From Physiology and Pharmacology
Karolinska Institutet, Stockholm, Sweden

OBJECTIVE DIAGNOSTICS OF TINNITUS

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Stockholm 2023

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2023.

ISBN: 978-91-8016-915-8
Cover illustration: “A brain answering questions while being bothered by a ringing sound, expressionist colorful painting” interpreted by Dall-E 2, February 2023.

Objective diagnostics of tinnitus

Thesis for Doctoral Degree (Ph.D.)

By

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The thesis will be defended in public at Sal: Nils Ringertz, Biomedicum Vån 3, Solnavägen 9, Karolinska Institutet. 2023-04-24, 10.00.

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Beware of the man who works hard to learn something, learns it, and finds himself no wiser than before. He is full of murderous resentment of people who are ignorant without having come by their ignorance the hard way.

- Kurt Vonnegut, Cat's Cradle

Popular science summary of the thesis

The experience of ringing or hissing sound, without an external sound source is a very common problem. The phantom sensation is called tinnitus and experienced by around 14% of the population. Over 120 million people world-wide perceive tinnitus as a major problem and it often leads to difficulties to concentrate, relax, sleep, stress and anxiety. Some techniques, like cognitive behavior therapy, can reduce the impact of tinnitus, but there are no treatments that reliably remove the phantom sound. The development and evaluation of novel treatments are hampered by two factors. Firstly, tinnitus is experienced very differently by those who have it and it is not clear if there are relevant sub-types of tinnitus that should be handled differently. Secondly, there are no objective measurements of tinnitus – all tinnitus diagnostics are based on self-report, i.e., questionnaires or rating scales. An objective biomarker of tinnitus would accelerate development of novel treatments and potentially enable the identification of relevant sub-types of tinnitus.

This thesis first investigates the association between tinnitus and three common conditions often reported by patients with tinnitus; temporomandibular joint (TMJ) pains, hyperacusis and headaches. The fourth study evaluates the clinical auditory brainstem response (ABR), an electrophysiological measurement of the auditory pathway, as a tool for tinnitus diagnostics. The final study initiates the adaptation of a stimulation protocol called GPIAS (Gap Pre-Pulse Inhibition of Acoustic Startle), commonly used for assessment of tinnitus in animal models. In animal models the read-out is commonly a muscular startle response. Here, we evaluate the cortical response in the brain using a scanning technique called MEG (magnetoencephalography).

The thesis concludes that TMJ pains are associated with tinnitus, especially severe tinnitus, and these patients may constitute a relevant sub-group. There is a strong association between tinnitus, hyperacusis and hearing loss and it is imperative that studies of tinnitus consider the interaction of these conditions. There is some association between headaches and tinnitus and reports of pain-syndromes should be noted in studies of tinnitus. A delay of the fifth wave of the ABR, corresponding to activity in the brainstem region of inferior colliculus, separates subjects with constant tinnitus from those who experience tinnitus occasionally and non-tinnitus controls. However, the high variance in this response limits its use as a biomarker for individual patients.

We show that a GPIAS protocol reliably produce inhibition of cortical responses with less variance than the muscle response analogues to the animal startle response. GPIAS together with MEG is a promising approach to developing a biomarker for tinnitus. Finally, a path for developing this protocol to use in a case-control study of tinnitus patients are described.

Populärvetenskaplig sammanfattning

Upplevelsen av ett pipande eller susande ljud, utan någon extern ljudkälla, är ett väldigt vanligt problem. Fantomljudet kallas för tinnitus och upplevs av ungefär 14% av befolkningen. Över 120 miljoner människor världen över upplever tinnitus som ett stort problem och det leder ofta till svårigheter med att slappna av, koncentration, sömn, stress och ångest. En del tekniker, som kognitiv beteende terapi, kan minska påverkan tinnitus har men det finns inga behandlingar som tillförlitligt tar bort fantomljudet. Utveckling och utvädering av nya behandlingar begränsas av två faktorer. För det första upplevs tinnitus väldigt olika av alla som är drabbade och det är inte klart om det finns relevanta sub-typer av tinnitus som bör hanteras olika. För det andra finns det ingen objektiv mätning av tinnitus – all diagnostik av tinnitus är baserad på självrapportering med t.ex frågeformulär eller skattningsskalor. En objektiv biomarkör för tinnitus skulle acclerera utvecklingen av nya behandlingar för tinnitus och potentiellt möjliggöra identifiering av relevanta sub-typer av tinnitus.

Denna avhandling börjar med att undersöka associationen mellan tinnitus och tre vanliga åkommor som ofta rapporteras av patienter med tinnits; käkledssmärtor, hyperacusis (ljudkänslighet), och huvudvärk. Den fjärde studien utvärderar klinisk hjärnstams-audiometri (ABR), en elektrofysiologisk mätning av nervbanorna för hörsel, som ett verktyg för diagnostik av tinnitus. Den femte studien anpassar ett stimulations-protokoll (kallat GPIAS) som är vanligt för att bedöma tinnitus i djurmodeller. I djurmodeller används ofta en muskelrespons som resultat av mätningen. Här utvärderar vi istället kortikala svar från hjärnan med en teknik kallad MEG (magnetoencefalografi).

Avhandlingen når slutsatsen att käkledssmärtor är associerade med tinnitus, särskilt fall av svår tinnitus, och dessa patienter kan utgöra en relevant sub-grupp. Det finns ett starkt samband mellan tinnitus, hyperacusis och hörselnedsättning och det viktigt att studier av tinnitus tar interkationen av dessa åkommor i beaktande. Det finns viss samverkan mellan huvudvärk och tinnitus och information om smärt-syndrom bör tas med i stuider av tinnitus. En försening av den femte vågen i ABR, motsvarande aktivitet i inferior colliculus, kan urskilja patienter med konstant tinnitus från de som upplever tinnitus ibland och kontroll-deltagare utan tinnitus. Dock gör den höga variansen i det enskilda resultatet att dess användbarhet som biomarkör för individuella patienter är begränsat.

Vi visar att ett GPIAS-protokoll producerar inhibition av kortikala responser med lägre varians än de muskelresponser som motsvarar mätningar i djurmodeller. GPIAS tillsammans med MEG är ett lovande tillvägagångssätt för att utveckla en objektiv biomarkör för tinnitus. Slutligen föreslås nästa steg för att vidareutveckla detta protokoll för använding i en fall/kontroll-studie av patienter med tinnitus.

Abstract

Background Tinnitus is the phantom perception of sound reported by around 14% of the population. For over 120 million people worldwide tinnitus is perceived as a major problem. Still, tinnitus is a heterogenous condition with no stratified sub-types or biomarkers for objective assessment. This severely limits the potential for development and evaluation of novel therapies for tinnitus. This thesis aims to I) investigate the relationship between conditions commonly reported by tinnitus patients and II) evaluate the potential of electrophysiology or magnetoencephalography (MEG) to function as an objective biomarker for tinnitus.

Methods Studies I-III retrospectively analyzed questionnaire data, in total n = 5 593, collected in the Swedish Tinnitus Outreach Project (STOP) between November 2015 and January 2018. Multivariate logistic regression models were implemented to investigate the association between tinnitus and related conditions - temporomandibular joint (TMJ) pains, hyperacusis and headaches. Study IV used longitudinal data from The Swedish Longitudinal Occupational Survey of Health (SLOSH), in total 20 439 participants, with 53 273 observations. The transition from occasional to constant tinnitus was investigated using Generalized Estimating Equation (GEE) models. The second part of Study IV used ABR data from STOP (n = 405) to evaluate measurements of wave I, III & V amplitude and latency in distinguishing constant from occasional tinnitus, or non-tinnitus controls. Study V recruited n = 22 normal hearing, non-tinnitus participants for optimization of a GPIAS (Gap Pre-pulse Inhibition of Acoustic Startle) protocol for MEG. In this exploratory study sound pulses of 20 ms were presented in 60 or 70 dBA carrier noise with a 50 ms silent gap preceding the pulse by 240, 120, 60 or 0 ms. All MEG were recorded by the Elekta Neuromag TRIUX 306-channel system at NatMEG, Karolinska Institutet.

Results TMJ complaints increased to over 30% among those with severe tinnitus, compared to 19% in all participants with tinnitus. For headache, adjusted odds ratios (95% confidence interval) showed an association of OR: 3.8 (2.4-5.9) and a strong association with hyperacusis of OR: 12.1 (7.1-20.6) was found for those with severe tinnitus. Longitudinal analysis indicated that tinnitus progresses towards constant tinnitus and that once established is very unlikely to remit. Changes in the ABR response, particularly wave V latency, distinguished constant from occasional tinnitus and non-tinnitus controls, likely reflecting plastic changes related to this chronification. A GPIAS stimulation protocol with an inter-stimulus interval of 240 ms between silent gap and 90 dBA pulse produced N1-inhibition of ERF responses with much lower variability when compared to traditional EOG responses.

Conclusion We identified TMJ complaints and hyperacusis as important factors to consider in future studies of tinnitus. ABR wave V latency can distinguish constant tinnitus from occasional or non-tinnitus at a group level, but is likely not sensitive enough for individual diagnostics. Instead, GPIAS together with MEG is a promising approach to developing a biomarker for tinnitus.

List of scientific papers

I. **Edvall, N. K.**, Gunan, E., Genitsaridi, E., Lazar, A., Mehraei, G., Billing, M., Tullberg, M., Bulla, J., Whitton, J., Canlon, B., Hall, D. A., & Cederroth, C. R. (2019). Impact of Temporomandibular Joint Complaints on Tinnitus-Related Distress. *Frontiers in Neuroscience*, *13*, 879.

II. Cederroth, C. R., Lugo, A., **Edvall, N. K.**, Lazar, A., Lopez-Escamez, J.-A., Bulla, J., Uhlen, I., Hoare, D. J., Baguley, D. M., Canlon, B., & Gallus, S. (2020). Association between Hyperacusis and Tinnitus. *Journal of Clinical Medicine*, *9*(8).

III. Lugo, A., **Edvall, N. K.**, Lazar, A., Mehraei, G., Lopez-Escamez, J.-A., Bulla, J., Uhlen, I., Canlon, B., Gallus, S., & Cederroth, C. R. (2020). Relationship between headaches and tinnitus in a Swedish study. *Scientific Reports*, *10*(1), 8494.

IV. **Edvall, N. K**., Mehraei, G., Claeson, M., Lazar, A., Bulla, J., Leineweber, C., Uhlén, I., Canlon, B., & Cederroth, C. R. (2022). Alterations in auditory brainstem response distinguish occasional and constant tinnitus. *The Journal of Clinical Investigation*, e155094.

V. **Edvall, N.K.**, M. Vinding, D. Lundqvist., B. Canlon. & C.R., Cederroth. Inhibition of cortical responses to auditory stimuli measured by MEG - towards an objective measurement of tinnitus. *Manuscript*.

List of scientific papers not included in the thesis

I. Tserga, E., Nandwani, T., **Edvall, N. K.**, Bulla, J., Patel, P., Canlon, B., Cederroth, C. R., & Baguley, D. M. (2019). The genetic vulnerability to cisplatin ototoxicity: A systematic review. *Scientific Reports*, *9*(1), 3455.

II. Genitsaridi, E., Partyka, M., Gallus, S., Lopez-Escamez, J. A., Schecklmann, M., Mielczarek, M., Trpchevska, N., Santacruz, J. L., Schoisswohl, S., Riha, C., Lourenco, M., Biswas, R., Liyanage, N., Cederroth, C. R., Perez-Carpena, P., Devos, J., Fuller, T., **Edvall, N. K.**, Hellberg, M. P., … Hall, D. A. (2019). Standardised profiling for tinnitus research: The European School for Interdisciplinary Tinnitus Research Screening Questionnaire (ESIT-SQ). *Hearing Research*, *377*, 353–359.

III. Trpchevska, N., Bulla, J., Prada Hellberg, M., **Edvall, N. K.**, Lazar, A., Mehraei, G., Uhlen, I., Schlee, W., Canlon, B., Gallus, S., Lopez-Escamez, J. A., & Cederroth, C. R. (2020). Sex-Dependent Aggregation of Tinnitus in Swedish Families. *Journal of Clinical Medicine*, *9*(12).

IV. Genitsaridi, E., Kypraios, T., **Edvall, N. K.**, Trpchevska, N., Canlon, B., Hoare, D. J., Cederroth, C. R., & Hall, D. A. (2021). The spatial percept of tinnitus is associated with hearing asymmetry: Subgroup comparisons. *Progress in Brain Research*, *263*, 59–80.

Contents

List of abbreviations

ABR	Auditory Brainstem Response
AC	Auditory Cortex
ANOVA	Analysis of Variance
DPOAE	Distortion Product Otoacoustic Emission
ECG	Electrocardiogram
EOG	Electrooculogram
ERF	Event Related Field
ESIT	European School for Interdisciplinary Tinnitus Research
FTQ	Fear of Tinnitus Questionnaire
GEE	Generalized Estimating Equation
GP	Gap + Pulse trial
GPIAS	Gap-Prepulse Inhibition of Acoustic Startle
HADS	Hospital Anxiety and Depression Scale
HQ	Hyperacusis Questionnaire
IC	Inferior Colliculus
ICA	Independent Component Analysis
ISI	Inter-stumulus Interval
LDL	Loudness discomfort levels
MEG	Magnetoencephalography
MRI	Magentic Resonance Imaging
PO	Pulse Only trial
PSQ-30	Percieved Stress Questionnaire
SFR	Spontaneous Firing Rates
SLOSH	Swedish Longitudinal Occupational Survey of Health
STOP	Swedish Tinnitus Outreach Project
TCS	Tinnitus Catastrophizing Scale
TFI	Tinnitus Functional Index
THI	Tinnitus Handicap Inventory
TMJ / D	Temporomandibular Joint / Disorder
TSCHQ	Tinnitus Sample Case History Questionnaire
VAS	Visual Analogue Scale
WHO-QoL	World Health Organization Quality of Life

1 Introduction

Tinnitus is the phantom perception of sound, commonly reported as hearing a beeping or hissing sound. Around 2.3% of the population, 120 million people world-wide, suffer from severe tinnitus (Jarach et al., 2022), but treatment options for these patients are limited. While cognitive behavior therapy alleviate the negative impact of tinnitus (Cima et al., 2012), there is currently no treatment that eliminate the phantom sound. The main obstacle to development and evaluation of novel treatments is the complete lack of an objective biomarker of tinnitus. The innovation of a method for objective assessment would facilitate detailed diagnostics, and accelerate development of treatments of this common, but still poorly understood, condition.

1.1 Prevalence and assessment

There is a wide range of values reported for the prevalence of tinnitus, primarily due to inconsistencies of methods. The overall prevalence has been reported to be between 5.1% and 42.7%, with the plurality of studies using the definition of tinnitus as 'tinnitus lasting for more than five minutes at a time' reporting a prevalence of 11.9% to 30.3%. The prevalence of bothersome tinnitus was reported to be between 3.0% and 30.9% (McCormack et al., 2016). The highest prevalence reported (30.3%) are from a study of older adults (>55 years of age; (Sindhusake et al., 2003), while the prevalence of 'any tinnitus' the general public is estimated to be 14.4% (Jarach et al., 2022). Clearly, a consensus on the terminology used for tinnitus needs to be established. Indeed, it has recently been proposed that the term *tinnitus* should be used to refer to "The conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source" while *tinnitus disorder* should specify tinnitus "associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioral changes and functional disability." (De Ridder et al., 2021). This distinction would clearly separate those who experience tinnitus-associated emotional distress or functional disability, resulting in a more well-defined patient group for clinical intervention.

The experience of tinnitus varies widely. The perceived sound can be constant or only manifest occasionally, consist of a pulsating or static sound, vary in pitch and loudness and be perceived in one, both ears or originate from inside the head. One effect of the heterogeneity inherent to tinnitus is a lack of agreement on how to assess and evaluate tinnitus both clinically and in a research setting. In 2017, only five countries were found to have clinical guidelines for the assessment and treatment of tinnitus (T. E. Fuller et al., 2017). A systematic review of instruments used to assess primary outcome in clinical trials showed that 78 different instruments were used among the 228 identified trials. The most common instrument, still used in only 15% of trials, was the Tinnitus Handicap Inventory (THI; Hall et al., 2016).

1.2 Societal impact

The economic burden of tinnitus is still not well known, with only a handful of studies evaluating healthcare and personal costs. In the United Kingdom, it has been estimated to 717 GBP/year/patient, adding up to a total healthcare cost of 750 million GBP per year (Stockdale et al., 2017). In the United States the per patient cost is in a similar range, averaging at 660 USD yearly (Goldstein et al., 2015). A study in the Netherlands showed that under the assumption that all tinnitus patients were seeking care, the total cost would be 1 544 EUR/year/patient (Maes et al., 2013). A nation-wide study in Sweden showed an increased risk for disability pension for those with tinnitus when compared to a reference group with a previous non-otoaudiological sick leave, an incidence rate ratio of 3.30 (CI: 2.95 -3.68; Friberg et al., 2012).

1.3 Personal impact

The global burden of disease study found that hearing loss with tinnitus provides an increased burden to hearing loss alone (GBD 2019 Hearing Loss Collaborators, 2021). However, due to inconsistent tinnitus definitions across studies and countries, an estimate of Years-Lived with Disability (YLDs) is still missing for tinnitus alone but several studies report a significant impact of tinnitus. A meta-analysis of studies that included participants with chronic tinnitus have shown that the presence of their tinnitus has a negative impact on emotional well-being and health-related quality of life (Trevis et al., 2018). Tinnitus affecting sleep is common, with as many as 71% of tinnitus patients reporting sleep problems (Andersson et al., 1999), and correlation between sleep disturbance and tinnitus severity have been reported (M. Meikle & Taylor-Walsh, 1984). Anxiety and depression are common among tinnitus patients with 26.1% of those with tinnitus reporting anxiety and 25.6% reporting depression (Bhatt et al., 2017) and tinnitus severity have been shown to correlate with the degree of both anxiety and depression (Hu et al., 2015). However, specific studies (e.g. with a longitudinal design) are missing to clarify the causal relationship between tinnitus and these conditions.

Tinnitus patients seeking medical care are often dissatisfied with the support they receive. In a survey of 936 tinnitus patients in the UK, 67.7% were discharged without treatment after assessment in an ENT/Audiology department (McFerran et al., 2018). Patients with sensorineural hearing loss and tinnitus in Sweden complained that they had been offered hearing aids but no treatment for their tinnitus (Zarenoe & Ledin, 2014). There is indeed some disagreement between tinnitus patients and their intended caregiver, as surveyed audiologists commonly define treatment success as “decreased awareness” and “stress/anxiety relief” while tinnitus patients sought “reduction of tinnitus loudness” or “complete elimination of tinnitus” (Husain et al., 2018). Importantly, severe tinnitus is increasing the risk for suicidal attempts and this risk is no longer observed for individuals who have sought medical care for their tinnitus (Lugo et al., 2019). Clearly, this

is not a patient group that should be dismissed with the advice "they have to learn to live with it" as is often the case (McFerran et al., 2018).

1.4 Current theories for mechanism of tinnitus

As tinnitus is a hearing sensation, it was previously assumed that the perceived sound was generated in the ear. This is true for cases of *objective* tinnitus related to hearing blood flow or muscle contractions (Lockwood et al., 2002) and rare cases of extreme spontaneous otoacoustic emissions (Penner, 1992). However, there is now consensus that the common, *subjective* tinnitus, is related to neural generators in auditory cortex or subcortical nuclei in the auditory pathway (Eggermont & Roberts, 2012). Current theories on the pathophysiology of tinnitus, emerging from animal and human studies, propose that tinnitus results from a compensation to diminished sensory input. Different mechanisms for this maladaptive plasticity have been described (Shore et al., 2016). Hereafter, tinnitus refers to *subjective* tinnitus.

1.4.1 Neuronal "gain"

In models of increased central gain, tinnitus is an effect of neural noise being elevated to a conscious percept (Schaette & McAlpine, 2011). Indeed, studies have shown that the cochlear nucleus (CN), the first major structure of the auditory pathway, show increased spontaneous firing rates (SFR) (Kaltenbach et al., 2004) and steepened level-dependent firing rates (Dehmel et al., 2012) in animals with behavioral signs of tinnitus after noise trauma. These changes are likely due to homeostatic plasticity caused by reduced auditory input. There is a decrease in GABAergic inhibition (Middleton et al., 2011), a reduction in the number of inhibitory glycine receptors (Wang et al., 2009) as well as an increase of the vesicular glutamate transporter VGLUT-2 (Barker et al., 2012) in the CN when input is reduced. Hyperactivity in the fusiform cells of the CN has been shown to, at least in part, be caused by a reduction of potassium channel (Kv7.2/3) activity (Li et al., 2013). Mice with the ability to compensate for activity reduction in this channel proved to be more resilient to tinnitus after noise trauma, suggesting a potential therapeutic target (Li et al., 2015).

Increased SFR are also found in the inferior colliculus (IC) in animal models following noise trauma (Berger & Coomber, 2015) but this activity has been suggested to be relayed from the cochlear nucleus rather than generated in IC (Manzoor et al., 2013). It has also been shown that inner hair cell loss after ototoxic administration of carboplatin leads to reduced compound action potentials (CAP) generated by afferent neurons but a much smaller reduction of evoked responses in the IC and an exacerbated cortical response (Salvi et al., 2016) suggesting a compensatory mechanism in the auditory pathway.

In studies of human fMRI, blood-oxygen-level-dependent (BOLD) responses to auditory stimuli are increased in IC (Boyen et al., 2014) and IC and medial geniculate body (MGB)

(Melcher et al., 2009). However, these results were replicated for participants with hyperacusis and tinnitus but not tinnitus only (Gu et al., 2010), complicating the interpretation of results not controlling for hyperacusis.

Studies performing single unit recordings in the cat auditory cortex after noise trauma found increased SFR compared to baseline. Interestingly, it was also found that cross-correlation between recording sites increased together with SFR and were related to reorganization of the cortical tonotopic map. The finding of increased neural synchrony points to the involvement of Hebbian plasticity in tinnitus generation. However, tinnitus was not evaluated behaviorally in the included animals and the described results are possibly effects of hearing loss (Noreña & Eggermont, 2003). Later studies that did evaluate tinnitus behaviorally in the rat has shown that noise induced tinnitus widen tuning curves for auditory cortex neurons, increase synchronization, (Engineer et al., 2011) and result in tonotopic map reorganization (Yang et al., 2011). Furthermore, Engineer et al. (2011) reversed both the physiological and behavioral tinnitus correlates by pairing auditory and vagus-nerve stimulation intended to release neuromodulators known to promote plastic changes. Yang et al. (2011) reversed tinnitus behavior by administrating vigabatrin, a GABA-inhibitor, suggesting noise induced tinnitus is caused by a reduction of inhibitory synaptic transmission.

The terminology of "increased gain" may be a useful heuristic to tinnitus generation. However, it is not a specific mechanistic description as neuronal excitability is dependent on both intrinsic factors and inhibitory and excitatory synaptic responses, all of which have been suggested to be altered in tinnitus (Auerbach et al., 2014).

1.4.2 Frontostriatal gating

It has been hypothesized that the ventromedial prefrontal cortex (vmPFC) and nucleus accumbens (NAc) of the brain together work to assign affective meaning to received sensory signals, the so-called model of frontostriatal gating. Changes in this system could result in lack of suppression of irrelevant signals, or the assignment of negative meaning to a benign neural signal (Rauschecker et al., 2015). Structural MRI analyzed by voxel based morphometry have shown reduced grey matter volume of the vmPFC in patients with tinnitus compared to normal controls (Mühlau et al., 2006). Tinnitus patients also show stimulus-evoked hyperactivity in NAc in fMRI (Leaver et al., 2011). Consequently, the pathophysiology of tinnitus very much resembles that of chronic pain (Rauschecker et al., 2015). However, it is still unknown if changes of the circuits involved are a consequence of tinnitus that maintains the perception or if an imbalance of frontostriatal gating can lead tinnitus.

1.4.3 Predictive Coding

All sensory systems have random, spontaneous neural activity. In the tinnitus model of predictive coding this activity is thought of as a tinnitus "precursor". Conceptually, in the normal auditory system, this precursor is expected, or predicted, by top-down processes and ignored. However, this *status quo* can be disrupted if afferent input is increased through increased spontaneous or synchronous firing rate to a degree where the prediction error reaches some threshold. Then, tinnitus is perceived, and later maintained, as the top-down prediction of "silence" changes with focused attention, promoting the release of acetylcholine, and memory structures select the tinnitus percept as a new default environment (Sedley et al., 2016).

1.4.4 Thalamocortical dysrhythmia

Activity in the gamma band (>30 Hz) have been shown to reflect sound intensity (Schadow et al., 2007), and be modulated by prediction errors in audio-visual tasks (Kaiser et al., 2006). For patients with tinnitus, gamma activity has been shown to correlate with tinnitus loudness in studies using both EEG (van der Loo et al., 2009) and MEG (Müller et al., 2013). The model of thalamocortical dysrhythmia proposes that a decrease in peripheral input re-organizes the central auditory pathway in a way that decrease the frequency of alpha rhythms. As a result GABA-mediated inhibition is decreased which in turn facilitate and sustained gamma activity (De Ridder et al., 2015; Llinás et al., 1999).

1.5 Established risk factor

The most common risk factor for tinnitus is hearing loss, and tinnitus has been reported as a symptom of virtually all otological conditions (Baguley et al., 2013; Sanchez, 2004). A recent systematic review of risk factors for tinnitus confirmed this relationship for various hearing related factors (Biswas et al., 2022). For non-otological risk factors temporo-mandibular joint disorder (TMJD), depression, chronic obstructive pulmonary disease, and hyperlipidemia were identified. Others risk factors have been suggested throughout the literature, as summarized below, but results are rarely replicated making level of evidence is generally low.

1.5.1 Hearing loss

In an Australian cohort of n = 1 292, aged > 48 years, the 5 year incidence of tinnitus was 18.0% and any hearing loss (defined as pure tone average of 0.5, 1, 2 and 4kHz thresholds [PTA4] >25 dB HL) was significantly associated with a doubling in incidence with an age and sex-adjusted odds ratio (OR) of 2.13 (95% CI: 1.40 – 3.24) (Gopinath et al., 2010). A similar cohort study in the US of n = 3 737 participants aged 48 – 92 reported that those with hearing loss (PTA4 > 25 dB HL in the worse ear) at baseline had an 83% higher risk of developing tinnitus at follow-up. This translated to an OR of 1.83 (95% CI: 1.21 – 2.75) for

hearing loss in a multivariate logistic regression model. For otosclerosis specifically the OR was higher at 8.85 (CI: 1.42 – 55.14). However, otosclerosis was only reported by seven participants at baseline, providing low statistical power. There was no significantly increased risk from conductive hearing loss, defined as air-bone-gap of 15 dB in either ear (Nondahl et al., 2002). In a follow-up study (n = 2 922), the hazard ratio (HR) of hearing loss for 10 year incidence of tinnitus was significant for women at 2.59 (95% CI: 1.79 – 3.74) but not men (HR: 1.19, 95% CI: 0.82 – 1.72; Nondahl et al., 2010). The authors suggest the lower HR for men may be caused by the greater severity of hearing loss found in men at baseline leading to earlier onset of tinnitus, i.e. already at the previous 5-year follow-up. The overall 10-year incidence was higher for men (14.8%, 95% CI: 12.7 - 16.9) than for women (11.2% 95% CI: 9.7 – 12.7), suggesting other factors than hearing loss still driving tinnitus onset for men.

A cross-sectional study of the offspring from the previous cohort (n = 3 267, aged 21-84) later reported an odds ratio, corrected for age and sex, of 3.60 (95% CI: 2.67 - 4.84) for hearing loss (Nondahl et al., 2011). However, cross-sectional designs are not sufficient to reveal the causal relationship between often coinciding tinnitus and hearing loss. Longitudinal cohort studies, as those referenced above, are necessary to accurately determine relationships between tinnitus and lifestyle factors but are relying on large studies that incorporate agreed on terminology and definitions. While questionnaire studies are relatively easy and cheap to perform over the internet, the risk of specific types of hearing losses to cause tinnitus still require clinical visits for accurate measures of hearing. A recent study highlighted that around 1 *billion* young people (12-34 years of age) are at risk for hearing loss due to unsafe listening practices (Dillard et al., 2022) and it is very likely many of these will also suffer from tinnitus.

1.5.2 Lifestyle and environment

As for hearing loss, there is a severe lack of longitudinal cohort studies investigating lifestyle factors and tinnitus. Despite current knowledge being based on cross-sectional studies some patterns of association have been emerging. Tinnitus and stress are commonly reported as being associated but the magnitude and direction of this relationship is largely unknown. A recent review of 50 studies showed that in three studies investigating tinnitus onset, some patients (13.5% - 28.3%) associate the onset of tinnitus with stress (Elarbed et al., 2020). Fifteen studies reported a statistically significant, positive correlation between tinnitus and stress. The strength of which varied with instrument used for evaluation. A major finding was that tinnitus patients tended to report their tinnitus as louder when stressed (Elarbed et al., 2020), which highlights the importance of controlling for stress levels in tinnitus research. Other lifestyle or environmental factors that have been associated with tinnitus are obesity (Gallus et al., 2015), smoking (Nondahl et al., 2010), cardiovascular disease, epilepsy and burnout (Basso et al., 2020).

1.5.3 Genetics

In recent years there has been increasing interest in investigating the genetic risk factors for tinnitus, but the complex combination of auditory and non-auditory molecular pathways and heterogeneity of the condition have so far limited discovery (Vona et al., 2017). Early studies showed a low but significant effect of familial correlation (0.15; Hendrickx et al., 2007) and heritability (0.11; Kvestad et al., 2010). However, recently it has become increasingly clear that in a genetic context, tinnitus will have to be considered not as one single entity, but a collection of sub-types that presents as a similar experience to the patient (Lopez-Escamez et al., 2016). A study of Swedish twin pairs revealed a heritability score of 0.40 (Bogo et al., 2017) and a later twin study revealed an even higher heritability score of 0.56 for bilateral tinnitus specifically, compared to 0.27 for unilateral tinnitus (Maas et al., 2017). A result that clearly underlines the importance of accounting for separate phenotypes of tinnitus in further investigations. Recently, a large genome-wide association study (GWAS) in the UK Biobank (172 995 individuals) revealed the first replicated single-nucleotide variants (SNVs) in tinnitus. Furthermore, genetic variation associated with tinnitus showed a positive correlation with hearing loss, insomnia, major depressive disorder and neuroticism (Clifford et al., 2020). Genetics have also been suggested to play a role in severe tinnitus in adoptees (Cederroth et al., 2019), and severe tinnitus aggregates in families more so in women than in men (Trpchevska et al., 2020), suggesting that the genetics of severe tinnitus are influenced by sex. Consistent with these results, a recent whole exome sequencing study identified multiple rare variants in genes from patients with severe tinnitus (Amanat et al., 2021). Severe tinnitus may thus constitute a subtype identifiable using genetic markers.

1.6 Treatment

A European guideline was recently published by TINNET[1] (TINnitus NETwork) with the goal of standardizing assessment and treatment of patients with tinnitus (Cima et al., 2019). Recommendations for treatments were made based only on high level evidence (randomized control trials and systematic reviews) and are summarized in Table 1. The only strong recommendation *for* a treatment was made for cognitive behavioral therapy (CBT) as it has been proven to decrease tinnitus distress. However, it should be noted that CBT does not aim to remove the tinnitus percept per se but rather reduce its negative impact on the patient. Hearing aids are recommended for the management of hearing loss but can be an option for management of tinnitus for patients with hearing loss and tinnitus. Drug administration are weakly recommended against as there is no evidence for any drug to be effective in the treatment of tinnitus but evidence for potentially significant side effects (Langguth et al., 2019). Similar evidence is found for

[1] https://tinnet.tinnitusresearch.net/

dietary/alternative therapies with e.g. gingko biloba potentially interacting with blood thinners to increase risk of bleeding. However, the guideline does note that psychiatric comorbidities of tinnitus (e.g. anxiety and depression) may need drug treatment.

Recommendation for	
Strong	Cognitive behavioral therapy
Weak	Hearing aids
Recommendation against	
Weak	Drug/pharmacological
	Repetitive transcranial magnetic stimulation
	Dietary and alternative therapies
No recommendation	
	Cochlear implants
	Neurostimulation
	Vagus nerve stimulation
	Acoustic coordinated reset (CR®) neuromodulation
	Invasive neurostimulation treatments
	Tinnitus retraining therapy
	Sound therapy
	Acupuncture

Table 1. Summary of treatment options and evidence-based recommendations from the TINNET multidisciplinary guideline for tinnitus (Cima et al., 2019).

In summary, there are many treatments for tinnitus suggested and some are tentatively used, but most lack evidence of sufficient efficacy for wide implementation. One major obstacle for evaluating and developing treatments are the lack of diagnostic tools to assess both the presence and grade of tinnitus. A significant development would be that of such a tool or technique, which may also pave the way for stratification of tinnitus subtypes.

1.7 Diagnostics

Currently there are no reliable objective measurements of tinnitus - clinical evaluations and research are still reliant on self-reported measurements such as questionnaires, visual-analogue scales (VAS) or psychoacoustic listening tests. A review from 2019 found 21 studies investigating objective measurements of tinnitus, broadly fitting in to categories of *blood test* (n = 2), *electrophysiology* (n = 15), *radiology* (n = 2) or *balance* (n = 2), did not identify any reliable objective measurement (Jackson et al., 2019). In guidelines for tinnitus assessment, the Tinnitus Handicap Inventory (THI), Tinnitus Functional Index (TFI) and different VAS are commonly recommended (T. E. Fuller et al., 2017). These same tools are common instruments for assessing outcome of clinical trials,

however, many unique tools or self-developed tools exist and are commonly used (Hall et al., 2016). This section on diagnostics will focus on instruments or methodologies that are commonly used or have demonstrated a novel or promising approach to tinnitus diagnostics.

1.7.1 Self-reported measures

The THI was developed as a clinical tool to quantify the impact of tinnitus on daily living. It comprises of 25 items with response options "Yes", "Sometimes" or "No". Originally, the THI was designed with three subscales in mind but are commonly reported only as a total score between 0-100 (Newman et al., 1996) with ranges for "No" (0-16), "Mild" (18-36), "Moderate" (38-56) and "Severe Handicap" (58-100) (Newman et al., 1998). The TFI was developed to scale with the impact of tinnitus, measure treatment related change and be functional for early assessment (M. B. Meikle et al., 2012). It consists of 25 items, 8 subscales (e.g. "Auditory", "Sleep", "Intrusiveness") and calculates to a total score between 0-100. The THI and TFI have been shown to be strongly linearly correlated (Henry et al., 2016) but since its creation, the TFI has been growing in popularity over the THI, possibly due to its rigorous development process, coverage of multiple symptom domains and sensitivity to change (Fackrell et al., 2016).

Visual analogue scales (VAS) are a collective term for an item where the response is a mark along an axis. Commonly, questions used for these items are of the nature "How loud do you perceive your tinnitus to be?". The response is often quantified as a number (e.g. between 1-10) which somewhat blurs the line between visual analogue- and numerical rating scales. Though simplistic, these scales have been shown to capture reductions in tinnitus severity in clinical trials (Adamchic et al., 2012), display adequate convergent validity in a test-retest (Zenner & De Maddalena, 2005) and correlate strongly with results from the TFI (Raj-Koziak et al., 2018). The strength of the VAS may be its ease of implementation. However, this comes with a lack of standardization regarding formulation and terminology. Results should be interpreted with caution, especially if only a single timepoint is available.

1.7.2 Psychoacoustic measurements

After self-reported questionnaires, the most common instruments for outcome evaluation in clinical studies of tinnitus are psychoacoustic matching tasks.

Tinnitus loudness matching are reported as the primary outcome in 4%, and secondary outcome in 3%, of clinical trials for tinnitus. For pitch matching the proportion is 2% and 4% respectively (Hall et al., 2016). However, psychoacoustic assessment is not included in any clinical guideline (T. Fuller et al., 2020). This is surprising, as a relationship between the tinnitus percept and audiogram configuration has been reported (Schecklmann et al.,

2012) and many sound-therapies suggested for tinnitus rely on frequency specific amplification.

There are three common methods for performing a tinnitus match and all three can be used for matching both pitch and loudness. Commonly pitch is matched in a first step followed by a loudness match at the pitch matched frequency. In the method of "two alternative forced choice" (2AFC) the subject is presented two tones and asked to select the one closest to their tinnitus. The subject is then presented two new tones that after a number of trials performed in a stepwise fashion will settle at the putative tinnitus frequency (Vernon & Meikle, 2003). This method is fast and can be performed with a standard audiometer. However, the result assumes a single frequency as representative of the tinnitus pitch, which is not necessarily an accurate representation. A "Tinnitus likeness rating" (TLR) has been suggested to better reflect the actual tinnitus percept. For TLR the tinnitus subject is presented a range of different tones or sounds in a random order and asked to rank them (e.g. on scale of 0-10) based how much it sounds like their tinnitus (Norena et al., 2002). The TLR method has shown improved reproducibility over 2AFC with 84% of tinnitus subjects matching a concordant dominant frequency between two visits with TLR, compared to only 23% for 2AFC (Hébert, 2018). However, it has been shown that when visits are separated by three months, the TLR pitch match only reach acceptable agreement on a group level, *not* for individual subjects (Hoare et al., 2014).

Finally, in the "method of adjustment" (MOA) the tinnitus subject themselves are given direct control of the sound presented, often by turning a dial to change the frequency. This method was first described by Tyler & Conrad-Armes (1983) in a study that compared the three methods for pitch matching in a sample of ten patients with chronic tinnitus. This study also performed the 2AFC method and showed that average standard deviations after seven matches per method were SD = 925 and SD = 473 for the 2AFC and MOA methods respectively. The general conclusion was that because of large individual differences in results and performance, a minimum of seven tinnitus pitch matches should be performed in a clinical setting to acquire a reasonable average (Tyler & Conrad-Armes, 1983).

More recently, all three methods described here were compared for n = 59 tinnitus patients who performed a matching with each method 5 times (Neff et al., 2019). Intraclass correlation coefficients showed good reliability (0.63-0.69) for all three methods. However, differences were found in that the 2AFC method had significantly larger within-subject variability and lower participant-satisfaction than the other methods. Also, the TLR method was the most time- consuming one to perform (Neff et al., 2019).

1.7.3 Gap-prepulse inhibition of acoustic startle (GPIAS)

The gap-prepulse inhibition of acoustic startle (GPIAS), first described by Turner et al. (2006), is now a common method for assessing tinnitus in different animal models. The

method is based around a silent gap embedded in a continuous carrier noise inhibiting the startle response to a following loud sound pulse (see Figure 1). The startle response is commonly measured by a force-plate embedded in the animal test chamber. When the carrier noise is filtered to be centered around the putative tinnitus frequency, tinnitus interferes with the ability of the gap to suppress the startle response. The relative startle response with a preceding gap is suppressed by around 55% of a startle only trial for healthy control animals compared to around only 35% for an animal with noise induced tinnitus (Turner et al., 2006).

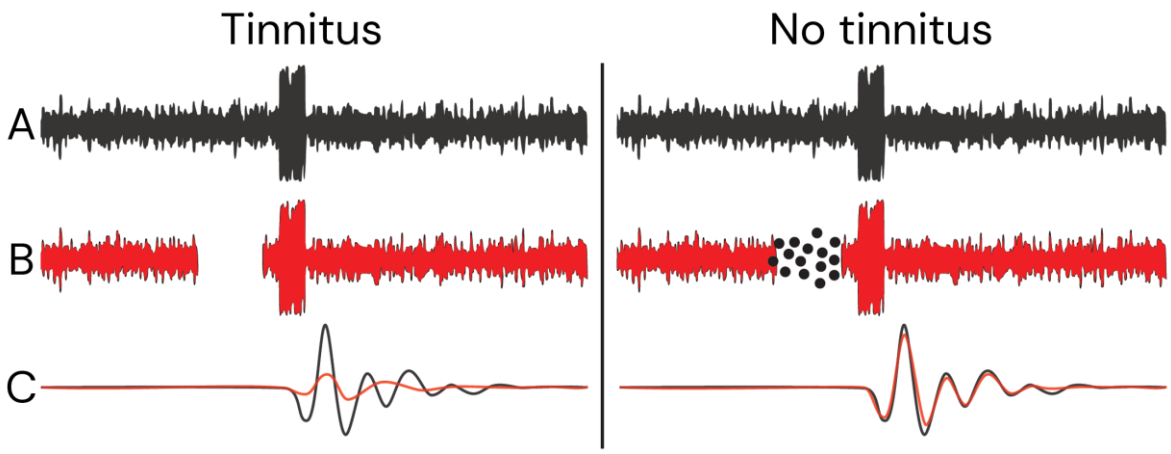

Figure 1. A schematic representation of the gap-prepulse inhibition of acoustic startle (GPIAS). **A** represent a startle pulse that evoke the same response in both the *No tinnitus* and *Tinnitus* case as seen by the respective amplitudes **C**. In **B**, a gap precedes the startle which reduces response for the *No Tinnitus* case only as tinnitus, represented by a swarm of black dots, interferes with the gap and limit its inhibition.

It has been shown that the response is sensitive to i) acoustic parameters (Longenecker & Galazyuk, 2012), ii) the specific genetic background of the animal strain used (Yu et al., 2016), and iii) temporal parameters such as duration of the silent gap, startle pulse and interstimulus interval (ISI), the time between the gap and the startle pulse (Yu et al., 2016). Thus, careful optimization of the environment and settings is required to achieve a dynamic range sufficiently large to assess tinnitus.

In translating this muscular reflex response to human, Fournier & Hebert (2013) measured the electromyographic response of the orbicularis oculi muscle, an approach successfully used for evaluating sensorimotor gating in patients with schizophrenia (Braff et al., 1992). On average, the tinnitus participants (n = 15) displayed higher response magnitudes to startle pulses and decreased inhibition by the preceding gap compared to controls (n = 17) and results were confirmed in a retest after 20 weeks (Fournier & Hébert, 2013).

However, the study suffers from several limitations. Firstly, it included a heterogeneous group of participants having experienced tinnitus between 0.5 and 37 years. Secondly, the tinnitus group displayed significantly higher scores for hyperacusis. Finally, thirteen out of the fifteen tinnitus participants matched their tinnitus pitch between 11 and 16 kHz, well above the highest carrier noise center frequency of 4 kHz. Taken together, the translation of GPIAS to humans remains to be appropriately tested. Interestingly, several studies have shown that participants with tinnitus do **not** struggle to **perceive** gaps in noise compared to controls (Boyen et al., 2015; Campolo et al., 2013; Zeng et al., 2020). That is, the mechanism of reduced gap inhibition cannot be explained by psychoacoustic perception of the gap or conscious prediction, rather GPIAS involves a reflex mechanism by which tinnitus interferes with the ability of the gap to suppress the startle response.

1.8 Electrophysiology

There have been many approaches to using electrophysiological responses as potential biomarkers for tinnitus including both evoked responses and resting state measurements. This section summarizes the most well researched methodologies and their findings.

1.8.1 Auditory brainstem response (ABR)

The ABR is an evoked response commonly used in a clinical setting for assessment of auditory nerve function. Stimuli are most often broadband clicks presented around 80 dBnHL as this ensures synchronous neuronal firing, providing the highest signal to noise ratio. Other stimuli (e.g. tone bursts or chirps) can be used where applicable. Recording is commonly done with one central reference electrode placed along the midline (Cz or forehead) with an active electrode placed on the mastoid behind the stimulated ear. The contralateral electrode, or a fourth electrode in case of bilateral stimulation, placed on the subject's cheek functions as ground. Recordings are performed for 10 ms after stimuli presentation and averaged over ~1000 presentations to minimize the noise floor. The recorded response consists of five waves corresponding to neuronal firing in nuclei along the auditory pathway. These are numbered I-V and represent activity from the auditory nerve, cochlear nucleus, superior olivary complex, lateral lemniscus and inferior colliculus respectively (Möhrle et al., 2016). The standard quantitative measurements of the ABR then considers the peak amplitude and latency for each of these five waves.

A systematic review of studies evaluating differences in the ABR among those with tinnitus included 19 studies in quantitative meta-analysis (Milloy et al., 2017). The meta-analysis included 1 240 subjects with tinnitus and 664 controls and showed no significant differences between groups with normal hearing. However, for the groups with hearing loss the participants with tinnitus showed increased latencies and lower amplitudes for all major ABR features (wave I, III and V). This result underlines the importance of controlling for hearing loss in comparisons including groups of tinnitus subjects and the necessity of proper reporting of methods. Individual studies reviewed did report group

differences in ABR measures. Two out of five studies which reported wave I amplitudes found significantly lower amplitudes for the tinnitus group. Latency changes were more commonly reported with three out of nine studies reporting increased wave I and III latency, and three of ten increased wave V latency for the tinnitus group (Milloy et al., 2017). A more recent review and meta-analysis of 27 studies comparing auditory evoked potentials again found significant differences for latency, but not amplitude measurements. This result from meta-analysis of standardized mean difference was only significant in studies comparing tinnitus patients without hearing loss to controls with considerable variability in results between different studies (Jacxsens et al., 2022).

Despite some promising reports of changes in the ABR as a potential biomarker for tinnitus, it may be that the methods variability is too high even for identifying group differences. Studies published so far have used a wide range of equipment, stimulus- and recording parameters, as well as heterogenous or ill-defined tinnitus participants, hampering meta-analysis.

1.8.2 Electroencephalography

In studies using electroencephalography (EEG), it has been shown that subjects with tinnitus have a decreased amplitude and area under curve 100-250 ms after stimuli presentation for frequency and silent deviants in a mismatch negativity paradigm (Mahmoudian et al., 2013). This result was interpreted as a deficit in change-detection causing tinnitus to lead to a constant prediction error, meaning tinnitus is constantly interpreted as a novel stimulus, resilient to habituation (Mohebbi et al., 2019). A systematic review and meta-analysis (n = 21 studies) of late auditory evoked potentials found that the P300 component had significantly lower amplitude and longer latency. However, the impact confounding factors such as age and hearing levels could not be established (Cardon et al., 2020).

It has been shown that when the frequency of the stimuli was closer to the putative tinnitus frequency differences decreased, lending credence to the theory of tinnitus arising from a prediction error (Asadpour et al., 2020). In another implementation of the MMN paradigm Sedley et al. (2019) found evidence of an asymmetry between upward and downward loudness deviants for n = 26 patients with chronic and n = 15 with acute tinnitus but not n = 26 hearing and age matched controls or n = 20 hearing impaired controls with simulated tinnitus. This “intensity mismatch asymmetry” is in line with the hypothesis that tinnitus generates a prediction error from silence that influence the N100 response. This metric evaluated by a receiver operating curve (ROC) showed and area under curve of 0.77 which is considered “fair” diagnostic accuracy (Sedley et al., 2019).

1.8.3 GPIAS and EEG

Since GPIAS has been shown to be mediated at the level of the auditory cortex (Ison & Bowen, 2000; Weible et al., 2014), EEG measures could be used instead of EMG to capture the evoked responses to gap and startle stimuli, which would hypothetically mimic the startle response.

A recent review of studies involving EEG measurements of gap stimulation reported a trend of reduced gap salience in tinnitus, but that the evidence is inconclusive due to only a small number of studies found (n = 8) and varying methods (Duda et al., 2020). In guinea pigs with salicylate induced tinnitus, Berger et al. (2017) found gap-induced reductions of evoked potentials measured with electrocorticography (ECoG) in the rostral part of the auditory cortex (AC), suggesting a neural analogue of the standard GPIAS test. In a later study, similar results were found for guinea pigs with tinnitus induced by unilateral presentation of 120 dB SPL narrow band noise between 8-10 kHz. Evoked potentials showed decreased gap inhibition specifically for the carrier noise frequency corresponding to the noise trauma (8-10 kHz) in AC of the contralateral hemisphere (Berger et al., 2018).

In humans, Ku et al. (2017) investigated the effect of gap durations of 20, 50 and 100ms with pure tone carriers of 600Hz or 8 kHz on the ALR. Results for the tinnitus group (n = 16) which had matched their tinnitus pitch to 8 kHz, showed an inhibition deficit at the 8kHz carrier for the 20ms gap while the control group did not. However, both groups showed a deficit at the "non-tinnitus" frequency of 600 Hz questioning the influence tinnitus may have on the measured response (Ku et al., 2017). In this study, the stimulus following the gap was a 1 kHz pure tone at 65 dB SL, which differs from the conventional methodology using a broad band noise burst, often at higher levels.

1.8.4 TCD and EEG

In EEG data, it has been shown that those reporting tinnitus (n = 153) had significantly higher spectral power between 2-4 Hz and 14-44 Hz compared to healthy controls (n = 264). This finding is in line with the tinnitus model of thalamocortical dysrhythmia. A support vector machine (SVM) learning algorithm included the theta, alpha and gamma frequency bands of the auditory cortex in a model for using oscillatory brain activity to distinguish those with tinnitus from controls with an average accuracy rate of 87.7% (Vanneste et al., 2018). However, this study used the sLORETA approach (Pascual-Marqui, 2002) for source reconstruction (i.e. an average, template cortical surface). This fact coupled with the already limited spatial resolution of EEG and the reuse of the training dataset are limiting the interpretation of the SVM findings.

1.9 Magnetoencephalography (MEG)

In the space of techniques for measuring brain activity, MEG is situated somewhere between EEG and MRI. MEG results in a number of signal vectors as outputs, but the main outcome measurement is most often source localization of activity on the cortical surface. As neuronal populations create current flows when active, MEG uses sensors sensitive to magnetic field fluctuations to measure this activity. It has the benefit over EEG to suffer from less field spread as the magnetic fields measured are unaffected by passing through tissue, the skull and scalp. This provides excellent, sub-millisecond, temporal resolution and with careful co-registration of individual MRI scans, spatial resolution on the order of ~5mm. However, as MEG sensors need to be cooled to cryogenic temperatures by liquid helium, MEG comes with higher cost and limited availability compared to EEG.

A handful of studies have investigated tinnitus using MEG. Analyzing five minutes of resting state data, Weisz et al. (2005) found a decrease in the power of the alpha band and an increase in delta for n = 17 participants with chronic tinnitus compared to normal hearing controls. This abnormal activity pattern, particularly over temporal regions, was strongly correlated with tinnitus related distress as measured by a tinnitus questionnaire (Weisz et al., 2005). A later study from the same lab found inter-areal decrease of power in the alpha band and increase in the gamma band for n = 41 participants with tinnitus compared to n = 21 non-tinnitus controls (Schlee, Hartmann, et al., 2009). In a later source-space analysis of n = 23 participants with chronic tinnitus group differences were found compared to healthy controls (n = 24) that showed a global network connected to the temporal cortex and correlated positively with tinnitus distress (Schlee, Mueller, et al., 2009). A network of similar nodes was also found when analyzing functional connectivity for an amplitude modulated tone matched to tinnitus pitch but not control conditions (Schlee et al., 2008). Together, these results provide some credence for the tinnitus model of thalamocortical dysrhythmia discussed previously. Unfortunately, they suffer from some common limitations including no or imprecise source reconstruction, no control for hearing loss, or a heterogenous tinnitus group.

1.10 Neuroimaging

Despite many neuroimaging studies, using both structural and functional MRI methods, positron emission tomography (PET), functional near-infrared spectroscopy (fNIRS) and combined methods having been performed to elucidate a neuronal mechanism for tinnitus - the large variety in methodologies and inclusion criteria used have produced little in terms of aggregate understanding. Some common findings do reoccur in multiple studies, but none are yet sensitive enough to be the basis for a clinical measure or diagnostic criteria (Elgoyhen et al., 2015). Studies using voxel-based morphometry have shown a reduction in grey-matter volume of the vmPFC (Leaver et al., 2011; Mühlau et al.,

2006). This change is suggested to be involved in reducing a top-down inhibitory system that may underlie tinnitus, but has also been shown to be a result of hearing loss rather than tinnitus specifically (Melcher et al., 2013).

Studies of resting state fMRI (Maudoux et al., 2012) and source localized EEG (Vanneste, Heyning, et al., 2011; Vanneste, Plazier, et al., 2011) have reported increased functional connectivity between auditory cortex (AC) and the parahippocampal (PHG) area (Elgoyhen et al., 2015) and this finding is corroborated by intervention studies. In a study of tDCS responders differed from non-responders in resting state activity of the AC and PHG (Vanneste, Focquaert, et al., 2011). Similarly, responders to rTMS were found to be characterized by increased functional connectivity between dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), PHG and AC (De Ridder et al., 2013). One study injected amobarbital, a GABAergic inhibitor in the anterior choroidal artery that supplies blood to the amygdala and hippocampus, as treatment for six tinnitus patients. After injection, three patients with chronic unilateral tinnitus reported tinnitus suppression of 60–70% (De Ridder et al., 2006).

The anterior insula and anterior cingulate cortex (ACC) of the brain have been described as mediating a "salience network" that coordinate bottom-up salience of incoming stimuli and the subsequent switching of attention to other brain networks (Menon & Uddin, 2010). Increased activation of the ACC and insula has been observed repeatedly in tinnitus subjects with both fMRI, EEG and PET (Elgoyhen et al., 2015). Theoretically, the involvement of a salience network in tinnitus seem reasonable, as a misrepresentation in such a network may cause the inability to habituate tinnitus and keep it maintained as a salient percept.

A handful of studies have investigated using functional near-infrared spectroscopy (fNIRS) to investigate tinnitus with shared findings of increased sound-evoked activity over auditory cortex in tinnitus patients compared to controls (Schecklmann, Giani, et al., 2014), or increased connectivity between AC and non-auditory areas (San Juan et al., 2017). One study showed that resting state connectivity was significantly higher for a group (n = 25) of participants with chronic tinnitus compared to controls (n = 21). A machine learning algorithm (artificial neural network) then classified those with tinnitus from controls with an accuracy of 87.3% (Shoushtarian et al., 2020). However, this high accuracy was only reported for one of four employed machine learning algorithms and suffers from the "black box problem" of providing little in terms of enhanced understanding of an underlying mechanism.

2 Research aims

The over-arching aim of this thesis was to move the field towards a clinically viable, objective biomarker for tinnitus.

Aim 1: Investigate the relationship between conditions commonly reported by tinnitus patients.

The relationship between temporomandibular joint disorders, headaches, hyperacusis and tinnitus and its severity were investigated. The purpose of this aim was to improve understanding on what factors may distinguish a clinically relevant subtype of tinnitus patients.

Aim 2: Evaluate the potential of the auditory brainstem response (ABR) to function as an objective biomarker for tinnitus.

Previous studies of the ABR to evaluate tinnitus has been lacking in sample size, controlling for factors often reported to co-occur with tinnitus, and used simple statistical methods of hypothesis testing. The purpose of this aim was to perform a state-of-the art, well-controlled analysis on a large ABR-dataset to advance the knowledge of the methods' role in tinnitus diagnostics.

Aim 3: Develop and evaluate a Gap-Prepulse Inhibition of the Acoustic Startle (GPIAS)-protocol for magnetoencephalography (MEG) as a diagnostic tool for tinnitus.

GPIAS is a commonly used method to assess tinnitus in animal models but its reliance on a muscular reflex response has hindered translation to human subjects. The purpose of this aim was to investigate the methods' implementation with neuroimaging and elucidate its cortical mechanisms to develop an objective biomarker for tinnitus that can be translated back to animal models.

3 Materials and methods

3.1 Material

The first aim of the thesis was to identify and describe relevant factors that define a subtype of tinnitus. For this purpose, the Swedish Tinnitus Outreach Project (STOP) was created in 2015 to gather auditory, lifestyle and tinnitus specific information from a large representative sample of the general public. The project was approved by the Regional Ethics Review Board in Stockholm (2015/2129-31/1). Participants 18 years of age and above were invited through social media channels and partnership with local cohorts, including LifeGene (Almqvist et al., 2011), to register for the project via a purpose-built website[2]. After providing informed consent the participants were invited to an online survey platform. STOP collected questionnaire data from 5 593 participants between November 2015 and January 2018. Questionnaires included are summarized in Table 2.

	Questionnaire	**Original publication**	**α**
TSCHQ	Tinnitus Sample Case History Questionnaire	(Langguth et al., 2007)	
THI	Tinnitus Handicap Inventory	(Newman et al., 1996)	0.93
TFI	Tinnitus Functional Index	(M. B. Meikle et al., 2012)	0.97
FTQ	Fear of Tinnitus Questionnaire	(Cima et al., 2011)	0.71
TCS	Tinnitus Catastrophizing Scale	(Cima et al., 2011)	0.93
HQ	Hyperacusis Questionnaire	(Khalfa et al., 2002)	0.90
PSQ-30	Perceived Stress Questionnaire	(Levenstein et al., 1993)	0.94
HADS	Hospital Anxiety and Depression Scale	(Zigmond & Snaith, 1983)	0.83-0.85
WHO-QoL	World Health Organization Quality of Life	(The Whoqol Group, 1998)	0.69-0.84

Table 2. Overview of questionnaires available in STOP. Cronbach's α for internal consistency from (K. Müller et al., 2016).

STOP was further expanded to include the newly developed ESIT Screening Questionnaire (ESIT-SQ; (Genitsaridi et al., 2019) which was submitted by 4 591 participants in the last two months of 2018. The final extensive questionnaire dataset from STOP laid the foundation for studies 1-3.

[2] https://stop.ki.se

STOP participants who replied to the online questionnaires were invited to an auditory assessment. The majority of assessments were performed at Karolinska Hospital Rosenlund (Stockholm) and included:

- Otoscopy
- Tympanometry
- Distortion Product Otoacousitc Emissions (DPOAE)
- High frequency audiometry (0.125-16 kHz)
- Loudness discomfort levels (LDL)
- Speech-in-noise testing
- Tinnitus pitch and loudenss matching
- Auditory Brainstem Response (ABR)

Between August 2016 and December 2019, auditory measurements were collected for 927 participants. This dataset enabled the electrophysiology analysis that constitutes Study 4.

3.2 Study I

Study 1 investigated the potential impact self-reported temporomandibular joint disorder (TMJD) may have on tinnitus and what variables may separate tinnitus patients that suffer from TMJD from those that do not. Participants from STOP were included in the analysis if they reported experiencing any tinnitus and answered *Yes* or *No* to the question "Do you suffer from temporomandibular joint disorder?" This resulted in a final sample consisting of 2 482 subjects, 44% of the subjects in STOP. Questionnaire scores were calculated for the different instruments in STOP according to their design and compared between subjects with or without TMJD for different stratifications of tinnitus. Sociodemographic variables (e.g. Age, Sex, Education level) and specific categorical tinnitus factors of interest (e.g. pitch of tinnitus, if tinnitus is affected by loud noise, stress or poor sleep) were also investigated.

Scores for several continuous variables deviated from normal distribution and hypothesis was therefore performed using the non-parametric Wilcoxon's test. Categorical items were compared using the Pearson's X^2-test. Correction for multiple comparisons were conducted using the Benjamini & Hochenberg method (Benjamini & Hochberg, 1995).

3.3 Study II

Study 2 investigated the association between tinnitus and hyperacusis and aimed to identify phenotypic traits related to tinnitus with accompanying hyperacusis. First, the association between tinnitus and hyperacusis was established in the dataset. Inclusion criteria included the subject to have filled out the newly developed ESIT-SQ and resulted in 1 984 subjects with tinnitus, and 1 661 subjects with no tinnitus. Of particular interest was the subset of participants that reported severe tinnitus. These were stratified both according to the Swedish clinical standard threshold for clinically significant tinnitus (Idrizbegovic & Kjerulf,

2011), a THI score ≥ 58, and the single item B4 from the ESIT-SQ ("Over the past year, how much does your tinnitus worry, annoy or upset you when it is at its worst?"). Odds ratios and 95% confidence intervals (CI) were calculated (SAS 9.4; SAS Institute, Cary, NC, USA) in unconditional multiple logistic regression models adjusted for sex, age, education level and self-reported hearing. The item A12 from ESIT-SQ "Over the last week, have external sounds been a problem, being too loud or uncomfortable for you when they seemed normal to others around you?" was used as the dependent variable. Response categories for "small" or "moderate problem" were recoded as "moderate" and "big" or "very big problem" were recoded as "severe" to keep the number of parameters manageable.

The following investigation of tinnitus phenotype stratified by hyperacusis did not rely on items from the ESIT-SQ and included an additional 448 subjects with tinnitus from the STOP database. This resulted in 2 432 subjects with tinnitus, of which 1 388 reported hyperacusis and 1 044 reported no hyperacusis. The questionnaires described in 3.1 were analyzed using JMP 13 (SAS Institute Inc.) and R (R Core Team, 2017) with Pearson's X^2-test for categorical items, the non-parametric Wilcoxon's test for all other items and multiple comparison corrections with the Benjamini & Hochenberg method (Benjamini & Hochberg, 1995).

3.4 Study III

Study 3 used the same two step-design as the previous study, first investigating the association between tinnitus and headaches, with a follow-up analysis of tinnitus phenotype stratified by self-reported headaches. The analysis of association was based on item A15: "Do you suffer from any of the following pain syndromes?" from the ESIT-SQ with 'Yes, headache' being the response option of interest. The expanded phenotype analysis instead relied on the TSCHQ item "Do you suffer from headache?" and included 2 539 subjects with tinnitus. The main difference in methodology from Study 2 was the use of the Tinnitus Functional Index (TFI), instead of a single tinnitus severity-item from the ESIT-SQ, in conjunction with the THI definition of 'severe tinnitus'. Statistical methods used were identical to those reported for Study 2.

3.5 Study IV

3.5.1 Longitudinal analysis

In collaboration with the Stress Research Institute at Stockholm University, Study 4 first investigated tinnitus as reported in the longitudinal Swedish Longitudinal Occupational Survey of Health (SLOSH; (Magnusson Hanson et al., 2018)). A prospective study focusing on work environment and health, first initiated in 2006. Between 2008 and 2018, data on tinnitus were collected every 2 years. This study included all participants of responded to the postal questionnaire at least twice within this time frame. In a total this resulted in 20 439 participants, with 53 273 observations. The questionnaire item on tinnitus was phrased as "Have you, during the most recent time, experienced sound in any of the ears without there

being an external source (so-called tinnitus) lasting more than 5 minutes?" with response options "no", "yes, sometimes", "yes, often", or "yes, constant". The outcome of constant tinnitus was controlled for age, sex, previous experience of tinnitus, time of response, and education. The covariate "previous experience of tinnitus" was derived from the 1-time lag from the previous questionnaire response. That is, the self-report of tinnitus in the same questionnaire two years prior. Using the method of Generalized Estimating Equation (GEE) models with an unstructured correlation or exchangeable correlation structure both produce similar results to a naïve logistic model. The procedure Genmod in SAS (version 9.4) was used to run all the GEE models.

3.5.2 Electrophysiology of tinnitus

Data from the audiological test battery performed within STOP was analyzed in conjunction to the data from SLOSH. Testing was performed at the Karolinska Hospital Rosenlund (n = 778), Karolinska Hospital Solna (n = 120) and Department for Audiology, Lunds University, Lund (n = 29). This study included pure tone, fixed frequency Bekesy audiometry with a pulsed pure tone (550 ms, 50% duty cycle) measured using the Madsen Astera 2 clinical audiometer (Otometrics). Standard frequencies between 0.125-16kHz were tested using HDA200 (Sennheiser) headphones.

Two different clinically available systems for measurement of the Auditory Brainstem Response (ABR) were used, the EP200 Chartr (Otometrics) and the Eclipse (Interacoustics). Settings for both systems were identical, with high and low pass filters of 0.1 and 3 kHz, respectively, with 100 μs click stimuli of alternating polarity presented at 9.1 clicks/s at 90 dB nHL through insert earphones, with contralateral masking of –40 dB relative to the stimulus ear. Each recording consisted of 2000 accepted clicks. The participants were relaxed in a reclined position in a dimly lit room during the recording. From the total of 927 audiological assessments 492 were excluded, most commonly due to reported noise sensitivity or low LDL thresholds (n = 205) or excessive wax in the ear canal (n = 77). The final sample included three groups: 177 participants with no tinnitus, 92 with occasional tinnitus and 136 with constant tinnitus.

The common prominent ABR features of latency and amplitude for wave I, III and V were identified through an automated process and confirmed or corrected by two separate, blinded audiologists experienced in working with ABR data.

Sociodemographic variables and questionnaire scores were compared between the three groups using Pearson's X^2-test for categorical variables, an ANOVA for numerical variables available for all groups and the 2-tailed Student's t-test for tinnitus-specific questionnaires.

To evaluate the ability of any ABR feature to contribute as an objective biomarker of tinnitus a stepwise selected model controlling for age, sex, hyperacusis, pure tone average (0.5, 1, 2, 4 kHz), high frequency pure tone average (10, 12.5, 14, 16 kHz) and ABR-equipment was

constructed for each ABR variable of interest. Covariates were included to minimize the Bayesian Information Criterion (BIC) evaluating both backward and forward selection. Data analysis was performed using R (Heinzen et al., 2021; R Core Team, 2017; Revelle, 2022) or JMP 14 (SAS Institute Inc.)

3.6 Study V

Following the previous studies, aimed to better understand potential homogenous subtypes of tinnitus and evaluate proposed objective biomarkers, the final goal of the thesis culminated in evaluating the cortical response of a GPIAS-stimuli in human subjects. To be able to measure responses with high temporal resolution and good spatial resolution, magnetoencephalography (MEG) co-registered with structural T1 MRI-images were used. As this was a novel approach, the study was designed in incremental steps so that each level of data collection could be optimized based on earlier findings The study was approved by the local ethics committee, Regionala etikprövningsnämnden in Stockholm, (Dnr: 2019-05226).

We first analyzed stimuli parameters known to effect saliency of the gap and following pulse; carrier noise and pulse-level. 60 and 70 dBA were used for the carrier noise level, and pulse levels were presented from +5 dB above background, increasing in 5-dB steps to a maximum of 95 dBA. Also, the major temporal parameter affecting inhibition of the response, the inter-stimulus interval (ISI) was varied between 0, 60, 120 and 240 ms in trials with a pulse preceded by a silent gap. Ten blocks were repeated for a total of 50 presentations of each trial type, the total scanning time was around 90 minutes. During measurement surface electrodes on around the eyes and on the collar bones recorded electrocardio- and electrooculo-gram (ECG and EOG) to control for artefacts from heartbeat, eye-blinks and movement.

We recruited n = 22 normal hearing, non-tinnitus participants for audiological assessment, MEG, and structural MRI. All MEG data was collected at national facility for magnetoencephalography (NatMEG) at Karolinska Institutet using a 306-channel Elekta Neuromag TRIUX system with a sample rate of 5 000 Hz.

The EOG channel for detecting eyeblinks were analyzed separately for comparison between the traditionally used muscle reflex and cortical responses. Peak amplitude responses for all trials were analyzed with a one-way analysis of variance (ANOVA). Peak amplitudes were also compared with paired t-tests and p-values reported are corrected for multiple comparisons using the Benjamini & Hochenberg method (Benjamini & Hochberg, 1995). The percentage of inhibition for the four different ISIs were calculated as [1-(GP/PO)] where GP represent amplitude in trials with a Gap preceding the Pulse and PO trials with a Pulse Only.

The sensor with maximum amplitude response for the majority of participants were identified on the left and right side of the array separately and used for analysis. ERF

amplitudes for combined gradiometers for GP and PO trials and inhibition in the presence of a silent gap were analyzed the same as for EOG channels. We identified the canonical N1 response (50–150 ms) as a particular time window of interest. Topographic distributions of the N1 time window were inspected to rule out muscle artefacts and confirm the validity of the identified sensors.

4 Results

4.1 Study I-III

In participants with any tinnitus, 19% reported TMJ complaints and the proportion rose for those who reported tinnitus as a big problem. Stratified by a TFI score ≥ 48, 30% reported TMJ, and with a THI score ≥ 58 this proportion was 36%. Conversely, greater tinnitus burden was found in subjects with any tinnitus and TMJ complaints, with statistical significance for all the questionnaires investigated. With increasing tinnitus severity, fewer differences were found between participants with and without TMJ complaints. This points to some contribution of TMJ disorders to tinnitus severity and underlines the importance of gathering information on TMJ complaints in studies of tinnitus. Factors consistently found to differ between subjects with or without TMJ complaints, irrespective of tinnitus stratification, were the ability to modulate tinnitus by head movement or touch, if tinnitus was affected by stress and experiencing neck pain. The ability to modulate tinnitus points to a somatosensory component involved in tinnitus generation and may distinguish this patient group as good candidate for studies manipulating tinnitus to elucidate its mechanism of generation.

A similar pattern was identified in Study 2 in which the increase in the proportion of participants who reported tinnitus grew to 86% in the group with severe tinnitus (THI ≥ 58) compared to 24% for the control group and 59% for the group reporting any tinnitus. That the occurrence of hyperacusis increase to such a degree with tinnitus severity strongly points to a tight relationship between the two. Odds ratios (95% confidence interval; CI) of reporting hyperacusis, corrected for age, sex, education level and hearing ability, increased from 3.5 (2.9-4.1) for the any tinnitus-group to 12.1 (7.1-20.1) for the severe tinnitus-group. For those reporting severe hyperacusis, this relationship appeared even stronger going from 9.54 (5.6-15.8) to 77.4 (35.0-171.3). The ORs for both Study 2 and Study 3 are summarized in Table 3. Importantly, hearing ability was a clear confounding factor for both tinnitus and hyperacusis with an OR of 137.6 (62.8-301.2) for severe difficulties hearing, in the severe tinnitus-group. If omitting to control for hearing as a factor, the OR for severe hyperacusis was calculated to 251.7 (120.4-526.6) compared to 71.1 (24.7-204.9) in the full model.

Using the same methodology to investigate the association between headaches and tinnitus (Study 3), the prevalence of headaches also increased with tinnitus severity. 26% of subjects with any tinnitus reported headaches and this proportion rose to 46% in subjects with severe tinnitus (THI ≥ 58). ORs (CI), using the same correction factors as previously, was 2.2 (1.8-2.6) for experiencing headache in the any tinnitus group and 4.3 (3.0-6.2) and 3.8 (2.4-5.9) when stratified by TFI ≥ 48 and THI ≥ 58 respectively. The association between headaches and tinnitus are clearly not as strong as for hyperacusis and importantly is less impacted by hearing ability. Study 3 reports two models, one not including hearing ability as a covariate.

These two models showed only minor differences, and results from the more conservative model, including hearing ability, are reported here.

	No tinnitus	Any Tinnitus		Severe Tinnitus (Self-reported)		Severe Tinnitus (THI > 58)	
	n (%)	n (%)	OR (CI)	n (%)	OR (CI)	n (%)	OR (CI)
Headache							
No	1421 (85.6)	1458 (73.5)	**Ref**	156 (59.3)	**Ref**	94 (59.9)	Ref
Yes	240 (14.4)	526 (26.5)	2.19 (1.81-2.64)	107 (40.7)	4.29 (3.0-6.2)	63 (40.1)	3.80 (2.4-5.9)
Hyperacusis							
No	1255 (75.6)	822 (41.4)	**Ref**	51 (21.3)	**Ref**	21 (13.3)	**Ref**
Yes	406 (24.4)	1162 (58.6)	3.51 (2.99-4.13)	188 (78.7)	7.43 (5.06-10.9)	136 (86.6)	12.1 (7.1-20.6)
Moderate	387 (23.3)	970 (48.9)	3.24 (2.75-382)	105 (43.9)	5.18 (3.5-7.7)	71 (45.2)	8,.15 (4.7-14.2)
Severe	19 (1.1)	192 (9.7)	9.54 (5.75-15.8)	83 (34.7)	48.0 (24.7-93.3)	65 (41.4)	77.4 (35-171.3)

Table 3. Overview of results from multivariate logistic regression models adjusted for age, sex, education and hearing ability from Study 2 and Study 3. Odds Ratios (OR) and 95% Confidence Intervals (CI). Results from Cederroth et al. (2020) and Lugo et al. (2020).

4.2 Study IV

4.2.1 Longitudinal analysis

The GEE model showed that the dynamic progression from occasional to constant tinnitus is greater with increasing frequency of occasional tinnitus. Adjusted odds ratios (CI) increased from 5.6 (4.8-6.6) for experiencing tinnitus *sometimes* to 29.7 (25.7-34.4) with reports of experiencing tinnitus *often*. For those who had reported constant tinnitus previously the probability of reporting constant tinnitus in a following evaluation increased massively, to an OR of 603 (524.7-692.9). This indicates a progression towards constant tinnitus that once established is very unlikely to remit.

4.2.2 Auditory brainstem response (ABR)

The ABR parameters that significantly distinguished constant tinnitus from either occasional tinnitus or non-tinnitus controls are summarized in Table 4. With the control group as reference, wave III and V latencies in the ABR, for the left ear (OR: 12.3, [3.1-52.2] and 4.31, [1.9-10.5]) remained as significant variables in their respective model after stepwise selection together with Age, HQ score, PTA 4 and PTA HF. For the right ear wave III latency (10.4, [2.5-

45.7]) and amplitude (0.03, [0.004-0.2]), and wave V amplitude (0.07, [0.01-0.55]) were included with the same variables except PTA 4. When the group reporting occasional tinnitus was used as a reference, only latency for wave I and V when stimulating the left ear survived stepwise selection (41.8 [2.5-848.4] and 7.21, [2.5-22.3]) together with Age and PTA 4. Left ear wave V latency was the only ABR variable that consistently distinguished constant tinnitus from occasional tinnitus and the non-tinnitus control group.

Ear	Variable	OR	95% CI	p-value
Reference: non-tinnitus controls				
L	III lat.	12.27	3.14–52.19	0.001
L	V lat.	4.31	1.85–10.53	0.002
R	III lat.	10.44	2.52–45.73	0.002
R	III amp.	0.03	0.004–0.21	0.001
R	V amp.	0.07	0.01–0.55	0.013
Reference: Occasional tinnitus				
L	I lat.	41.75	2.50–848.43	0.011
L	V lat.	7.21	2.51-22.34	<0.001

Table 4. Overview of significant ABR parameters included after stepwise selection. Data from Edvall et al. (2022).

4.3 Study V

Pulse levels in PO (Pulse Only) trials required to be 85 dBA or higher to elicit a detectable EOG response in 60 dBA broadband carrier. In the 70 dBA carrier, only 90 and 95 dBA pulses elicited a response. A one-way ANOVA showed significant effect of pulse level in both the 60 dBA ($F(5) = 8.43$, $p < 0.001$) and 70 dBA carrier ($F(4) = 7.04$, $p < 0.001$). In the GP (Gap + Pulse) trials, all four inter-stimulus intervals (ISIs) tested disrupted the EOG response to the pulse, a one-way ANOVA showed no significant difference between ISIs in either the 60dB ($F(3) = 1.13$, $p = 0.34$) or 70dB carrier ($F(3) = 1.96$, $p = 0.13$). The highest level of inhibition was reached at an ISI of 60 ms (GP mean = -2.11, SD = 1.61 and PO mean = -5.94, SD = 6.06 [$\times 10^{-5}$ Volt]) with an inhibition of 64.5%, calculated as [1-(GP/PO)]. Paired t-test for all ISIs showed a significantly lower response in GP trials compared to PO in the 60 dBA ($t(21) > 2.98$, $p < 0.01$) but not 70 dBA carrier ($t(21) < 2.25$, $p > 0.056$). That is, the 60 dBA carrier was more appropriate to produce reliable inhibition in GP trials. Most likely, this is because of the larger dynamic range of the PO response in the 60 dBA carrier, and higher amplitude response in the 90 dBA pulse level condition specifically.

Analyzing cortical event related field (ERF), responses were more reliably elicited already at lower pulse levels, +10 dB above background, compared to EOG. As for the EOG response,

the 60 dBA carrier provided the best dynamic range of PO response and inhibition and are reported here. Results from ANOVA showed a significant effect of pulse level in both the right ($F(5) = 10.93$, $p < 0.001$) and left sensors ($F(5) = 13.53$, $p < 0.001$) but there was no effect of ISI on either side ($F(3) = 0.169$, $p = 0.917$ and $F(3) = 0.485$, $p = 0.694$, for left and right side respectively). The highest level of inhibition was 49.6% for the right sensor with 240 ms ISI (PO mean = 5.68, SD = 2.82 and GP mean = 2.86, SD = 1.51 [$\times 10^{-12}$ T/cm]). In general, the right sensor produced larger responses in both PO and GP trial, but both sensors measured statistically significant inhibition in all ISIs (paired t-test, $t(21) > 3.94$, $p \leq 0.001$).

The shorter ISIs of 0 and 60 ms had response components from the gap itself overlapping with the time window of interest (50-150 ms) analyzed here. Because of this, and the fact the longest ISI of 240 ms gave the best percentage of ERF inhibition (49.6%), the 240 ms ISI was identified as the best candidate for a follow-up experiment using narrow-band carrier noises.

5 Discussion

One of the major hurdles in tinnitus research and clinical management is that tinnitus is experienced very differently by those who have it. There is no consensus of what factors should be included for stratification of valid subtypes of tinnitus. Among the many proposed co-morbidities for tinnitus, here we studied temporomandibular joint (TMJ) complaints, headache and hyperacusis. We found a clear association between TMJ complaints and tinnitus and suggest that information on TMJ and somatosensory modulation of tinnitus should be included in studies of tinnitus. This finding was recently confirmed in a large systematic review of tinnitus risk factors (Biswas et al., 2022). As reported in a previous study (Vielsmeier et al., 2012), we found that this group more often can modulate their tinnitus by head or neck movement. This may enable a study design in which this patient group can function as their own internal control during tinnitus modulation. Some intervention studies of this patient group have shown tinnitus alleviated after TMJ treatment (Tullberg & Ernberg, 2006; Van der Wal et al., 2020; van der Wal et al., 2022), but the mechanism and causal relationship between TMJ and tinnitus is still poorly understood.

Previous studies of tinnitus and headache have described a relationship between the laterality of the conditions (Langguth et al., 2015) and that the two conditions present an additive effect (Langguth et al., 2017). To our knowledge, Study III was the first to compare the association between tinnitus and headache to a control group and calculate and adjusted odds ratio. Notably, subjects with headaches were more likely to also report "Other pain syndromes" independent of tinnitus severity. Tinnitus and pain have many similarities in that they are both a subjective experience that lack an objective biomarker (Reckziegel et al., 2019). We showed a significant association between tinnitus and headache, and other studies have investigated this relationship for other, chronic, pain syndromes (Ausland et al., 2021). As both tinnitus and pain syndromes are diagnostically nebulous conditions, investigating them simultaneously is problematic and may introduce unknown confounding factors. Instead of using information on headache or other pain syndromes to stratify groups in studies of tinnitus, or using such factors as covariates, a preferred design uses pain syndromes as an exclusion criterion to study one condition at a time. The sample of subjects included in Study 4 showed no statistically significant difference in ANOVA comparing the three groups ($p = 0.417$) which is why headache could reasonably be ignored for the subsequent analysis.

Hyperacusis has been described as a common comorbidity with tinnitus (Schecklmann, Landgrebe, et al., 2014) but the strength of this association was not known before the publication of Study II. The substantial association, particularly when both conditions are severe, call into question whether previous studies finding neural correlates of tinnitus may have confused these for correlates of hyperacusis.

The strong association between tinnitus and hyperacusis warranted the inclusion of hyperacusis as a covariate in Study 4. It was highlighted as a significant factor in all models where ABR parameters distinguished constant tinnitus from non-tinnitus controls. A previous study with a design that compared subjects with tinnitus to those with tinnitus and hyperacusis also showed a differential ABR, predominantly in the wave V latency, response (Hofmeier et al., 2021). The recurring finding that wave V latencies are affected in subjects with tinnitus, even when hearing thresholds are controlled for, point to involvement of plastic changes in the human brainstem as an underlying factor. These group level findings indicate differences probably too small to be useful metrics for individual diagnostics in isolation, but may be useful as a part in a larger test battery. Importantly, it is necessary to take hyperacusis in to account for the ABR response to have any validity as a contributor to a biomarker for tinnitus.

The wave I amplitude response has been shown to be affected by cochlear synaptopathy in mouse models of tinnitus after noise exposure (Hickox & Liberman, 2014). However, attempts to link this phenomenon to tinnitus in human subjects have been less than successful with results rarely replicated (Milloy et al., 2017; K. Turner et al., 2022). In Study 4 we used two different clinical ABR systems for data collection and found that these produced different readout, even with all parameter settings identical. A test re-test experiment of the two systems revealed that the intraclass correlation coefficient for latency measurements were generally good to excellent (ICC3 > 0.75; Supplementary table S7, Study 4). Reliability for peak amplitude were generally low (ICC3 < 0.5), with only the wave I amplitude for one system being acceptable (ICC3 = 0.96) among all amplitude measurements. That is, the inherent inter-subject variability for amplitude measurements in the ABR may dismiss it as potential biomarker of tinnitus. This conclusion is seemingly shared by a recent review that reported ABR wave I, III & and V latency, but not amplitude, measures differed for tinnitus patients and controls in a meta-analysis (Jacxsens et al., 2022). However, the authors noted that the included studies not controlled for confounding factors such as age, gender and hearing status. Results from Middle latency (MLR; 10-80 ms) and Frequency Following responses (FFR) were inconclusive.

It should be noted that evaluation of using ABR is somewhat hindered by the difficult to access, or opaque, detailed specifications of clinical measurement devices. Future studies, potentially with simulated ABR data, should evaluate if more advanced analysis methods (e.g. cluster-based permutation test; Maris & Oostenveld, 2007) could increase statistical power when analyzing ABR data, compared to traditional amplitude and latency measures.

In study V we compared the MEG response in GPIAS trials to the EOG response, analogues to the muscular reflex response used in animal models of tinnitus. In general, the EOG produced slightly higher levels of inhibition but with a much higher inter-subject

variability. That is, many participants did not respond to the stimuli by blinking or quickly habituated the stimuli while the cortical response provided a reliable readout.

The ISI have been shown to be an significant factor in animal models but importantly, the particular impact of ISI on startle suppression is dependent on the specific genetic strain tested (Yu et al., 2016). We found comparable levels of inhibition for all four ISIs tested indicating human subjects may be less sensitive to shifting ISIs. However, a specific study with a finer resolution of ISIs tested in a larger and more diverse sample will be necessary to draw conclusions. Based on or findings, a 240 ms ISI is optimal for eliciting cortical inhibition of the N1-response in MEG. This longer ISI also provides the added benefit of separating response components related to the on- and offset to the actual gap from those produced by the following pulse.

The gap offset specifically (i.e. the point when the carrier noise returns) have been shown to play a specific role in gap related inhibition. Optogenetic suppression of inhibitory interneurons in auditory cortex, improve gap inhibition, while suppressing excitatory attenuate the response (Weible et al., 2014). A study including varying gap durations, comparing on- and offsets, could shed some light on the interaction of the different response components involved. Potentially, a silent gap of a certain duration may produce a different response between subjects with or without tinnitus independent of a following sound pulse.

To optimize GPIAS inhibition in animal models, it has been suggested that the optimal level of the startle pulse be about 75% of the level that produces the maximum response (Longenecker & Galazyuk, 2012). To keep the MEG test session duration manageable, we chose 90 dBA as the pulse level to present in GP-trials. Comparing responses for 90 and 95 dBA pulses EOG responses showed a difference of 64%. That is, there may still be room to elicit a stronger EOG response with a louder sound pulse. For the ERF, the differences were 91% and 101% for the left and right sensors respectively indicating that the 90 dBA pulse level was already close to, or hitting, the ceiling. The pulse level of 90 dBA therefore seems to have provided a good balance for the two modalities tested. Potentially, lower pulse levels produce better inhibition of ERF in a protocol applicable to subjects with hyperacusis. However, this notion should also be evaluated in subjects with varying hearing abilities and would eliminate the possibility of simultaneous recording of EOG responses.

Most MEG studies record EOG for the purpose of removing muscle artefacts from eye movements or blinking from the data. Here, the EOG channels were used to evaluate the blink as a response, “one man’s noise is another man’s data” as it were. The common strategy of independent component analysis where EOG components are removed from the dataset was therefore omitted. Extra caution had to be taken to not confuse any EOG responses with a cortical ERF response. Two findings confirm that this distinction was

correctly assumed in the analysis pipeline. Firstly, the sensors of interest for left and right hemispheres were objectively identified to be approximately located over auditory regions. Any muscle artefact from EOG responses are orders of magnitude stronger than ERFs produced by cortical sources and would have identified sensors in the frontal part of the sensor array. Secondly, plots of the topographic distribution (See Study V, figure 2) show a common pattern for an equivalent current dipole in auditory regions. Future studies incorporating source reconstruction will have to continue to work around this quirk of the experimental setup, for example by using specific regions of interest for analysis.

6 Conclusions

- Temporomandibular joint pains or complaints are associated with tinnitus, especially severe tinnitus. Future studies of tinnitus should gather information on TMJ complaints.

- There is a strong association between tinnitus and hyperacusis and the severity of the two conditions seem linked. The association is confounded by underlying hearing-loss and considering the interaction of all three conditions is imperative in future studies.

- There is some association between tinnitus and headaches and future studies would benefit from phenotyping pain-syndromes in their research participants. However, both tinnitus and pain are diagnostically nebuolous and a study design that evaluates both conditions is difficult.

- Longitudinal data of self-reported tinnitus indicate a progression towards constant tinnitus that once established is very unlikely to remit.

- The wave V latency of the auditory brainstem response can distinguish constant from occasional tinnitus and non-tinnitus controls at a group level. This measurement may play a role in a larger test battery for tinnitus but is likely too variable to function as a stand-alone biomarker.

- A GPIAS stimulation protocol reliably produce inhibition of ERF responses with much lower variability compared to traditional EOG responses, analogous to the startle responses used in animal models of tinnitus. GPIAS + MEG is a promising approach to developing a biomarker for tinnitus.

7 Future directions

The auditory brainstem response (ABR) exists in a gray area in that it is simultaneously a basic, clinical standard measurement, and a tool still in development for research implementation. Most people seeking help for their tinnitus will pass through an audiology clinic and most audiology clinics are capable of collecting ABRs. Yet, a review of ABR as tool for tinnitus evaluation found that studies included on average only 28 participants with tinnitus (Milloy et al., 2017). With the foresight to include ABRs as a standard measurement in clinics that see tinnitus patients, the threshold to gathering thousands of data points is not zero - but relatively low. The same case can be made for collection of blood samples (Cederroth et al., 2017) and middle ear muscle reflexes (Wojtczak et al., 2017). Both standard techniques suggested to provide important information for tinnitus diagnostics. A concerted effort to standardize data collection and setup an infrastructure for data sharing between clinics and research institutions provides scientific, financial, and public health benefits. Furthermore, improved data availability would help in developing new analysis tools. Reducing the ABR response to values for peak-to-peak amplitude and latency may discard a lot of information that could be useful in, for example, machine learning models.

In Study V we show that a GPIAS protocol reliably produce inhibition of cortical responses. Work is ongoing to evaluate if this result is replicated in a narrow-band noise. As most patients report their tinnitus as a combination of tones in a limited frequency range, a narrow-band carrier is a more relevant comparison to the actual perception of tinnitus. In addition, narrow-band noises can be presented on- and off-frequency of the individual subject's pitch match. This provides an advantageous study design were each subject can function as their own internal control in GPIAS trials with a narrow-band carrier. Following this validation, the next step is to perform a case-control study. Preferentially in tinnitus subjects with normal hearing and no hyperacusis to limit confounding factors. However, as noted previously, these conditions are closely associated, and such stringent recruitment may be difficult in practice.

Studies have shown that some tinnitus patients experience short but complete tinnitus relief after lidocaine administration (Berninger et al., 2006; Kalcioglu et al., 2005). MEG measurements before and during treatment may therefore elucidate mechanisms of tinnitus and inform its usability as an outcome measure for future treatments.

MEG has the advantage of offering excellent temporal resolution with good spatial resolution when co-registered with MRI. However, its high cost and limited availability often limits its clinical use. Fortunately the auditory N1 response is generally comparable between MEG and EEG, which is both cheaper and widely available (Virtanen et al., 1998). However, future studies implementing simultaneous recordings with M/EEG will have to compare the methods for the specific protocol proposed.

8 Acknowledgements

The people who inspired, helped, and supported me, in chronological order.

My parents **Karin** and **Anders Edvall** who gave me everything I needed and more. My grandparents **Göte** and **Barbro Edvall** who made sure I never missed the music lessons where my interest for sound and hearing started. **Carl Stenqvist** who told me about the audiology program in Lund and **Daniel Reimers** who made my time there enjoyable. **Anders Jönsson**, who inspired me, educated me, and introduced the world beyond the clinic. **Jonas Brännström** for mentorship and always asking the right questions. **Gary Rance** for introducing me to research in the friendliest possible way. **Christopher Cederroth** who took me on a journey that provided me with all the experience, never gave up, and became a good friend. **Barbara Canlon** for encyclopedic knowledge, providing discipline, experience, and an always open door. **Jan Bulla** for teaching me statistics and **Eleni Genitsaridi** for teaching me how and why to use R. **Evangelia Tserga** for keeping the lab running. **Natalia Trpchevska** for charting the map of being a PhD student and still have energy to hear me complain. **Daniel Lundqvist** for introducing me to MEG and convincing me I can learn how to use it. **Mikkel Vinding** for teaching me how to use MEG and being a fountain of knowledge. **Andreas Gerhardsson** for making data collection possible and having the patience of an angel. **Charlie**, for keeping me sane. **Christoph Pfeiffer** for showing me indexing in the form: idx = 3*t[tix]+1+1*b[bix] and making NatMEG an inspirational lab to be in.

If it was not for **Frida Åstrand Melin**, I fear I would always have followed the path of least resistance. She motivates me to be the best version of myself and when I forget what that is, she reminds me.

Of course, a happy PhD student is a productive PhD student, but I can't name all the people who make me happy. You know who you are.

None of my research would be possible without all the research participants, generously contributing their time and energy volunteering as subjects. Thank you all!

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