hallam, 1996), was used by Andersson et al. (2000);

f) Tinnitus Severity Index Questionnaire (TSI; Meikle, Griest, Stewart, & Press, 1995), was used by Dornhoffer et al. (2006).

This makes it difficult to compare levels of tinnitus severity across studies, not only because a score from one scale cannot be translated directly to an equivalent score of another scale, but also because different topics make up different proportions of different tinnitus questionnaires (Kennedy et al., 2004), meaning different questionnaires measure different aspects of tinnitus related difficulties. The developers of tinnitus questionnaires typically report descriptive statistics on how the tinnitus population scores on their questionnaire. The comparison of levels of tinnitus severity in studies using different questionnaires to assess tinnitus severity could be put into context by also referring to the studies' levels of severity compared to the descriptive statistics reported by the questionnaire developer. This is done below by reporting the different studies' mean tinnitus severity scores along with the median score reported for different scales used.

Apart from previous studies measuring tinnitus severity in different ways, they have also been using different approaches regarding tinnitus severity when recruiting participants. They have either tried to recruit participants with higher degree of tinnitus severity (Andersson et al., 2000; Rossiter et al., 2006) (as it "maximized the chances of obtaining significant results from a sample of manageable size" [Rossiter et al., 2006]), aimed for tinnitus sufferers with low degrees of tinnitus severity in order to investigate whether cognitive impact is present even for that subpopulation (Jackson et al., 2014), or just reported tinnitus severity among participants to range from mild to severe without indicating a specific recruitment aim (Cuny et al., 2004; Heeren et al., 2014; Leong et al., 2020; Stevens et al., 2007).

In Studies I and II, the TQ was used to examine tinnitus severity, and in Studies III and IV the THI was used, meaning that the only other studies that both examined the same cognitive domain and reported levels of tinnitus severity that are possible to make direct comparisons with is the ones reported by Leong et al. (2020) and Stevens et al. (2007) (compared to Study I). The tinnitus participants in the study reported by Stevens et al. (2007) had a higher mean score (47.6) and a slightly wider but completely overlapping range (2-81 out of 82) on the TQ compared to Study I (mean: 40.1; range: 16-61). However, in the context of the range of the scale, the mean levels of tinnitus severity are similar in the two studies, both close to the TQ median: 43 points. In addition, other studies examining executive attention have reported negative impact of tinnitus on task performance similar to (Stevens et al., 2007) regardless if the participants' showed low (Jackson et al., 2014) or high (Andersson et al., 2000) mean levels of tinnitus severity. The tinnitus participants in the study reported by Leong et al. (2020) had a lower mean score (14.4), far below the TQ median of 43 points. Taken together, this indicates that the differences in results between Study I and previous studies examining executive attention in tinnitus sufferers are not attributed to differences in degrees of tinnitus severity.

Despite above mentioned shortcomings in comparability across studies, it is possible to put reported levels of tinnitus severity next to each other in order to give a rough indication of possible differences that may have impacted the results. For WM (examined in Studies II and III in the present project), Rossiter et al. (2006) reported moderate mean level of tinnitus severity (mean: 36.4, range: 0-72 on the TRQ ranging from 0-104, median point of the scale being 27 points), which is somewhat comparable to the levels reported in Study II (mean: 35.2, range: 15-72 on the TQ ranging from 0-82, median point of the scale being 43 points) and Study III (mean: 35.3, range: 6-84 on the THI ranging from 0-100, median point of the scale being 36 points) – again not clearly indicating the differences in results between this project and previous studies to be attributed to differences in tinnitus severity.

As Study IV is the first study investigating the association between tinnitus and performance on and exertion due to office-like tasks, it is of limited purpose to directly compare levels of tinnitus severity to previous studies'. However, the tinnitus severity among participants in Study IV seems to be similar to levels reported by majority of previous studies, with its wide range of tinnitus severity averaging just below the median point of the scale used to assess tinnitus severity (mean: 35.3, range: 6-84 on the THI ranging from 0-100, median point being 36).

Another aspect to keep in mind when comparing the levels of tinnitus severity in the present project to previous studies' is that the present project aims to investigate the isolated direct effect of tinnitus on cognitive performances. The main argument suggesting higher degree of tinnitus severity leading to greater negative cognitive impact is that higher tinnitus severity seems to be related to higher degrees of anxiety and emotional distress, which in turn may have negative impact on cognitive performances (Jackson et al., 2014; Rossiter et al., 2006; Stevens et al., 2007). This model implies anxiety and emotional distress, rather than presence of tinnitus, to cause the self-reported cognitive difficulties among tinnitus sufferers, suggesting an indirect link between tinnitus and cognitive performance, which is not the type of impact the present project is aiming to target.

Sample sizes

When reporting absence of previously reported findings it is important to compare sample sizes between studies. The smaller effect sizes you are looking for, the bigger your number of observations has to be in order to have a reasonable chance of detecting said effect. In other words, if you report absence of previously reported findings but your sample size deviates from previous studies', it is difficult to determine whether you see different results because the effect is absent (true negative finding) or because you have too few observations to reach statistical significance despite actually looking at the same effect (false negative finding).

Previous studies have reported tinnitus to have negative impact on executive attention when analysing performances in groups of 23 tinnitus sufferers compared to 23 control participants (Andersson et al., 2000), 11 tinnitus sufferers compared to 11 control participants (Stevens et al., 2007), 33 tinnitus sufferers compared to 33 controls (Jackson et al., 2014), and 18 tinnitus sufferers compared to 15 controls (Leong et al., 2020). In Study I, I reported tinnitus not to be associated with poorer executive attention when analysing performances in a group of 20 tinnitus sufferers compared to a group of 20 control participants. When calculating effect sizes based on the findings presented in previous studies reporting impact of tinnitus on executive attention, I found that the smallest significant effect size was found in the study reported by (Andersson et al., 2000), where the significant differences in response times between tinnitus sufferers and control subjects on the Stroop test (stimuli: tinnitus control words) implied an effect size of Cohen's d = 0.984. With our two groups of 20 individuals each, our statistical chance of finding an effect of comparable size was 99%, meaning that the risk of committing a type II error (i.e. not rejecting a false null hypothesis) was 1%. In the light of this, I argue that the differences in results between Study I and previous studies examining executive attention in tinnitus sufferers is probably not attributable to differences in sample size.

Rossiter et al. (2006) reported tinnitus to have negative impact on WM capacity when analysing performances in groups of 19 tinnitus sufferers compared to 19 control participants. In Studies II and III, I reported tinnitus not to be associated with poorer WM capacity when analysing performances in groups of 31 tinnitus sufferers compared to a group of 31 control participants, and groups of 38 tinnitus sufferers compared to 38 control participants. Rossiter et al. (2006) reported significant differences between tinnitus sufferers and control participants in terms of numbers of errors in the category naming condition of the reading span test, implying an effect size of Cohen's d = 1.217. In our study with smallest sample size investigating impact of tinnitus on WM capacity (Study II), our two groups of 31 individuals each gives a statistical chance of > 99% for finding an effect of comparable size, meaning that the risk of committing a type II error (i.e. not rejecting a false null hypothesis) was < 1%. In Study III, the chance of committing a type II error was even smaller, as the sample size was greater. In the light of this, I argue that the differences in results between Study I and previous studies examining WM in tinnitus sufferers is probably not attributable to differences in sample size.

As the present project is the first to report a study investigating the potential impact of tinnitus on office-like tasks (Study IV), there are no previous effect sizes with which to compare it.

As tinnitus is a very heterogeneous symptom, affecting individuals differently, it would be optimal to examine far more individuals despite having reached sufficient statistical power with our sample sizes. After all, there might be subpopulations with difficulties and underlying mechanisms differing from the rest of tinnitus sufferers. These are aspects which the present project cannot illuminate, which may be regarded as a limitation. On the other hand, as the recruitment of participants became very time consuming due to our strict matching criteria regarding age, sex and educational background, reaching sample sizes with sufficient statistical power was a big enough challenge itself.

Weakness of design

A limitation of the studies of the present project, as well as all previous studies exploring the link between tinnitus and cognitive performance, is that we tend to compare the performances on cognitive tests in two (or more) groups at a given time. This research design gives us information regarding how one group performs compared to another, but it does not tell us if the performances of the tinnitus group have changed compared to pre tinnitus debut. This use of a cross-sectional research design is not useless as it is cost effective, less time consuming, and gives valuable clues regarding any relationships amongst the variables of interest. Arguably, if tinnitus would have clear negative effect on cognitive performance, then we would probably see differences between the performances of tinnitus sufferers and carefully matched control subjects on cognitive tests. However, we do not know what effect size we are looking for as this initial investigation is exploratory. We do not know how subtle a change in cognitive performance can be post vs pre tinnitus debut for a tinnitus sufferer to be bothered. In order to truly determine whether tinnitus changes the individual's cognitive performance, we would have to measure cognitive performance pre and post tinnitus debut. A way of doing so could be letting individuals working in environments implying high risk of tinnitus undergo cognitive screening batteries periodically regardless of tinnitus status, and keep track of new cases of tinnitus. If done on large scale, this would allow for longitudinal study designs capable of accounting for aspects such as aging and the effect of undergoing a cognitive test multiple times. The use of such designs could obtain a better measure of how tinnitus affects an individual's cognitive performance.

After studying the previous literature on the link between tinnitus and cognitive performance, and carrying out a few studies trying to compensate for previous studies' lack of control for hearing status, a consistent shortcoming was identified; all studies had used short duration intense tasks designed to measure specific cognitive domains. While being an adequate strategy for evaluating specific cognitive abilities, it has low ecological validity as the tests used do not resemble of anything the average person encounters in their every-day life. In addition, all studies had used achieved scores and response times on mentioned tests as primary outcome. Such way to measure cognitive performance fails to address tinnitus sufferers complaining about feeling exhausted when performing cognitive tasks, as two individuals can achieve similar scores with very different levels of effort. In Study IV, I tried to address these shortcomings by comparing individuals with and without tinnitus in terms of performances on an office-like task (developed by colleagues at Linköping University [Hua et al., 2014]), as well as self-reported exertion due to performing the office-like task. This test was more similar to a task you might encounter at work, and took about four times longer to finish compared to the tests used in previous studies. However, the office-like task still only took just over 20 minutes to finish (for the individuals with longest response times). Such increase of test duration is probably positive when trying to take cognitive endurance into account, however, when comparing the test duration to what most individuals are expected to endure at work, the test might still be too short. Measuring perceived exertion due to a cognitive task, as done in Study IV, is an important first step towards broadening the outcome measures when exploring the effect of tinnitus on cognitive abilities. However, previous studies on perceived exertion on physical tasks has shown that simultaneous music listening can alter the relationship between objective and perceived exertion (Boutcher & Trenske, 1990; Potteiger, Schroeder, & Goff, 2000). At the time of writing, it is not possible to tell if this effect was due to music specifically (or if this was true for any type of auditory distraction, such as tinnitus). Nor is it possible to tell if the effect was applicable to cognitive tasks. This uncertainty calls for inclusion of more objective measures of exertion in future studies of the link between tinnitus and cognitive abilities.

Another limitation is that hearing aid use was not controlled for in Studies III and IV. As previously mentioned, evidence suggests use of hearing aids could slow down cognitive aging in individuals with hearing impairment (e.g. Dawes et al., 2015; Lin et al., 2011). In Studies III and IV, individuals with and without hearing impairment were included. On group level, the participants with hearing impairment had mild to moderate hearing impairment. It usually takes considerable time for patients to seek help for hearing impairment (Davis et al., 2007), but hypothetically, individuals with mild hearing impairment and tinnitus may be more motivated to seek help compared to individuals with mild hearing impairment but without tinnitus, as tinnitus may draw greater attention to the impairment and may worry the tinnitus sufferer. This implies that hearing aid use could, hypothetically, have been more common among the tinnitus participants with hearing impairment compared to control participants with hearing impairment in Studies III and IV. If true, this difference might have been an advantage for the tinnitus group and could have masked any negative association between tinnitus and cognitive performance. However, countering this argument are the two studies I performed with individuals with normal hearing only (Brännström & Waechter, 2018; Waechter et al., 2019), which indicated presence of tinnitus not being associated with WM capacity or every-day life task performance (in the form of immediate and delayed recall on a reading comprehension task). As those results are in line with Study III and IV, the likelihood that absence of significant associations between tinnitus and cognitive performance and exertion was due to not controlling for use of hearing aids decreases.

Ethical considerations

While the ethical risks of studies in the present PhD project have been deemed to be acceptable by the Regional Ethical Review Board, there may be ethical risks post conduction of the studies. The clearest risk is probably related to how our findings will be interpreted by others. It is possible that our findings will be *misinterpreted* as indications of

a) tinnitus sufferers not being honest regarding the consequences of their condition,

b) tinnitus not having any negative consequences, or

c) health care providers not understanding how tinnitus impacts the tinnitus sufferer.

The first example of potential misinterpretations could occur as diagnosis of tinnitus is currently based on the patient's subjective experience rather than objective measures. In addition, tinnitus sufferers may (depending on degree of tinnitus severity) receive governmental support actions. The combination of these circumstances may create a sense of suspicion. The findings of the current project could worsen such suspicions, even though our research group does not question the subjective experiences of tinnitus sufferers but strives to bring clarity to the underlying causes to the difficulties experienced by the present patient group. This hypothetical scenario could also contribute to stigmatization for a patient group that currently often seems to feel like they are being disregarded by the health care system.

The second example of potential misinterpretations could occur as it is not uncommon for society at large to draw generalized conclusions regarding health conditions based on data that only tells us about specific aspects of the condition (e.g. Dijkstra, Kok, Ledford, Sandalova, & Stevelink, 2018; Sigman, 2014). This would be negative as it could make tinnitus sufferers less motivated to seek health care. Such a scenario would be worrying, partly because not receiving adequate health care can have negative impact on life quality for the tinnitus sufferer but also because tinnitus can be caused by critical underlying causes such as vestibular schwannoma (Baguley et al., 2006; May et al., 2011), carotid stenosis (Carlin et al., 1997; Emery et al., 1998; Kirkby-Bott & Gibbs, 2004) or aneurysm (Cuellar et al., 2018; Depauw et al., 2001; Kim et al., 2018). The negative consequences typically increase with longer diagnosis latency, and the chances to diagnose those patients in time and offer potentially mitigating interventions decreases if tinnitus sufferers do not seek health care.

All above mentioned potential misconceptions could result in fewer tinnitus sufferers seeking health care. This is a possible effect as there already seems to be a common experience among tinnitus sufferers that modern health care offers nothing for them but information regarding the lack of a universal cure for tinnitus and how to best cope with always hearing the tinnitus. All of the above mentioned potential misconceptions could also lead to decision makers down prioritize funding of both tinnitus health care and research, which is the opposite to the conclusion of our research group.

CONCLUSIONS

The present PhD project indicates no significant association between tinnitus per se and cognitive performance (specifically on tests measuring executive attention and working memory capacity, as well as performance and perceived exertion on an office-like task) when controlling for hearing status. Instead, I found hearing thresholds at 10 to 16 kHz was negatively associated with working memory capacity and performance on the office-like task in adults with and without tinnitus.

SAMMANFATTNING PÅ SVENSKA

Tinnitus, det vill säga att höra ljud utan yttre ljudkälla, förmodas drabba omkring 15% av alla vuxna och är därmed en av de vanligast förekommande hörselrelaterade åkommorna. Personer med tinnitus tenderar att uppleva att ljuden, som av de drabbad ofta beskrivs som kroniskt ringande eller tjutande, leder till problem i form av ångest, depression, sömnsvårigheter eller försämrad koncentrationsförmåga. Denna avhandling fokuserar på det sistnämnda problemet.

Tidigare studier har indikerat att tinnitus har negativ inverkan på ett flertal olika kognitiva mått, däribland exekutiv uppmärksamhet och arbetsminneskapacitet. En genomgående svaghet bland dessa studier har varit bristande kontroll av deltagarnas hörselstatus. Detta är problematiskt eftersom en klar majoritet av tinnitusdrabbade har någon form av hörselnedsättning, och kopplingen mellan hörselnedsättning och försämrade kognitiva prestationer sedan tidigare är väl belagd. Detta gör det svårt att veta till vilken grad tidigare studiers rapporterade skillnader i kognitiva prestationer beror på deltagarnas tinnitus eller deras hörselstatus. I dagsläget finns ingen evidensbaserad intervention för den aktuella patientgruppen, och bristerna bland tidigare studier har gjort det omöjligt att utforma sådana.

Mot bakgrund av detta undersöker det aktuella doktorandprojektet vilka av tidigare föreslagna kognitiva mått faktiskt påverkas av tinnitus då vi kontrollerar noggrant för hörselstatus. Vidare utforskar vi mått som tydligare relaterar till de tinnitusdrabbades vardag, genom att undersöka hur tinnitus påverkar prestation på och upplevd ansträngning vid kontorsliknande uppgifter, aspekter som förbisetts helt av tidigare studier.

Vi har genomfört fyra studier där kognitiva prestationer hos totalt 89 tinnitusdrabbade och 89 välmatchade kontrolldeltagare jämförts. Resultaten indikerar att tinnitus vare sig har negativ inverkan på exekutiv uppmärksamhet, arbetsminneskapacitet eller prestation och upplevd ansträngning vid kontorsliknande uppgifter, när vi kontrollerar för hörselstatus, grad av ångest och depression, ålder, kön och utbildningsnivå.

Däremot indikerar våra studier, *oberoende av tinnitus*, signifikanta samband mellan hörselnedsättningar ovanför 8 kHz och sämre kognitiv prestation i form av arbetsminneskapacitet och prestation vid kontorsliknande uppgift. Detta är ett frekvensområde som i dagsläget ytterst sällan undersöks varken kliniskt eller inom forskning, men som det aktuella doktorandprojektet belyser vikten av att vidare utforska.

DEUTSCHE ZUSAMMENFASSUNG

Tinnitus, oder die Wahrnehmung von Geräusche ohne äussere Schallquellen, plagt ca. 15% alle Erwachsene und ist damit eine der häufigsten hörbedingte Störungen. Individuen mit Tinnitus erleben oft, dass die Geräusche, die Sie hören, zu Problemen wie Angstzustände, Depressionen, Schlafschwierigkeiten und Konzentrationsstörungen führen. Diese Dissertation fokussiert auf das letztere Problem.

Frühere Studien deuten darauf hin, dass Tinnitus mehrere kognitive Fähigkeiten, zum Beispiel exekutive Aufmerksamkeit und Arbeitsgedächtniskapazität, negativ beeinflusst. Eine allgegenwärtige Schwäche dieser Studien war die mangelnde Kontrolle des Hörstatus der Teilnehmer. Dies ist problematisch, da eine klare Majorität der Individuen mit Tinnitus an irgendeiner Form von Hörverlust leidet, und die Verbindung zwischen Hörverlust und beeinträchtigter kognitiver Leistung zuvor klar dokumentiert wurde. Dies macht es schwierig zu wissen, inwieweit die in früheren Studien gemeldeten Unterschiede in der kognitiven Leistung vom Tinnitus der Teilnehmer oder ihrem Hörstatus abhängen. Derzeit gibt es keine evidenzbasierte Intervention für die aktuelle Patientengruppe, und die Mängel früherer Studien haben es unmöglich gemacht, eine solche zu entwerfen.

Deshalb untersucht das aktuelle Dissertationsprojekt, welche der zuvor vorgeschlagenen kognitiven Massnahmen tatsächlich von Tinnitus betroffen sind, wenn wir für den Hörstatus sorgfältig kontrollieren. Dazu untersuchen wir Massnahmen, die sich deutlicher auf den Alltag von Tinnitus betroffenen beziehen, sowie wie Leistungen und die wahrgenommene Anstrengung bei büroähnlichen Aufgaben auswirkt. Diese Aspekte wurden in früheren Studien völlig übersehen.

Wir haben vier Studien fertiggestellt, in denen die kognitiven Leistungen von insgesamt 89 Tinnitus betroffenen und 89 sorgfältig abgestimmten Kontrollpersonen vergleichen wurde. Die Ergebnisse indizieren, dass Tinnitus exekutive Aufmerksamkeit, Arbeitsgedächtniskapazität und büroähnliche Aufgaben *nicht* negativ beeinflusst, da wir für Hörstatus, Grad von Angstzuständen und Depressionen, Alter, Geschlecht und Bildungsniveau kontrollieren.

Unsere Studien indizieren jedoch, *unabhängig von Tinnitus*, signifikante Zusammenhänge zwischen Hörverlust über 8 kHz und einer schlechteren kognitiven Leistung in Bezug auf die Arbeitsgedächtniskapazität und bei büroähnlichen Aufgaben. Dies ist ein Frequenzbereich, der derzeit äusserst selten weder klinisch oder in der Forschung untersucht wird. Das aktuelle Dissertationsprojekt unterstreicht jedoch die Bedeutung weiterer Untersuchungen.

SAMANTEKT Á ÍSLENSKU

Eyrnasuð, eða að heyra hljóð án utanaðkomandi hljóðgjafa, er talið hafa áhrif á um 15% allra fullorðinna og er þar með einn algengasti heyrnartruflunin. Fólk með eyrnasuð hefur tilhneigingu til að upplifa að hljóðið, sem oft er lýst sem langvarandi hringingum eða væla, valda vandamálum í formi kvíða, þunglyndis, svefnörðugleika eða skertrar einbeitingar. Þessi ritgerð fjallar um síðara vandamálið.

Fyrri rannsóknir hafa bent til þess að eyrnasuð hefur neikvæð áhrif á margvíslegar vitsmunaaðgerðir, þar með talið stjórnunar athygli og vinnuminnisgetu. Einn helsti veikleiki þessara rannsókna hefur verið skortur á mælingu á heyrnarstaða þátttakenda. Þetta er vandasamt vegna þess að skýr meirihluti fólks með eyrnasuð er með einhvers konar heyrnartap, og tengsl milli heyrnartaps og skertra vitsmunalegra frammistöðu hafa verið vel staðfest áður. Þetta gerir það erfitt að vita hve miklu leyti tilkynntur munur á vitsmunalegum árangri í fyrri rannsóknum á veltur á eyrnasuðið þátttakendar eða heyrnarstöðu þeirra. Sem stendur er engin gagnreynd íhlutun fyrir þessi sjúklingahóp og gallarnir meðal fyrri rannsókna hafa gert það ómögulegt að hanna slíka.

Með hliðsjón af þessu rannsakar þessi doktorsverkefni hvaða vitsmunalegum aðgerðum er í raun og veru fyrir áhrifum eyrnasuðs þegar við athugum vandlega áhrif af heyrn. Ennfremur skoðum við ráðstafanir sem eru skýrari tengdar daglegu lífi fólks með eyrnasuð, með því að skoða hvernig eyrnasuð hefur áhrif á frammistöðu og skynja áreynslu í skrifstofutengdum verkefnum, þætti sem ekki var horft til í fyrri rannsóknum.

Við gerðum fjórar rannsóknir þar sem borinn var saman vitsmunalegur árangur hjá alls 89 þátttakendum með eyrnasuð og 89 vel samsvarandi einstaklingi án eyrnasuðs. Niðurstöðurnar benda til þess að eyrnasuð hafi *ekki* neikvæð áhrif á stjórnunar athygli, vinnuminnisgetu eða frammistöðu og upplifað áreynslu í skrifstofulíkum verkefnum þegar ráðandi með tilliti til heyrnarstöðu, kvíða og þunglyndis, aldurs, kyns og menntunarstigs.

Aftur á móti benda rannsóknir okkar, *óháð eyrnasuð*, marktækum tengslum milli heyrnarskertra yfir 8 kHz og lakari vitsmunalegum árangri í formi vinnuminnisgetu og frammistöðu í skrifstofulíkum verkefnum. Þetta er tíðnisvið sem nú er sjaldan mælt hvorki klínískt né innan rannsókna, en þar sem núverandi doktorsverkefni undirstrikar mikilvægi frekari rannsókna.

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