Tinnitus Profiling to Guide Personalized Therapeutic Decisions – Diagnosis Improved with Large-Scale, Longitudinal Data

Doctoral Thesis
In fulfillment of the requirements
for the doctoral degree
(Dr. sc. hum.)

At the
Faculty of Medicine
Of Regensburg University

Submitted by
Jorge Piano Simões
from
Rio de Janeiro, Brazil

In the Year of
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Abstract

Tinnitus is a condition characterized by the perception of auditory phantom perceptions without a corresponding external stimulus. Tinnitus can be debilitating despite usually being considered a benign condition, with current estimations that 1% of the population suffers from bothersome tinnitus. Factors such as loudness, laterality, type of perceived sound, loudness fluctuations throughout the day, and ability to concentrate vary between individuals. Additionally, comorbidities such as hyperacusis, detrimental sleep, anxiety, and depression are common complaints among the tinnitus population. Together, those variables highlight how heterogenous tinnitus is, as clinical cases are always composed of a unique mosaic of demographics, tinnitus characteristics, and psychopathological profile.

Researchers and clinicians are increasingly aware of the potential role of heterogeneity in the clinical manifestation of tinnitus. Heterogeneity could explain why only a subset of patients respond to certain clinical treatments available. It would be of great relevance to identify which markers are relevant for individualized interventions. The aim of this doctoral thesis was to advance the understanding of tinnitus heterogeneity towards this goal.

This thesis contains six chapters. In the introduction, a brief overview of tinnitus is given alongside some key concepts that are further articulated in the discussion section; in Chapter 1, I used crowdsensed data from thousands of online users with tinnitus to investigate whether demographics and tinnitus characteristics could predict the outcome of 26 tinnitus-related treatments. In Chapter 2, I investigated the role of personality traits on tinnitus habituation over time. In Chapter III, I researched how often total tinnitus remission takes place in a clinical sample and tried to identify predictors of remission. Additionally, I tried to identify additional predictors of tinnitus habituation, and to map how often comorbidities were experienced by the clinical population, and how often those patients sought tinnitus-related treatments. In chapter IV, I used ecological momentary assessment from users of a mobile app mapping everyday variables related to their tinnitus, like loudness, distress, and concentration to investigate whether those variables were solely state-dependent or whether those states carried over to the following day. This study used state-of-the-art methods to model how those variables interplay with one another at the individual level. Lastly, I discuss current challenges towards untangling tinnitus heterogeneity, and proposals are made to include a quantitative pathopsychological framework to integrate different levels of tinnitus heterogeneity.

Zusammenfassung

Tinnitus ist ein Zustand, der durch die Wahrnehmung von auditiven Phantomwahrnehmungen ohne einen entsprechenden externen Stimulus gekennzeichnet ist. Tinnitus kann beeinträchtigendsein, obwohl er normalerweise als harmlose Erkrankung angesehen wird. Nach aktuellen Schätzungen leidet 1 % der Bevölkerung an einem störenden Tinnitus. Faktoren wie Lautstärke, Lateralität, Art des wahrgenommenen Geräusches, Lautstärkeschwankungen im Verlauf des Tages und Konzentrationsfähigkeit sind von Person zu Person unterschiedlich. Zusätzlich sind Komorbiditäten wie Hyperakusis, Schlafstörungen, Angstzustände und Depressionen häufige Beschwerden in der Tinnituspopulation. Zusammengenommen verdeutlichen diese Variablen, wie heterogen Tinnitus ist, da klinische Fälle immer aus einem einzigartigen Mosaik aus demographischen Merkmalen, Tinnitus-Charakteristika und psychopathologischem Profil bestehen.

Forscher und Kliniker sind sich zunehmend der möglichen Rolle der Heterogenität bei der klinischen Manifestation von Tinnitus bewusst. Heterogenität könnte erklären, warum nur eine Untergruppe von Patienten auf bestimmte verfügbare klinische Behandlungen anspricht. Es wäre von großer Relevanz zu identifizieren, welche Marker für individualisierte Interventionen von Bedeutung sind. Das Ziel dieser Doktorarbeit war es, das Verständnis der Tinnitus-Heterogenität in Richtung dieses Ziels voranzutreiben.

Die vorliegende Arbeit umfasst sechs Kapitel. In der Einleitung wird ein kurzer Überblick über Tinnitus gegeben, zusammen mit einigen Schlüsselkonzepten, die im Diskussionsteil weiter ausgeführt werden. In Kapitel 1 habe ich Crowdsense-Daten von Tausenden von Online-Nutzern mit Tinnitus verwendet, um zu untersuchen, ob demographische und Tinnitus-Merkmale das Ergebnis von 26 tinnitusbezogenen Behandlungen vorhersagen können. In Kapitel II untersuchte ich die Rolle von Persönlichkeitsmerkmalen bei der Tinnitus-Gewöhnung im Laufe der Zeit. In Kapitel III untersuchte ich, wie oft eine vollständige Tinnitusremission in einer klinischen Stichprobe stattfindet und versuchte, Prädiktoren für die Remission zu identifizieren. Außerdem habe ich versucht, zusätzliche Prädiktoren für die Tinnitus-Gewöhnung zu identifizieren und zu erfassen, wie häufig Komorbiditäten in der klinischen Population auftraten und wie häufig diese Patienten tinnitusbezogene Behandlungen in Anspruch nahmen. In Kapitel IV verwendete ich ökologische Momentaufnahmen von Nutzern einer mobilen App, die alltägliche Variablen im Zusammenhang mit ihrem Tinnitus,

wie Lautstärke, Stress und Konzentration, abbildeten, um zu untersuchen, ob diese Variablen ausschließlich zustandsabhängig waren oder ob diese Zustände auf den nächsten Tag übertragen wurden. Diese Studie verwendete modernste Methoden, um zu modellieren, wie diese Variablen auf individueller Ebene miteinander interagieren. Abschließend diskutiere ich die aktuellen Herausforderungen bei der Entflechtung der Tinnitus-Heterogenität und schlage vor, einen quantitativen pathopsychologischen Rahmen einzubeziehen, um verschiedene Ebenen der Tinnitus-Heterogenität zu integrieren.

Introduction

A *Tintinnabulum* is a small bell found in Catholic basilicas and is often used in religious processions symbolizing the union between the Church and the Pope. The word also describes a phallic-shaped bell commonly used in Ancient Rome which would chime to fend off bad spirits and to bring good omens (1). Tintinnabulum, often translated from medieval texts as "the ringing of bells" shares an etymological root with the word *tinnitus:* the Latin word *Tinnire*, means "to jingle" or "to ring". Since time immemorial men have suffered from "jingling" in their ears; the first reports trace back to Hippocrates, 460 B.C (2). Since then, history has been filled with historical figures suffering from this ailment. Martin Luther, Ludwig van Beethoven, Vincent van Gogh, Michelangelo ,and Charles Darwin are some examples of such historical figures (3).

Nowadays, tinnitus is often described as a condition in which noises are perceived without an external source. As the Latin root word *Tinnire* may suggest, the perceived sounds usually take form of a ringing in the ears, but the sounds may also be perceived as "whistles", "cricket sounds", or "static noise". Tinnitus distinguishes itself from psychotic auditory hallucinations because those suffering from the latter retrieve meaning from what they hear; they may feel compelled to act in a specific manner because they are compelled by the commanding voices they hear (4,5). In other cases, patients may perceive acoustic hallucinations in the form of songs being played in their head without an external source (6). Conversely, the perceived sounds by tinnitus patients are devoid of meaning or complex patterns, often being described simply as "noise".

Pathophysiology

Around 50% of individuals experience a tinnitus-like phantom perception when placed in a quiet room and instructed to concentrate on their hearing (7,8). Therefore, some authors proposed that the condition constitutes a normal state of being, and both suffering and increased loudness perception being considered abnormal processes (9). Tinnitus has often been explained as an increase in gain, that is, a matching between input and output information in the brain in the form of increased spontaneous neuronal activity (10,11). Such activity has been proposed as a conventional mechanism adopted by the nervous system to maintain the homeostasis between input and output information. For example, gain is also present in the visual path: most individuals in a dark room do not see pitch black, but rather faint, abstract

figures due to spontaneous neuronal activation despite the lack of sensory input. Loss in auditory input due to deafferentation has been shown to increase spontaneous neuronal firing in different brain regions**,** and has been implicated as a precursor of tinnitus (10), irrespective of whether the former is detected by traditional hearing tests or not (12). It is believed that with the loss of auditory input due to deafferentation, the brain "dials up" with spontaneous neuronal firing to maintain homeostatic balance. This "dialing up", also referred as gain, is considered part of the reason why tinnitus is perceived.

However, gain alone cannot fully account for tinnitus. For example, it is well established that the severity of hearing loss does not strongly correlate with the severity of tinnitus, nor is tinnitus necessarily present despite hearing loss (12–14). The lack of a clear correlation between hearing loss severity and tinnitus suggests that other underlying mechanisms are at play. Therefore, proposals have been made to incorporate additional models that may explain the perception of tinnitus. An increasingly popular model stems from the free-energy principle (15), which postulates that the brain, as a system, minimizes the states it can be in order to minimize prediction errors coming from sensory input. The brain dynamically interacts with the surrounding environment by making predictions about it, and the degree to which those predictions match the observed reality is often termed as precision. In that context, tinnitus would arise as an "incorrect prediction" of silence because of too much precision in the auditory pathway (10,16). In other words, tinnitus would arise when spontaneous activity in the auditory pathway becomes an auditory prediction instead of a background noise, and thus starts interacting with other brain networks, such as the attention, salience, and emotion networks (11,17).

Prevalence of tinnitus

As previously mentioned, a large proportion of individuals may experience the condition, especially in transient states such as being placed in a quiet room, after being exposed to loud noises, or being exposed to ototoxic drugs (18). An altogether different question, and much more relevant for clinicians and patients with perduring tinnitus, is the proportion of those experiencing the condition continuously impaired by it, and which factors are associated with tinnitus-related suffering. Although prevalent, the exact proportion of individuals suffering from tinnitus remains uncertain. Past estimates ranged between 10 and 15% (19–21); of those, it is expected that 1% will suffer from bothersome tinnitus (20,22).

Those wide margins in the estimation of tinnitus prevalence reflect the fact that there is no universal definition of tinnitus and that prevalence is different across countries (23). Most researchers and clinicians focus their work on chronic (e.g., lasting at least three or six months), subjective, bothersome tinnitus. In the case of subjective tinnitus, only the patient can hear the perceived sound, whereas in objective tinnitus the sound may also be heard by an examiner (18). Common causes for objective tinnitus include turbulent blood flow and/or mechanic friction between the bones behind the ear, and after those underlying causes are treated, objective tinnitus tends to disappear. Chronic, subjective, bothersome tinnitus, the focus of this dissertation, remains a clinical challenge faced by clinicians, researchers, and patients alike, as no treatment is available to reliably suppress the phantom perception (18,24). It is well known, both from clinical practice and from anecdotal experiences (25), that patients react differently to treatments: whereas some patients may find relief with transcranial magnetic stimulation, others may find relief by meditating, attending counseling, taking medications, or other interventions. Also, for a considerable percentage of patients, no available clinical treatment brings tinnitus relief. Additionally, cognitive behavior therapy is the sole intervention with enough clinical evidence of its efficacy (26), but such interventions aim solely to reduce distress, that is, the phantom perception remains unsuppressed. Such variability in treatment responses has been implicated as a result of tinnitus heterogeneity, where different variables could have predictive power on response to specific treatments.

Heterogeneity in context

The word heterogeneity comes from the Greek word *heterogenes*. The prefix *hetero* means "different", and *genos* means "type", "gender", or "stock" (27). The word describes the quality of being different or unique, and since the beginning of the 20th century its use has steadily increased in the literature (28). The adjective "heterogeneous" can be used in different contexts such as geology (e.g., to describe the different properties of rocks (29), chemistry (e.g., on types of reactions, (30), genetics (e.g., on the different genetical make-up within and between species), (31) statistics (e.g., to describe sample characteristics) (32).

Of particular interest to this dissertation, psychologists and psychiatrists have increasingly adopted the term "heterogeneity" to describe the wide range of manifestations the abnormal mental phenomena, such as depressive mood, anxiety disorders, personality disorders, to name just a few, may present themselves.

In the following, a brief perspective of the developments in the other fields of psychopathology towards individualized models is provided. Psychopathology, that is, the study of mental disorders, is arguably the most personal area of medical research, as no two individuals experience suffering quite the same way. Additionally, suffering, unlike most of other medical conditions, is only accessible to its beholder. “Suffering from tinnitus” often describes different phenomena: while for some it can mean a sense of loss of control over one’s own body, for others it can mean sleep deprivation, or poor concentration. In other words, conditions such as tinnitus, depression, chronic pain, or anxiety (just to name a few examples) carry considerable, but often neglected intra-diagnose variability. Such differences among patients from a given diagnosis (or a combination of them) are often referred to as heterogeneity. Although such acknowledgments may be seen as truisms, i.e., most psychologists and psychiatrists, if not all, would agree that two patients are never quite the same. Despite sharing the diagnosis, efforts to untangle heterogeneity in the field of psychopathology only started to gain traction in the last decade.

A considerable portion of the scientific literature in mental health still relies on statistical methods comparing groups (33,34). Group comparisons remain a powerful, effective statistical method to drive insights on psychopathology, especially when applied to well-designed research (e.g., randomized clinical trials). Nonetheless, the last decade saw a significant push towards personalized psychopathology modeling. Such push stems from the limitations of traditional categorical nosology (see below) of mental health and aims to bridge practitioners and researchers by developing evidence-based practice (EBP) in psychopathology by “[…] integrating the best available research with clinical expertise in the context of patient characteristics, culture, and preferences” (35). According to Wright & Woods (36), the EBP stands on three pillars:

1) The current nosology of mental health, which emphasizes discrete disorders or syndromes and culminated on the Diagnostic and Statistical Manual of Mental Disorders (37), has been heavily scrutinized. This model originally conceived psychiatric diseases as separate entities with unique biological substrates (38). Such model has been updated in more recent iterations of the DSM, but it did so by setting a specific set of criteria that would define normal and abnormal mental health. Despite being widely used, this model lead to the dissatisfaction of many due to its lack of methodological rigor (39–41). Additionally, the reliance on cut-off points to define “normal” and “abnormal” mental processes has been implicated as a main source of

within-condition heterogeneity, as it fails to account for mental health holistically by defining arbitrary cut-offs to define diagnoses (42). Instead, there is growing momentum to understand psychopathology as a *spectrum* (33,34,36,43,44). Such movement relies on quantitative methods by applying factor analysis to identify the structure of mental phenomena in psychiatry. By doing so, it is possible to build a hierarchical structure that accounts for different dimensions of psychopathology (see discussion section).

2) Led by the ubiquity of smartphones, intensive longitudinal data has gained traction among clinical researchers. This development allowed the monitoring of patients' states as they occur in daily life (as opposed to the "artificial" setting of a clinical practice) over longer periods of time (i.e., weeks or months). Such methodology, often called as ecological momentary assessment (EMA), uses time-series to measure daily fluctuations in the behaviors, mood, and emotions of participants (45). This is accomplished as patients report their status (e.g., positive/negative affect, tinnitus loudness, stress, mood, etc.) usually through a minimally invasive push notification from the cellphone-app and/or passive sensing of data, such as environment noise (hence the term "ecological", as data is collected from the "natural environment" that users habituate), at a specific timepoint (hence the term "momentary"). The advantages of maximizing the ecological validity of data have been discussed (46).

3) Third, researchers currently have at their disposal a greater set of tools to analyze longitudinal intensive data. This availability has been fueled not only by a stronger processing power of personal computers, which allow the implementation of more complex, resourceful models to be run almost by anyone, as well as the development of models specifically to retrieve personalized information from longitudinal data. Network analysis and unified structural equation modelling (uSEM) are two examples of increasingly popular techniques in this field (34,47,48). The first uses principles and techniques from graph theory, a branch of mathematics focused on dynamic systems and complexity, whereas the second relies on structural equation modelling to retrieve patterns from both individuals and groups. A longer discussion of those methods is available (49). Chapter 4 contains an analysis of EMA using uSEM to obtain idiographic (i.e., at the individual level) models of tinnitus symptoms and behaviors.

Although the tinnitus field has seen a large increase in the use of EMA methodology in the last years (50–55), the field as a whole remains outside important conversations such as the

differences in categorical or quantitative nosology of psychopathology. Initiatives like HiTOP highlight the fact that the goal of many tinnitus researchers to better understand psychopathology is shared among psychometricians, psychologists, and psychiatrists from virtually all areas of psychopathology. One of the aims of this thesis was to harmonize the insights from current developments in the field of psychopathology in tinnitus research (Chapter 4 and Discussion sections).

Tinnitus heterogeneity and subtypes

In a recent editorial, Cederroth et al (56) discussed which dimensions would most likely encompass tinnitus heterogeneity. The authors highlighted the necessity of multidisciplinary approaches that account multiple aspects of tinnitus: from its biological substrate to its subjective, psychological, component. Within this framework, the authors suggested attention be given to the neurobiological and genetic make-up of tinnitus, and its auditory and psychopathological components (56).

Multiple neuroimaging modalities have been used to better understand the neurobiological substrate of tinnitus. For instance, resting state and task-based activations recorded by functional magnetic resonance imaging (fMRI) have been used to investigate which brain regions relate to the perception of tinnitus (57), its relationship with distress (58) and cognition (59). Structural MRI has also shown anatomical differences, such as reduced grey matter, in the auditory cortex, as well as abnormal brain regions such as the amygdala, cingulate cortex and insula of tinnitus patients. Brain networks, such as the default, attention, and salience networks has also shown abnormal functioning (57,60).

The field of quantitative genetics advanced in the previous decade mostly by the establishment of increasingly large biobanks with extensive phenotyping (61), the reduced costs of mapping the human genotype (62), and the advancement of statistical methods able to account for high volumes of data (31). A list of candidate genes implicated with tinnitus has been proposed (63), and these results were further developed by a recent genome wide association study which identified 3 loci and 8 genes associated with tinnitus (64). Additionally, Maas and colleagues showed that the heritability of tinnitus differs depending on the type of tinnitus (i.e., uni- or bilateral), and on the gender of the patient (65). Altogether, these results suggest that heterogeneity also plays a major role in the genetic makeup of tinnitus.

Tinnitus is often accompanied by a mosaic of comorbidities. Some of the most common include, but are not limited to depression, anxiety, hearing loss, hyperacusis, and insomnia (18).

Since no available clinical treatment can reliably and effectively suppress tinnitus, clinical guidelines recommend that treatable comorbidities should be prioritized to reduce suffering (18). Importantly, it remains mostly unknown to which degree such comorbidities impact treatment response. For example, one could argue that depressed tinnitus patients would particularly benefit from treatments such as antidepressants and/or psychological therapy. However, clinical trials often fail to account for baseline covariates, which hinders the interpretation of results. Considering how prevalent some of those comorbidities are, future studies are expected to systematically assess potential comorbidities to evaluate their potential impact in treatment response (Simoes et al, in preparation). In the discussion section, a proposal is made to integrate all those levels of heterogeneity, into the quantitative, empirical-based HiTOP framework previously discussed.

A greater understanding of tinnitus heterogeneity is expected to lead to improved, individualized care for patients (66). Guided by clinical trials that often show diverging treatment response within and between samples, previous commentaries suggested that it is of critical relevance to identify which markers, if any, are relevant for treatment response (67). For example, there is mounting evidence that personality factors may be predictors of response among tinnitus patients for cognitive behavior therapy (68), but not for acoustic stimulation (69)[1]. Indeed, one of the works presented in this dissertation investigated precisely which demographics and tinnitus characteristics could explain response to 26 treatments (see Chapter 1).

Another approach towards personalizing treatment consists of identifying subtypes of tinnitus. Such approach leverages modern statistical techniques that partition the data according to statistical similarities (70). Several attempts have been made in the past few years to cluster tinnitus patients in subgroups based solely on data-driven methods. A recent review identified 65 articles that tried to characterize tinnitus into subtypes (71). 55 of those studies tried to characterize tinnitus with hypothesis-driven methods, eight with data-driven methods, and two studies characterized tinnitus based on treatment response. One of those studies is part of this dissertation (Chapter 2). Regarding the data-driven studies, none of them had their models internally or externally validated, that is, it remained an open question whether those algorithms would reach the same results if trained with a new dataset.

[1] The author of this dissertation was responsible for the data analysis and co-authors the paper.

Admittedly, attempts to subgroup tinnitus were not all fruitless. On a landmark study, Holder and colleagues (72) showed that cochlear implants fully suppressed the phantom perception in 45% of unilateral tinnitus patients with single-side deafness. In other words, the authors showed that a specific subtype of tinnitus is treatable with a specific treatment. Those results highlight the current understanding that treatment strategies should be customized based on patients' individualities. Identifying which markers are relevant for which treatment remains a major challenge. Indeed, one of the works (Chapter 2) presented in this dissertation investigated whether demographic factors, tinnitus characteristics or treatment characteristic could be used to predict the outcome of 26 different treatments.

Those results highlight that, despite advancements towards untangling tinnitus heterogeneity in key areas, a unifying framework to integrate these findings remains missing. Simoes and other 23 early-stage tinnitus researchers (manuscript under revision)[2] provide multidisciplinary suggestions on how to disentangle tinnitus heterogeneity by combining relevant biomarkers from different areas of expertise (e.g., neuroimaging, genetics, psychopathology, see above) with novel methods. Although the tinnitus field is still away from such an integrated comprehension of subtypes and how to integrate multiple levels of data, the studies in this dissertation aimed to provide a small contribution towards this goal.

Scope of this dissertation

This doctoral study aimed to advance the current understanding of tinnitus heterogeneity and its potential implications for individualized treatments. Chapters 2-4 present findings previously published in peer-reviewed scientific journals. Consent was given by the journals to reproduce figures, tables, and passages from the original articles *in verbatim* in italic and within quotation marks. The chapters are presented according to the chronological order of publication.

Study 1:

In the first study (Chapter 1), we investigated to what extent treatment outcomes could be predicted from demographics and tinnitus characteristics. For this study, crowd-sensed data from almost 5000 users of the online platform Tinnitus Talk (25) was collected through an online survey and analyzed with ordinal least squared regression and with regularized regression through L1 and L2 penalization (70). The research aimed to address to what extent

[2] This manuscript was not included in this thesis.

variables such as demographics and tinnitus characteristics could infer participants' response to treatments.

Study 2:

Advancing on the previous results, a retrospective, longitudinal study with data from the tinnitus clinic Regensburg investigated whether personality traits could explain different courses of tinnitus over time (Chapter 2). Baseline data of 388 clinical patients was compared with a follow-up survey sent to participants by mail. The follow-up survey consisted of the same questionnaires previously reported by patients plus the Big Five Inventory 2, a questionnaire that captures five commonly dimensions of personality. Those dimensions, namely agreeableness, conscientiousness, extraversion, neuroticism, and openness, have shown impressive explanatory power in predicting academic and professional performance, economic outcome, quality of life, and mental health (73). The study presented in Chapter 3 investigates to what degree personality explains distress and (non)habituation over time.

Study 3:

Using the same dataset, a third study investigated a) how often chronic tinnitus remits, b) whether depression, quality of life, tinnitus characteristics, such as distress, loudness, type of perceived sound, laterality, pitch frequency, etc. change over time, c) what are the most common treatments patients sought for their tinnitus, and what are the most common comorbidities, and d) and whether the number of comorbidities experienced, the number of treatments sough correlate with changes on tinnitus distress over time (Chapter 3).

Study 4:

Lastly EMA data from the Track your Tinnitus (TYT) mobile app was used to investigate whether six variables, namely, tinnitus-specific distress, tinnitus loudness, overall stress, emotional arousal, concentration and mood are auto- and cross-correlated (Chapter 4). In other words, the study investigated whether one variable at a specific timepoint was correlated to itself or to another variable at another time point. For this study, daily recordings of 488 users of the app were used. Additionally, this study used uSEM (see section *heterogeneity in context)*, an idiographic statistical method to retrieve the individual and shared dynamics among those variables. Those findings illustrate novel ways to model unique dynamics among tinnitus patients, and the first to empirically show how uniquely tinnitus is experienced.

Chapter I

Toward Personalized Tinnitus Treatment: An Exploratory Study Based on Internet Crowdsensing[3,4]

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Abstract

Introduction: *Chronic tinnitus is a condition estimated to affect 10–15% of the population. No treatment has shown efficacy in randomized clinical trials to reliably and effectively suppress the phantom perceptions, and little is known why patients react differently to the same treatments. Tinnitus heterogeneity may play a central role in treatment response, but no study has tried to capture tinnitus heterogeneity in terms of treatment response.*

Research Goals: *To test if the individualized treatment response can be predicted using personal, tinnitus, and treatment characteristics.*[5]

Methods: *A survey conducted by the web platform Tinnitus Hub collected data of 5017 tinnitus bearers. The participants reported which treatments they tried and the outcome of the given treatment. Demographic and tinnitus characteristics, alongside with treatment duration were used as predictors of treatment outcomes in both an univariate as well as a multivariate regression setup. First, simple linear regressions were used with each of the 13 predictors on*

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[4] This chapter was directly adapted from the original article, including its tables and figures. Text copied *in verbatim* is highlighted in italic. References and citations were edited to the National Library of Medicine meet the requirements of the Faculty of Medicine, Regensburg.

all of 25 treatment outcomes to predict how much variance could be explained by each predictor individually. Then, all 13 predictors were added together in the elastic net regression to predict treatment outcomes.

Results: *Individual predictors from the linear regression models explained on average 2% of the variance of treatment outcome. "Duration of treatment" was the predictor that explained, on average, most of the variance, 6.8%. When combining all the predictors in the elastic net, the model could explain on average 16% of the deviance of treatment outcomes.*

Discussion: By demonstrating that different aspects predict response to various treatments, our results support the notion that tinnitus heterogeneity influences the observed variability in treatment response. Moreover, the data suggest the potential of personalized tinnitus treatment based on demographic and clinical characteristics.

Introduction

Tinnitus is a condition characterized by an auditory perception, usually in the form of ringing or hissing, for which there is no corresponding external source (19). The prevalence of tinnitus has been estimated between 10 and 15% in the adult population (18,21). From those, one fifth will require clinical intervention (74). Additionally, the mean annual cost of illness was estimated at 6.8 billion euros globally (75). On the individual level, tinnitus may be accompanied by comorbidities such as insomnia, anxiety and depression, constituting a high burden to patients (76). Current clinical guidelines recommend that clinicians target those potential comorbidities, and although no treatment has shown efficacy in randomized clinical trials to reliably and effectively suppress the phantom perceptions, it is clear that various treatment options result in different degree of improvements—most likely because of the underlying heterogeneity of the etiology and pathophysiology of tinnitus (18,24,77). The clinical guidelines also recommend different management strategies for tinnitus, including, but not limited to, psycho-education, counseling, cognitive behavior therapy, hearing aids when assessed as necessary and sound therapy (18). Importantly, the current clinical understanding is that certain treatments may not be suitable/effective for all, and clinicians should recommend treatments to patients in an individual basis (24). Thus, albeit the low evidence levels for treatments on a group level, these same treatments may be beneficial in specific cases on the individual level.

From a clinical perspective, bothersome, chronic, and subjective tinnitus is a common and challenging form of tinnitus (18,76). However, this form of tinnitus might be highly heterogeneous. In recent years, the notion of tinnitus as a complex, multi-faceted condition gained traction (78). For that reason, researchers and clinicians have drawn their attention to the different ways of tinnitus manifestation, including its etiology (e.g., sound blast, persistent loud noise exposure, whiplash, etc.), phenotype (e.g., type of sound perceived, laterality of the sound perception, presence of hearing loss, etc.), and accompanying comorbidities (e.g., insomnia, depression, anxiety, etc.). Such heterogeneity constitutes a complex puzzle that challenges both researchers and clinicians in their understanding of the pathophysiology of tinnitus and in the development of new treatments (19). Importantly, tinnitus heterogeneity may account for the low success rates of clinical trials at the group level, as well as why certain individuals respond positively to specific treatments (24,56).

Noteworthy efforts to capture tinnitus heterogeneity include the studies from Langguth et al. (79), Tyler et al. (80) and Van den Berge et al. (81). Overall, the studies showed modest results without a clear delineation of tinnitus subtypes. However, those studies were limited due to sample size and/or homogeneous samples recruited from specialized tinnitus clinics. It is yet unclear how representative samples from tertiary clinics represent the whole tinnitus population; thus, we consider a broader data sample necessary to capture a yet unexplored facet of tinnitus heterogeneity (82).

Crowdsourced health research studies have been proposed as a mean to circumvent the difficulties experienced during patient's recruitment, such as the increased costs of adding participants to a study and the homogeneous sample representation from tertiary clinics (83). Crowdsourcing can be defined as the collaborative collection of data in which individuals and/or institutions participate voluntarily (83,84). When the data is collected through mobile devices, such as smartphones, tablets, or wearable devices, the term crowdsensing is commonly used (54). The number of policy makers, health providers and academics using such technologies increased drastically in the last decade due to the ubiquity of mobile and sensing devices (85). Especially in tinnitus research, crowdsensing has been substantially used (50,53,54,82). Importantly, such technologies may yield new insights about phenomena hardly accessible to traditional settings.

To the best of our knowledge, no study tried to capture tinnitus' heterogeneity using crowdsensing technology, especially in terms of treatment response. Our study aims to fill that

research gap. We collected crowds sensed data from an online tinnitus self-help platform to explore tinnitus heterogeneity avoiding the aforementioned limitations during data collection, namely the reduced sample size and/or homogeneous patient representation. First, we investigated whether tinnitus heterogeneity could be expressed not only in terms of phenotype, etiology and comorbidities as has previously been done, but also in terms of treatment response. To investigate this hypothesis, we modeled each predictor (i.e., tinnitus characteristics and demographics) individually as an independent variable on single linear regressions with treatment outcomes for 25 different treatments as dependent variables. Second, we investigated whether tinnitus heterogeneity could predict treatment response from demographic factors and tinnitus characteristics. We operationalized this hypothesis by combining all predictors in a statistical model to predict the outcome of treatments.

Methods

Data for our sample were collected by Tinnitus Hub. Founded in 2015 by SH and MV, the Tinnitus Hub operates "Tinnitus Talk" (www.tinnitustalk.com), created in 2011, the largest online, anglophone self-help platform for tinnitus patients. The survey took place between February 8th and March 13th of 2016. Members of the forum received a link to the digital survey. We collected information of 5017 participants, from those 2916 reported trying at least one treatment and thus were included in the data set for the final analysis. It was not possible to obtain written informed consent from the users of Tinnitus Talk, but the "Terms and Rules" of the website informed the users that the collected data will be analyzed for scientific purposes. All the data were saved anonymously. A similar dataset was used in a former study (82).

Personal and tinnitus information was collected from participants of the survey alongside questions about which tinnitus-related treatments were tried and were used as independent values in our statistical models. In total, 13 factors were included in our analysis (Table 2). Additionally, participants were asked to rate how effective a given treatment was in reducing the distress and/or suppressing the noise perception, and the duration of the treatment retrospectively (1: "this treatment made my tinnitus much worse," 2: "this treatment made my tinnitus mildly worse," 3: "this treatment had no effect on my tinnitus," 4: "this treatment made my tinnitus slightly better," and 5: "this treatment made my tinnitus much better").

Our analysis included the outcome of 25 different treatments and used as dependent variables in our statistical model. Participants consented to have their anonymous data used for scientific research. Simple linear regressions were performed for individual predictors (i.e.,

demographics and tinnitus characteristics, and treatment duration) on treatment outcomes (i.e., dependent variable). Regressions were weighted based on the number of treatments that patients tried and p-values were adjusted for multiple comparisons using Hommel correction (86,87). Collinearity was assessed with the variance inflation factor (VIF). The VIF is the ratio of variance in a model with multiple predictors, divided by the variance of a model with one predictor alone (70). The high VIF values in our models indicated that models containing all 13 demographic factors and tinnitus characteristics as predictors would contain high collinearity. To address this issue, we used elastic net regularization(88). Elastic net accounts for collinearity by penalizing the coefficients in the model either by shrinking their values or by setting them to 0 (24). We ran a n-fold cross validated elastic net to estimate the optimal lambda (i.e., one of the penalizing coefficients from elastic net) over 11 different alpha values ranging from 0 (i.e., RIDGE regression) to 1 (i.e., Lasso Regression). For this analysis, the predictors encoded as factors were converted into dummy variables as a prerequisite from the statistical software. We selected the models with minimized mean squared error for our final analysis.

All statistical analysis was conducted with R statistical software (89), alongside the "tidyverse" package (90). Power analysis were calculated using the "effsize" package (91) and the elastic net was performed by the "GLMnet" package (88). Non-parametric tests were used when statistical assumptions of parametric tests were not met. P-values below 0.05 were considered statistically significant.

Results

Table 1.1 shows the frequency of each treatment in our sample. Clinical and demographic characteristics of the sample are summarized in Table 1.2. First, we applied linear regression models with individual predictors as independent variables on the self-reported treatment outcomes as dependent variables. The aim of this analysis was to test how much variance could be explained by individual predictors for the different treatments. Figure 1.1 shows the average amount of variance explained by each predictor on all 25 different treatments. A summary of all statistical models can be found in the Supplementary Materials. The amount of variance explained by single predictors over all treatments was 2% on average. Next, we investigated what type of predictor could explain most of the variance of treatment outcomes. For this analysis, we grouped predictors in three groups: personal, tinnitus and treatment

characteristics (Figure 1.2). Personal and tinnitus characteristics could explain, on average, the same amount of variance.

As shown in Figures 1.1 and 1.2*, the predictor "Duration of Treatment" explained on average more variance than the remaining predictors ($p < 0.05$). To further explore the relationship between treatment duration and treatment outcome, we clustered the average treatment outcomes based on their duration. The results can be found in Figure 1.3, where our analysis of variance showed no trend of time over treatment outcome ($p = 0.99$).*

Treatment	***n***
Self Sound Stimulation	1,562
Supplements and Herbal	1,157
Antidepressants	785
Hearing Aid	681
Acunpuncture	621
Masker	503
Chiropractor	489
Homeopathic	425
Psychologist	388
Cognitive Behavior Therapist	371
Tinnitus Retraining Therapy	370
Steroids	346
Off-label Medication	312
Psychiatrist	298
Neurofeedback / Meditation	270
Books / self help	254
Gabaergic medication	237
Notched Music	223
Soundcure	144
Acoustic Neuromodulation	120
Neuromonics	95
Low Level Laser Therapy	65
Retigabbine	53
Hyperbaric Oxygen Therapy	46
Transcranial Magnetic Stim.	45

Table 1.1 *Sample size of each treatment*

Next, we fitted all predictors as independent variables and self-reported treatment outcomes as the dependent variable in our elastic net regression model. This analysis aimed to measure how much of the deviance on treatment outcomes can be explained by combining all analyzed

items. Figure 1.3 shows the amount of deviance explained by all predictors for each of the 25 treatments. On average, 16% of the deviance could be explained by all predictors combined. Table 3 summarizes which predictors were considered statistically significant by the elastic net and linear regressions respectively.

Predictor	Levels	*n*	Percentage
Gender	Male	1,712	58.8%
	Female	1,181	40.5%
	Other	21	0.7%
Age	Under 18	13	0.4%
	18–24	162	5.6%
	25–34	364	12.5%
	35–44	427	14.7%
	45–54	606	20.8%
	55–64	869	29.8%
	65–74	405	13.9%
	75 +	58	2.0%
	Prefer not to say	10	0.3%
Tinnitus onset	Less than 3 months	147	5.0%
	4–6 months	156	5.4%
	6–12 months	293	10.1%
	1–2 years	427	14.7%
	2–3 years	359	12.3%
	3–5 years	347	11.9%
	5–10 years	388	13.3
	10–20 years	339	11.6%
	20 + years	458	15.7%
Noise reactiveness	Sounds have no affect	587	20.1%
	Some sounds make it a lot worse	627	21.5%
	Some sounds make it somewhat worse	354	12.1%
	Some sounds make it better and some make it worse	725	24.9%
	Some sounds make it somewhat better	212	7.3%
	Some sounds make it a lot better	113	3.9%
	NA	296	10.2%
Hyperacusis	No	1,006	34.5%
	Mildly	795	27.3%
	Moderately	776	26.6%
	Severely	291	10.0%
	NA	96	3.3%
Somatic	No	1,643	56.4%
	Yes	1,056	36.2%
	NA	215	7.4%
Jaw and neck problems	Problems with Jaw	261	9.0%
	Problems with Neck	503	17.3%
	Problems with Jaw and Neck	407	14.0%
	NA	1,743	59.8%
Hearing loss	Mild hearing Loss	1,265	43.4%
	Moderate hearing loss	400	13.7%
	Severe hearing loss	152	5.2%
	NA	1,097	37.6%
Laterality of hearing loss	Both ears	699	24.0%
	One ear	1,119	38.4%
	NA	1,096	37.6%

(Continued)

Table 1.2 Sample's demographic and tinnitus characteristics

Predictor	Levels	*n*	Percentage
Tinnitus frequency	Low (<1 kHz)	152	5.2%
	Mid (1–3kHz)	151	5.2%
	Mid high (3–8 kHz)	525	18.0%
	Very high (8 kHz +)	350	12.0%
	Several dis in Hearing	77	2.6%
	Unsure	563	19.3%
	Na	1,096	37.6%
Perception of tinnitus	One ear	688	23.6 %
	Both ears	1,031	35.4 %
	More in the brain	204	7 %
	In the ears and brain	952	32.6 %
	Not sure	39	1.3 %
Perception of tinnitus during the day	Does not change at all	774	26.6 %
	Fluctuates, no pattern	1,369	46.9 %
	Fluctuates, better in the morning	131	4.5 %
	Fluctuates, better in the evening	626	21.4 %
	NA	14	0.4 %

Table 1.2 Continued

Lastly, we conducted one exploratory analysis based on the coefficients obtained by both models to identify clinical markers of treatment success. From coefficients estimated by linear regression, we observed that participants who reported responding positively to sounds (i.e., rating a 4 or 5 in the Likert scale) reported more frequently benefiting positively to treatments with an acoustic component. Thus, we subset only patients who reacted positively to sounds and divided treatments with and without an acoustic component (Figure 1.4). Our group mean comparison analysis corroborated our data-driven hypothesis, as patients who reported reacting positively to sounds also reported higher outcomes with treatments with an acoustic component ($p = 0.02$, Cohen's $d = 1.07$).

Discussion

In this study we investigated whether personal, tinnitus, and treatment characteristics collected from an internet self-help platform population can be used to explain which patients are responding to different treatments. Similar attempts to predict treatment outcomes with patients' characteristics have been tried in a spectrum of mental conditions, including lower back pain (92), depression (93), post traumatic stress disorder (94), obsessive-compulsive

disorder (95), substance abuse (96), and tinnitus itself (97)*. To the best of our knowledge, this is the first study attempting to capture tinnitus' heterogeneity in terms of a wide range of treatment responses using crowdsensing technology. Moreover, whereas most studies tried to predict the outcome of a single treatment, our study aimed to predict the outcome of 25 different treatments.*

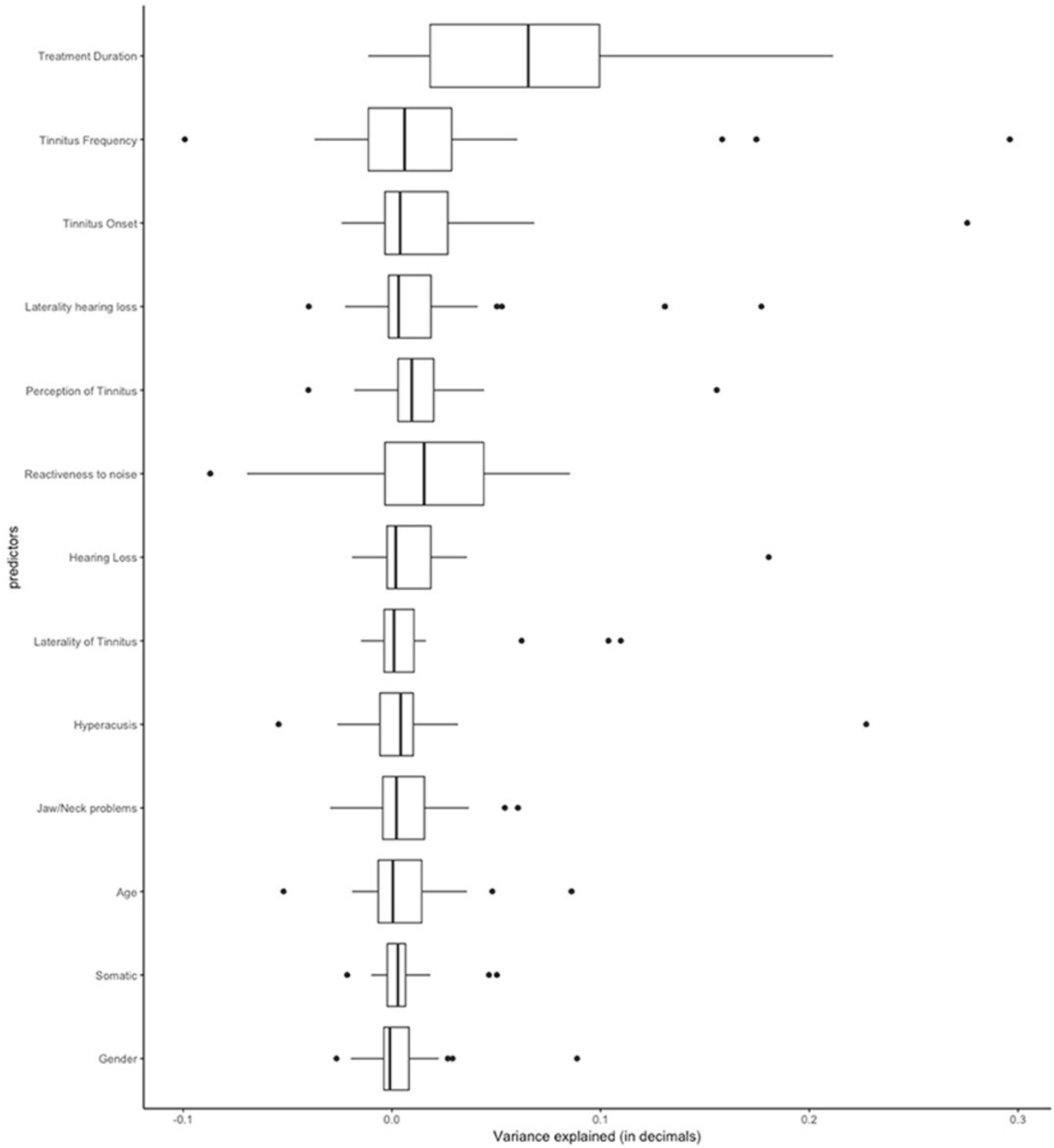

Figure 1.1 Amount of variance explained in the linear regression models by each predictor across all different 25 treatments.

Our results showed that 2% of the variance of treatment outcomes could be explained, on average, by individual predictors (Figure 1.2). Additionally, our analysis showed that both

personal characteristics and tinnitus characteristics, despite being significant predictors for multiple treatments (Table 1.3), could explain little variance on average. At first glance, it seems that the analyzed parameters have only a small impact on treatment outcome, but the average amount of deviance explained by the elastic net combining all 13 predictors into a single model was 16%, after accounting for covariance. We identified multiple statistically significant predictors in both regression setups (Table 1.3), but the individual amount of variance they could explain was limited. These results suggest that although no single predictor is paramount to predict the treatment outcomes, personal, tinnitus, and treatment characteristics may have a predictive role when combined. Altogether, those characteristics could be used in the future to predict treatment responsiveness in tinnitus, especially after better markers of treatment success are identified. For instance, our analysis did not include information about patients' personality, depression or tinnitus-related distress, nor did it collect information of the sequence in which treatments were tried or whether treatments were tried simultaneously.

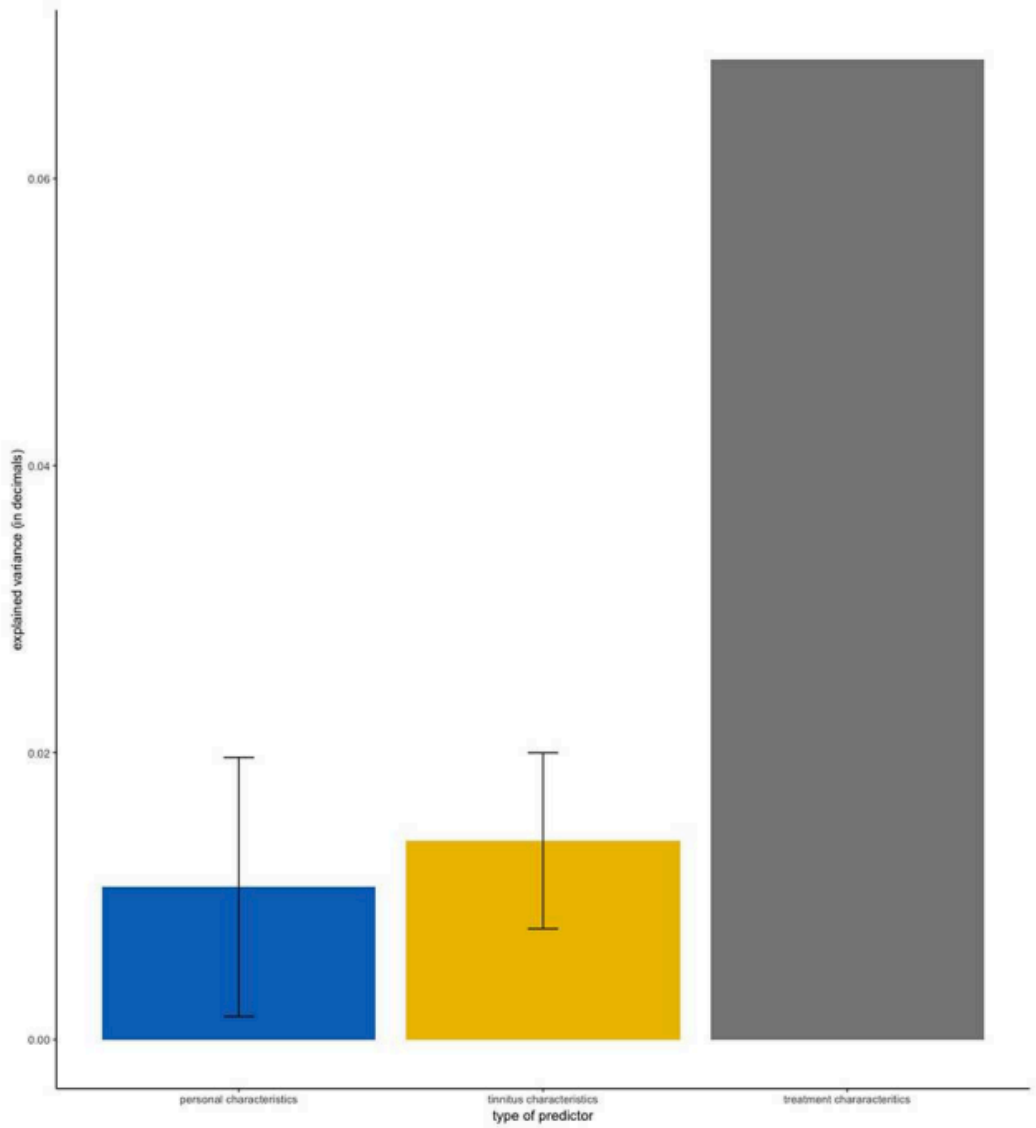

Figure 1.2 Mean amount of variance explained by type of predictor. Error bars represent standard deviation. "Personal Characteristics" contains the predictors Age, Gender and Tinnitus Onset. "Tinnitus Characteristics" contains the predictors Tinnitus Frequency, Laterality of Hearing Loss, Perception of Tinnitus, Reactivness to Noise, Hearing Loss, Laterality of Tinnitus, Hypearcusis, and Jaw/Neck Problems. "Treatment Characteristics" contains the predictor Treatment Duration.

Capturing tinnitus heterogeneity has been proposed as an important clinical and scientific goal, but previous attempts obtained limited results (80,81). Importantly, tinnitus heterogeneity may explain why only a subset of patients are responding to specific treatments (56). A broader comprehension of tinnitus, encompassing not only demographics and tinnitus characteristics, but also treatment response, could, for example, explain the limited treatment efficacy seen in clinical practice (18). For instance, it is yet unclear whether previous successful or

unsuccessful treatments have any predictive power on the outcomes of future treatments. Ultimately, the subtyping of tinnitus could lead to personalized care, a long-standing request by both clinicians and patients (76). Our results, though modest, suggest that personalized treatment for tinnitus patients based on patients' personal, tinnitus, and treatment characteristics should be feasible.

	Duration of treatment	Laterality of hearing loss	Fluctuation of sound perception	Noise reactiveness	Jaw/Neck problems	Onset	Age	Hyperacusis	Gender	Tinnitus frequency	Hearing loss	Somatic	Laterality of tinnitus
Acoustic Neuromodulation	X	X	X	X	X	X	X	X	X	X	X		
Hearing aid	X/O	X/O	X	X/O	X/O	X/O	X	X	X	X	X/O		O
Self Admin. Sound Therapy	X/O	X	X/O	X/O	X	X	X	X	X/O	X			
TRT	X/O	X	X	X	X	X	X/O	X		X	X/O		
Antidepressants	X/O	X	X/O	X	X	X	X/O	X/O		X			
Soundcure	X/O	X	X	X		X	X	X	X	X/O			
Psychiatrist	X	X	X	X		X	X	X	X		X		
Psychologist	X	X	X/O	X		X	X	X	X		X		
Supplements/Herbal admin.	X	X	X	X	X		X			X	X		
Homeopathic admin.	X	X	X	X	X	X	X		X				
GABA admin.	X/O			O	X/O		X/O	X		X	X		
In ear masker	X/O	X	X	O				X		X	X		
Acunpuncture	X	X	X		X/O	X	X		X/O				
Hyperbaxic Oxygen Therapy	X	X			X	X		X		X			
Notched music	X/O	X/O	X	X					X				
Off Label Medication admin.	X		X	X	X	X							
Self learning	X	X		X	X	X							
CBT	X		X/O					X	O				
Chiropractor	X				X								
Neurofeedback	X/O						X						
Steroids admin.					X	X							
LowLevelLaser Therapy	X												
Neuromonics	X												
Retigabine admin.		X											
Transcranianl Magnetic Stim.		X											

Table 1.3 Predictors identified as significant by the elastic net model (X) and linear regression (O)

One example of future implications that this type of analysis could lead to, is the effect of noise reactiveness in the outcomes of treatments with and without an acoustic component (Figure 1.5). Our results suggest that participants whose tinnitus respond positively to sounds tend to benefit more from treatments with an acoustic component than from treatment without such component. Although future studies should try to replicate these results, we believe that the insights from large data sets such as these could have meaningful effects in tinnitus care and research. For instance, such insights could help researchers define new, fine-grained inclusion criteria for future clinical trials in acoustic-based treatments.

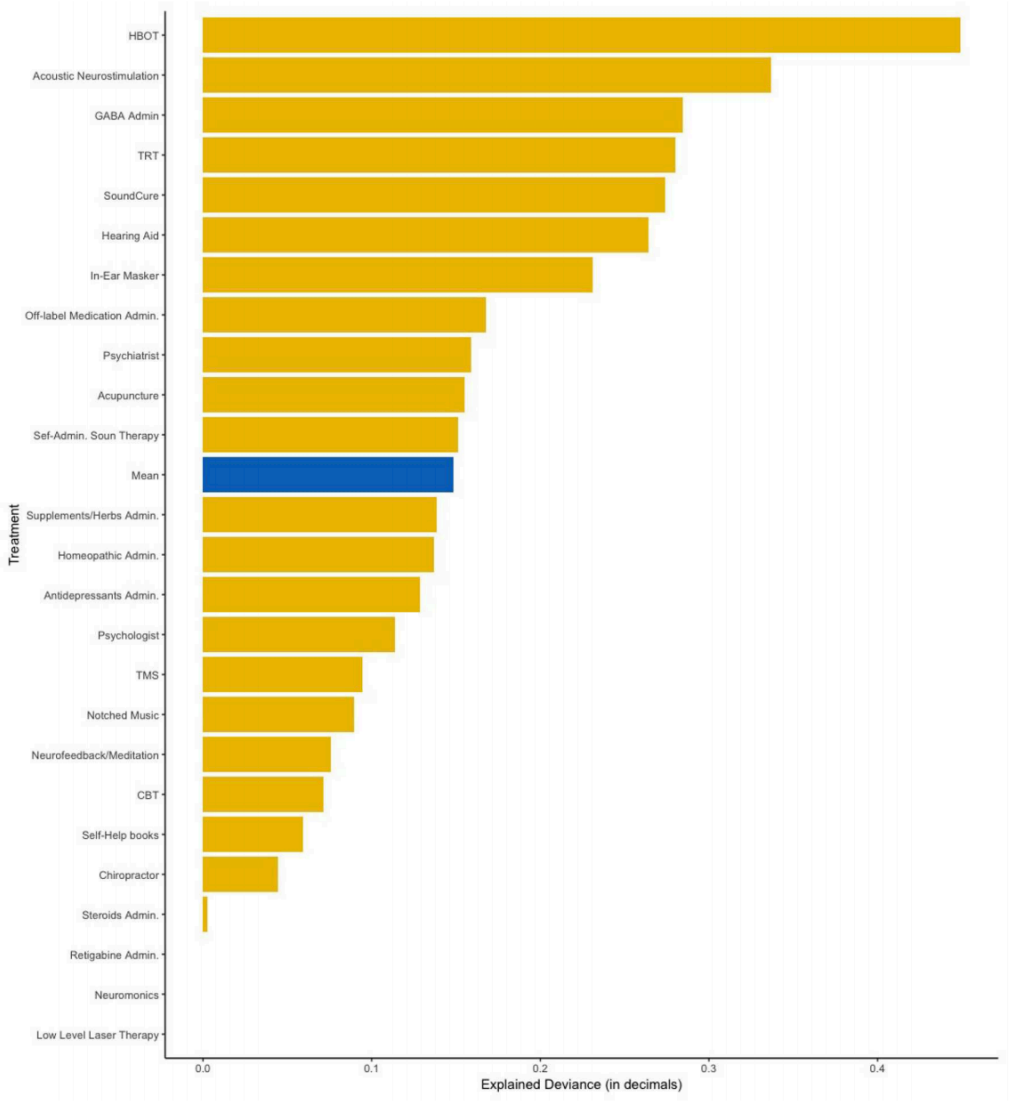

Figure 1.3 Amount of variance explained by the Elastic Net model with all the 13 predictors added simultaneously. HBOT, Hyperbaric Oxygen Therapy; TRT, tinnitus Retraining Therapy; TMS, Transcranial Magnetic Stimulation, CBT, Cognitive Behavior Therapy

Regarding treatment duration, the predictor that could, on average, explain most of the variance, did not show any statistically significant difference between time periods. These results should be interpreted with caution as it is well-known that certain treatments, such as cochlear implants, require some time for adaptation whereas other treatments, such as antidepressants, require longer periods to be effective. Nonetheless, our results support the notion that the duration of treatment is not inherently beneficial or detrimental to the treatment's efficacy.

Our study comes with some inherent limitations. First, we did not have access to information about treatments which were performed in an overlapping span of time, thus we were unable to account for possible interaction between treatments. Second, our outcome measure was retrospective and subjective, which could have biased the results. We consider a subjective metric, although coarser than an objective one such and the Tinnitus Handicap Inventory, adequate for this type of analysis given the multiple treatments that a single patient tried and the sometimes-long period of time between the administration of a treatment and the survey. Nevertheless, further prospective studies analyzing outcome predictors would be desirable. Third, although we examined 25 different treatments, this number was insufficient to capture the whole complexity of available interventions for tinnitus treatments. Cognitive Behavior Therapy (CBT), for example, can be performed in a span of days or months, sessions can be individual or in group, a wide range of techniques can be applied in each session, etc. Such variety of treatment details and subtypes were not exclusive to CBT, but rather a commonality across treatments. Fourth, we chose a limited number of potential predictors for the survey, but we might have missed other important items. Particularly we would expect that there may exist further items that may be relevant for response to some of the investigated treatments. Finally we are aware that the investigated sample, albeit large and international, might not be representative of all patients with tinnitus.

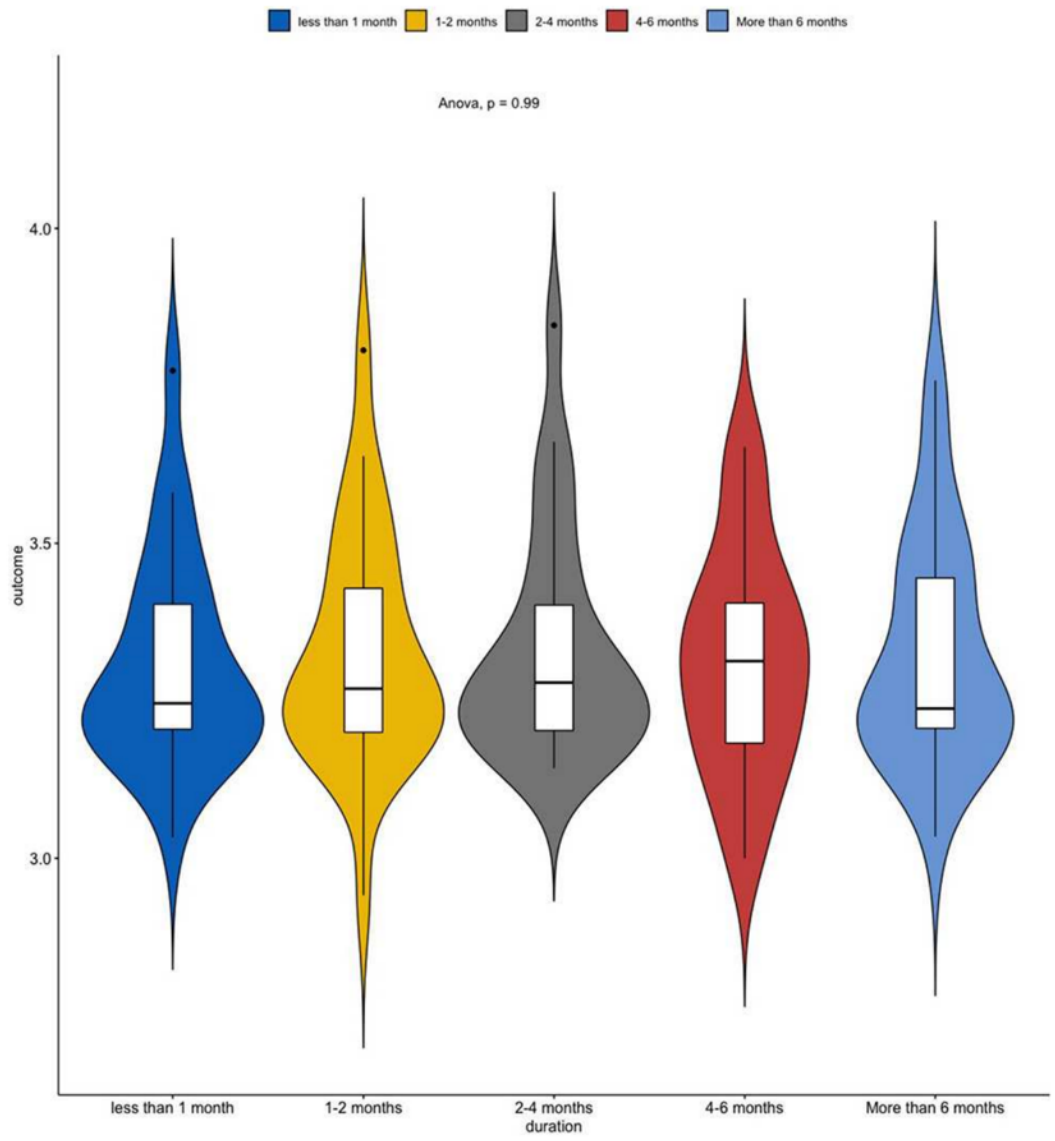

Figure *1.4 Mean treatment outcomes on a 1-5 Likert scale clustered by treatment duration*

Conclusion

Our results suggest that tinnitus heterogeneity could be expressed in terms of treatment response. The variance explained by individual predictors on treatment outcomes suggests that specific traits could explain why certain people are responding positively to a given treatment. In the future, especially with the availability of "big" multi-faceted data, a better understanding of the factors involved in treatment responsiveness could lead to individualized, optimal tinnitus management.

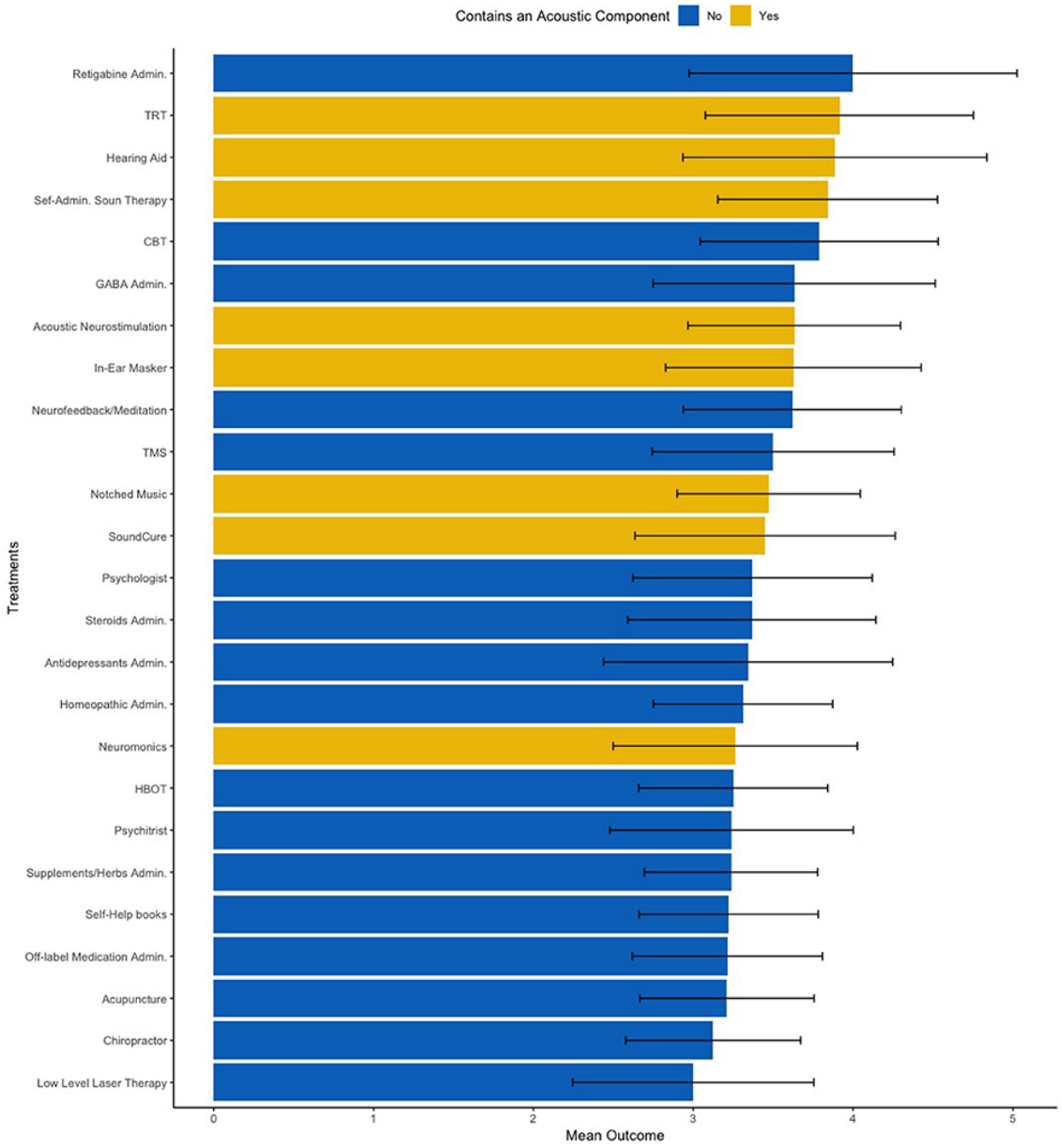

Figure 1.5 Mean treatment outcomes on a 1–5 Likert scale clustered by treatments with an acoustic component (yellow) and without an acoustic component (blue). Error bar accounts for the standard deviation across all 25 treatments. TRT, Tinnitus Retraining Therapy; CBT, Cognitive Behavior Therapy; TMS, Transcranial Magnetic Stimulation; HBOT, Hyperbaric Oxygen Therapy.

Ethics Statement

The data set was collected in 2016 through a survey in the tinnitus hub online forum (https://www.tinnitushub.com), and was shared to the authors.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interedt

Chapter II

Big Five Personality Traits are Associated with Tinnitus Improvement Over Time[6,7]

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Abstract

Previous studies have shown that personality traits are related to tinnitus distress as measured by the Tinnitus Handicap Inventory (THI) and the Tinnitus Questionnaire (TQ). However, little is known about the role of personality on tinnitus distress over time. We collected the THI and the TQ of 388 patients who visited a tertiary tinnitus clinic between 2012 and 2017, and who filled in a survey with the same questionnaires plus the Big Five Index 2 in 2018. We used personality traits and facets to predict tinnitus distress cross-sectionally and longitudinally. Neuroticism, extraversion, agreeableness, age and gender were significant predictors of the THI and TQ scores in cross-sectional linear regression setups. Next, based on previous literature, we clustered patients in three groups based in the difference THI and TQ between the two assessments: "clinically improved", "clinically stable" and "clinically worsened". The patients in the "clinically improved" and "clinically stable" groups scored statistically significantly lower in neuroticism and higher in extraversion than patients in the group "clinically worsened". Our results suggest that personality is associated with tinnitus distress over time and could be used to statistically distinguish patient groups with clinically relevant changes of tinnitus distress.

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[7] This chapter was directly adapted from the original article, including its tables and figures. Text copied *in verbatim* is highlighted in italic. References and citations were edited to the National Library of Medicine format to meet the requirements of the Faculty of Medicine, Regensburg.

Introduction

Tinnitus is a condition characterized by the subjective perception of sounds without an external source (76) that affects between 10 and 15% of the population in western societies (18). Currently, there is no treatment available to reliably and effectively suppress the phantom perception in chronic (i.e., lasting more than six months, (18), idiopathic presentation of tinnitus. In those cases, treatment focus on the condition's management, but response to treatments vary considerably across patients. It is yet not fully understood why clinically available treatments do not reliably and effectively suppress the distress associated with tinnitus, but heterogeneity may be a relevant explaining factor (66). Previous studies suggested that treatments' low evidence levels could be explained by individual factors (56,66,78), and whether personality could be one of such factors is not yet known.

The construct of personality can be described as the individual profile in characteristic patterns of thinking, feeling and behaving (98). Personality research has implications in a wide range of topics, including ones related to tinnitus such as memory (99) and sleep (100). Several models have been developed to characterize and quantify different personality aspects, such as the five factor model (FFM, also known as the "Five Factor Model" or "Big Five Personality Traits"). The model quantifies five traits of personality, namely agreeableness, conscientiousness, extraversion, neuroticism, and openness. John and Soto (101) recently developed the Big Five Index 2 (BFI-2), a revised version of the original questionnaire that quantifies each of those traits. This reviewed version includes features such as robust hierarchical structure, control for acquiescent responding, fidelity, and increased predictive power, while retaining key features of the original BFI such as its ease of understanding and conceptual focus (101). The BFI-2 also comprises 15 facets, or subtraits, describing different aspects of each trait (102). A brief description of the five traits and 15 facets can be found in Table 2.1, and a more in-depth analysis of the BFI2 and its constructs is available (101). Apart from the childhood and teenage years, personality is believed to be stable over time, especially after the age of 30 (103). It is also known that the stability of traits decreases with longer retest periods. However, previous studies showed high stability of personality traits over time, with scales presenting $r = 0.77$ and $r = 0.73$ in the 6 and 12 years retest interval period (104).

Looking at tinnitus specifically, Langguth and colleagues (105) used the FFM to describe the personality traits of tinnitus patients. The authors found that tinnitus patients tend to score higher in neuroticism, and lower in agreeableness. Additionally, a recent scoping review

(106) suggested that personality traits, such as high neuroticism and low extraversion, are common hallmarks of tinnitus patients. Previous works have investigated the prevalence of of the "type D" personality and tinnitus. The type D personality is characterized by both social inhibition and neuroticism, and has been shown to be prevalent in tinnitus patients (107,108). More recently, Strumila and colleagues (2017) investigated the association between personality, environment, anxiety, depression and distress. Overall, the authors found that anxiety and depressive states were associated with all personality traits apart from agreeableness, and that neuroticism was the only statistically significant predictor of tinnitus distress.

Traits and Facets	Example items
Neuroticism	
Anxiety	(19) Can be tense; Rarely feels anxious or afraid (R)
Depression	(9) Stays optimistic after experiencing a setback (R); (39) Often feels sad
Emotional Volatily	(44) Keeps their emotions under control (R); Is temperamental, gets emotional easily
Extraversion	
Sociability	(1) Is outgoing, sociable; (46) Is talkative
Assertiveness	(6) Has an assertive personality; (51) Prefers to have others take charge (R)
Energy level	(11) Rarely feels excited or eager (R); (41) Is full of energy
Agreeableness	
Compassion	(2) Is compassionate, has a soft heart; (17) Feels little sympathy for others (R)
Trust	(37) Is sometimes rude to others (R); (52) Is polite, courteous to others
Respectfulness	(12) Tends to find fault with others (R); (27) Has a forgiving nature
Openness	
Aesthetic Sensitivity	(35) Values art and beauty; (50) Thinks poetry and plays are boring (R)
Intelectual Curiosity	(25) Avoids intellectual, philosophical discussions (R); (40) Is complex, a deep thinker
Creative imagination	(15) is inventive, finds clever ways to do things; (30) Has little creativity (R)
Conscientiousness	
Organization	(3) Tends to be disorganized (R); (33) Keeps things neat and tidy
Productiveness	(8) Tends to be lazy (R); (38) Is efficient, gets things done
Responsibility	(13) Is dependable, steady; (28)

Table 2.1 Example items of facets in the BFI-2. (R) indicates reversed-keyed items.

However, studies assessing the putative role of tinnitus distress longitudinally are scarce. Recently, Kleinstäuber and colleagues (68) *investigated the role of personality traits on internet-delivered cognitive behavior therapy (iCBT) in chronic tinnitus patients. The results indicated that different traits can predict the outcome of an iCBT intervention after different time periods (e.g., 3, 6, 12 months after treatment), underscoring the often overlooked influence of personality on treatment outcomes in tinnitus. However, some questions remain*

unanswered: It is yet not clear if the effects of personality can predict tinnitus-related distress over time, disregard of whether a patient tried any type of treatment or not. It is also unclear whether personality mediates the outcome of psychological-based interventions or, in general, mediates all kinds of tinnitus-related interventions. From a clinical perspective, these open questions are of utmost importance to better understand differences in clinically relevant changes of tinnitus symptomatology. In the study at hand, we aimed at (1) replicating the previous results obtained by Langguth and colleagues (2007), but with a larger sample size; (2) investigating which facets of relevant personality traits account for tinnitus distress; (3) investigating the role of personality traits on tinnitus distress over time; and, of central interest, (4) evaluating whether such traits may be of clinically relevance to the treatment response.

	Frequencies and Means [SD]
Gender (f/m)	146/242
Hearing Loss*	245/152/16
Type of Tinnitus Sound**	232/31/72/46
Laterality of Tinnitus***	50/62/88/57/85/41
Age (years)	55.9 [11.9]
Duration of Tinnitus (months)	154.3 [104.1]
Loudness (1–100)	68.2 [53.3]
THI	49.5 [23.3]
TQ	42.2 [17.7]
Agreeableness	44.5 [5.9]
Conscientiousness	46.3 [7.3]
Extraversion	37.9 [7.8]
Neuroticism	35.7 [8.3]
Openness	39.8 [7.9]

*Table 2.2 Demographics of our sample. *From lef to right: Yes, No, No answer. **From lef to right: Tonal, Noise, Crickets, Other. ***From lef to right: right ear, lef ear, both ears (worse in right), both ears (worse in lef), both ears (equally bad), inside the head.*

Our hypotheses were: (1) neuroticism correlates positively with tinnitus distress over time (i.e., the higher neuroticism is, the lower distress tends to decline over time), whereas (2) *extraversion correlates negatively with tinnitus distress over time; (3) neuroticism correlates positively with changes in distress over time, and (4) neuroticism and extraversion inform differences in clinically relevant grading of the tinnitus distress questionnaires.*

Methods

Participants

Previous patients of the Tinnitus Outpatient Center of the University of Regensburg were invited to participate in this questionnaire survey by a letter with questionnaires and consent forms. 1213 letters were sent to patients who visited the clinic between 2012 and 2017, from which 388 sent back with signed consent forms. The study was approved by the ethical committee at the faculty of medicine of the University of Regensburg (Study Number 18-1041-101), and all methods were performed in accordance with the relevant guidelines and regulations of the institution. We obtained written informed consent from all participants who agreed on having their anonymized data stored and used for scientific purposes.

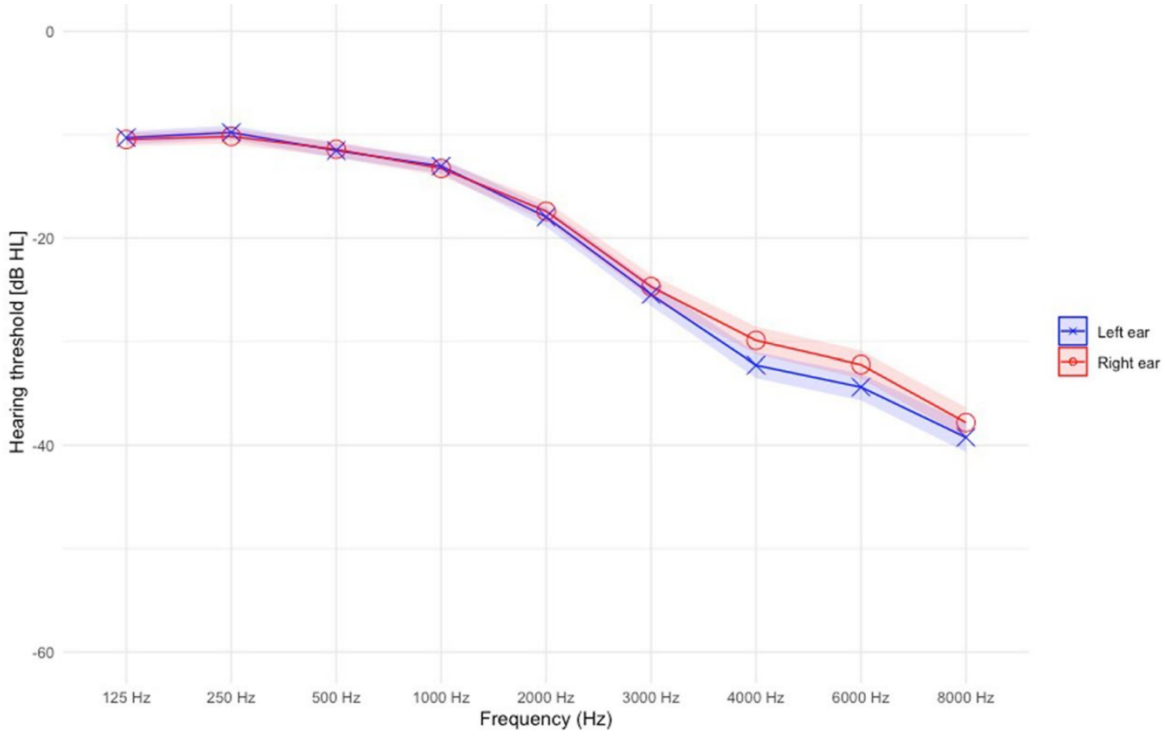

Figure 2.1 Audiogram of our sample. Ribbons represent the standard error

Data collection

The longitudinal analysis considered the first questionnaire assessment during the visit to the clinic as T1 and the assessment with the questionnaires delivered by mail in 2018 as T2. The THI, TQ and TSCHQ were collected at T1 and T2, and the BFI-2 and an informal in-house questionnaire asking patients which treatments they tried between T1 and T2. Regarding the BFI-2, patients filled in a previously validated German version of the questionnaire (110)

Statistical analysis

To evaluate the potential predictive role of the BFI2 on tinnitus distress over time, we grouped patients in three categories: clinically "improved", "stable", and "worsened". The groups reflect the difference of the THI and TQ scores as the difference in scores between the two time points, and followed the guidelines of Zeman et al. (111), and Adamchic et al. (112). More specifically, for the THI, a decrease in >7 points at T2 was considered a significant clinical improvement, an increase in >7 was considered a clinical significant worsening, and the patients who did not score at T2 higher or lower than seven points were grouped as "stable". For the TQ, the thresholds for improvement and worsening were, respectively, 5 points lower and 1 point higher in T2 compared to T1. Since T1 spanned between 2012 and 2017, the year of visit T1 was treated as covariate in the longitudinal analysis. All statistical analyses were conducted with R statistical software (version 3.4.4, R Development Core Team, 2008), alongside the "tidyverse" package (90). Effect sizes were calculated with the package "effsize" (91), and the panels with figures were generated with the "ggpubr" package. Non-parametric tests were used when test assumptions were not met. P values below 0.05 were considered statistically significant.

Results

Cross-sectional analysis of personality traits and facets

Demographics and tinnitus characteristics of our sample can be found in Table 2.2, and the audiogram of our sample is presented in Fig. 1. First, we applied multiple linear regressions with personality traits, age, and gender as independent variables and the scores of THI and TQ at T2 as dependent variables. Table 2.3 shows both statistical models. Both models showed a statistically significant negative association between extraversion and the questionnaire outcomes, while gender, agreeableness and neuroticism showed a positive association with the questionnaire's outcomes. As gender was encoded as a categorical variable, dummy variables

were created for each of its levels. Here, the gender "female" was used as reference. Therefore, our model estimated 6 and 4 points (i.e., the coefficients obtained from the models) increase in the THI and TQ respectively among men after controlling for the personality traits and age. Age was a statistically significant predictor of the TQ but not of the THI. Moreover, the models could explain 39% of the variance (R2 = 0.39, F(7,334) = 31.98, p < 0.001) with the THI as the dependent variable and 34% of the variance (R2 = 0.34, F(7,336) = 26.02, p < 0.001) with the TQ as the dependent variable.

	THI				TQ			
	Coeficients	Std. Error	t value	p value	Coeficients	Std. Error	t value	p value
Intercept	−16.92	14.93	−1.13	0.25	−10.23	12.34	−0.83	0.41
Agreeableness	0.62	0.21	3.06	**<0.01**	0.35	0.17	2.06	**0.04**
Conscientiousness	−0.25	0.16	−1.54	0.12	−0.14	0.13	−1.05	0.29
Extraversion	−0.47	0.16	−3.02	**<0.01**	−0.29	0.13	−2.20	**0.03**
Neuroticism	1.56	0.14	10.86	**<0.0001**	1.1	0.12	9.16	**<0.0001**
Openness	−0.11	0.15	−0.757	0.44	−0.19	0.12	−1.58	0.16
Age	0.07	0.08	0.865	0.39	0.26	0.07	3.75	**<0.001**
Gender: male	6.2	2.24	2.76	**0.01**	4.08	1.84	2.22	**0.03**

Table 2.3 Linear regression models with personality traits as independent variables and THI and TQ at T2 as dependent variables.

Next, we modeled the facets of agreeableness, extraversion and neuroticism as independent variables and the scores from T2 as the dependent variable as these two traits were statistically significant in the previous models. Results are presented in Tables 2.4, 2.5 and 2.6. Regarding the facets of neuroticism, both the models showed a statistical significant association between depression (positive) and emotional volatility and anxiety (negative) with the dependent variable. The effect size of both models was 28% (THI: R2= 0.279, F(5, 336) = 27.4, p < 0.001; TQ: R2= 0.282, F(5, 338) = 27.94, p < 0.001). We did not observe any of the facets of extraversion to be statistically significant in either of the regression setups (THI: R2 = 0.04, F(5, 336), p = 0.002; TQ: R2 = 0.04, F(5, 338) = 0.002). Regarding the facets of agreeableness, "respectfullness" and "trust" were positively and negatively associated with the THI (R2 = 0.05, F(5, 336) = 4.33, p < 0.001), but no facet reached significance in the model with the TQ as dependent variable (R2 = 0.07, F(5, 338) = 6.43, p < 0.0001).

	THI				TQ			
	Coeficients	Std. Error	t value	p value	Coeficients	Std. Error	t value	p value
Intercept	34.22	8.72	3.92	**<0.001**	14.7	6.85	2.15	**0.03**
Compassion	−0.21	1.01	−0.211	0.83	0.05	0.79	0.62	0.95
Respectfulness	−3.28	0.87	−3.78	**<0.001**	0.6	0.61	0.98	0.32
Trust	3.45	1.03	3.36	**<0.001**	−1	0.77	−1.29	0.19
Age	0.04	0.1	0.44	0.66	0.25	0.08	3.06	**<0.01**
Gender: male	6.25	2.68	2.33	0.02	2.62	2.16	7.22	0.22

Table 2.4 Linear regression models with the facets of the personality trait "agreeableness" as independent variable and THI and TQ at T2.

Difference in tinnitus distress Between T1 and T2

Next, we modelled a multiple linear regression with personality traits as independent variables and the difference in the THI and TQ between T2 and T1 as dependent variables. Since T1 represents a visit between 2012 and 2017, we added year of visit as an independent variable in the models. This way, we could account for a potential cumulative effect of time over tinnitus distress over time. The results are presented in Table 2.7. Conscientiousness was the sole personality trait to reach statistical significance (THI: $t = -1.98$, $p = 0.48$), whereas the year of the visit was a statistically significant predictor in both models (THI: $t = 2.32$, $p = 0.02$; TQ: $t = 2.45$, $p = 0.01$). Additionally, we can report statistical trends for neuroticism ($t = 1.8$, $p = 0.07$), and for conscientiousness ($t = -1.95$, $p = 0.05$) in the TQ. The model with the THI as dependent variable had 5% of the variance explained by the predictors ($R2 = 0.046$, $F(8,325) = 3.05$, $p < 0.01$), whereas the model with the TQ as the dependent variable had 5% of the variance explained ($R2 = 0.048$, $F(6,331) = 3.14$, $p = 0.001$).

	THI				TQ			
	Coefficients	Std. Error	t value	p value	Coefficients	Std. Error	t value	p value
Intercept	30.87	9.17	3.34	<0.001	12.35	7.3	1.69	0.09
Anxiety	−2.54	0.81	−3.12	**<0.01**	−1.6	0.65	−2.743	**0.01**
Depression	6.3	0.6	10.43	**<0.0001**	4.6	0.48	9.6	**<0.0001**
Emotional Volatility	−2.9	0.59	−4.89	**<0.0001**	−2.02	0.47	−4.273	**<0.0001**
Age	0.01	0.09	0.17	0.87	0.22	0.07	3.05	**<0.01**
Gender: male	3.15	2.27	1.386	0.167	2.53	1.8	1.4	0.16

Table 2.5 Linear regression models with the facets of the personality trait "neuroticism" as independent variable and THI and TQ at T2.

Personality and clinical significant differences between T1 and T2, and impact on treatment outcomes between T1 and T2

To further explore the potential role of personality traits on tinnitus distress over time, we grouped patients into three groups based on the difference between the scores of the THI and TQ on T2 − T1. The results are presented in Figs. 2 and 3. Neuroticism was statistically significantly lower in patients in the groups "improved" and "stable" compared to the "worsened" group in the THI (t = −3.3, p-value < 0.01, d = 0.5; t = −2.06, p-value = 0.04, d = 0.34). Likewise, patients in the "stable" groups in the TQ showed statistically significant lower neuroticism scores than the patients binned in the "worsened" group (t = −2.26, p-value = 0.03, d = 0.45). Whereas higher neuroticism was associated with worsening in tinnitus, higher extraversion was associated with improvement in tinnitus distress. Regarding the THI, the patients binned in the "improvement" group scored higher than patients binned in the "stable group" (t = 2.55, p-value = 0.01, d = 0.31) and higher than patients binned in the "worsened" group (t = 2.2, p-value = 0.03, d = 0.34).

	THI				**TQ**			
	Coeficients	**Std. Error**	**t value**	**p value**	**Coeficients**	**Std. Error**	**t value**	**p value**
Intercept	51.65	80.5	6.42	**<0.0001**	28.51	6.41	4.45	**<0.0001**
Sociability	−0.16	0.92	−0.18	0.86	−0.27	0.7	−0.37	0.71
Assertiveness	1.11	0.78	1.43	0.15	0.6	0.61	0.98	0.32
Energy Level	−2.27	0.97	−2.34	**0.02**	−1	0.77	−1.29	0.19
Age	0.06	0.1	0.57	0.57	0.25	0.08	3.06	**<0.01**
Gender: male	3.3	2.7	1.22	0.22	2.62	2.16	7.22	0.22

Table 2.6 Linear regression models with the facets of the personality trait "extraversion" as independent variable and THI and TQ at T2.

For this analysis, we clustered patients in two groups: patients who tried at least one tinnitus-related treatment between T1 and T2, and patients who did not. Results are presented in Figs. 2.4 and 2.5. Patients who did try at least one treatment between T1 and T2, and binned in the "improved" group for the THI scored lower in neuroticism than patients binned in the "worsened" group (t = −2.96, p-value < 0.01, d = −0.47). Similar results were observed with the TQ (t = −2.13, p = 0.03, d = −0.27). Regarding extraversion, we observed statistical significant differences between the "improved" and "stable" groups (t = 2.68, p-value < 0.01, d = 0.35), and between the "improved" and "worsened" group (t = 2.05, p-value = 0.04, d = 0.34) for the THI in the group of patients who did not try any treatment between T1 and

T2. For the TQ, we observed a statistical significant change between the groups "improved" and "worsened" among patients that tried at least one treatment between T1 and T2 (W = 51, p-value = 0.03).

	THI				TQ			
	Coeficients	Std. Error	t value	p value	Coeficients	Std. Error	t value	p value
Intercept	−11.36	13.63	−0.83	0.4	−21.03	9.76	−2.15	**0.03**
Agreeableness	0.12	0.18	0.68	0.49	0.11	0.13	0.89	0.37
Conscientiousness	−0.28	0.14	−1.98	**0.048**	−0.2	0.10	−1.95	0.05
Extraversion	−0.17	0.14	−1.21	0.22	0.01	0.1	0.03	0.98
Neuroticism	0.19	0.13	1.43	0.15	0.17	0.09	1.8	0.07
Openess	−0.04	0.13	−0.27	0.79	−0.01	0.09	−0.01	0.99
Year of Visit	1.19	0.52	2.32	**0.02**	0.9	0.36	2.45	**0.01**
Age	0.11	0.07	1.52	0.13	0.15	0.05	2.75	**<0.01**
Gender: male	1.57	2.02	0.77	0.43	2.03	1.44	1.41	0.16

Table 2.7 Linear regression models with the personality traits as independent variable and diference between the scores of THI and TQ in T2−T1.

Discussion

The present study was the first to systematically analyze the effect of personality on the longitudinal trajectory of tinnitus distress. We showed that neuroticism is related to changes in tinnitus distress, i.e., clinically relevant changes in the grade of tinnitus distress as measured by TQ and THI. More specifically and of central interest, neuroticism was higher in patients with worsened clinical status compared to patients with improved clinical status (measured with THI as well as TQ). Looking at extraversion, the group showing clinical improvement exhibited significantly higher scores compared to the groups of stable and worsened clinical status (measured with THI but not significant for TQ).

Our cross-sectional analysis between personality and tinnitus distress reproduced previous findings (105,106,113,114) as both neuroticism and agreeableness showed a positive association with tinnitus distress, while extraversion had a negative association with distress. We partially reproduced the findings of Strumila and colleagues, who identified neuroticism as the sole predictor of the THI (109), which could be explained by differences in the demographics of both samples 2.

We identified the three facets of neuroticism, anxiety, depression and emotional volatility, to be significant predictors of the THI and TQ cross-sectionally. We also identified energy level, a facet of extraversion, to be a significant predictor of the THI. Interestingly, those facets are

characteristic of the "type D" personality, which is prevalent among high distressed tinnitus patients (106,107). A previous review (113) discussed the challenges of separating depression and tinnitus, as the symptoms presented by both groups and the underlying mechanisms between the two conditions are often convoluted (e.g., neuronal mechanisms (115)). Future studies could investigate the relation between the two conditions by comparing acute depression (e.g., as measured by the Beck's or Major Depression Inventory), depressive personality (e.g., as measured by the "depression" facet) and biomakers of depression, such as the brain-derived neurotrophic factor (116).

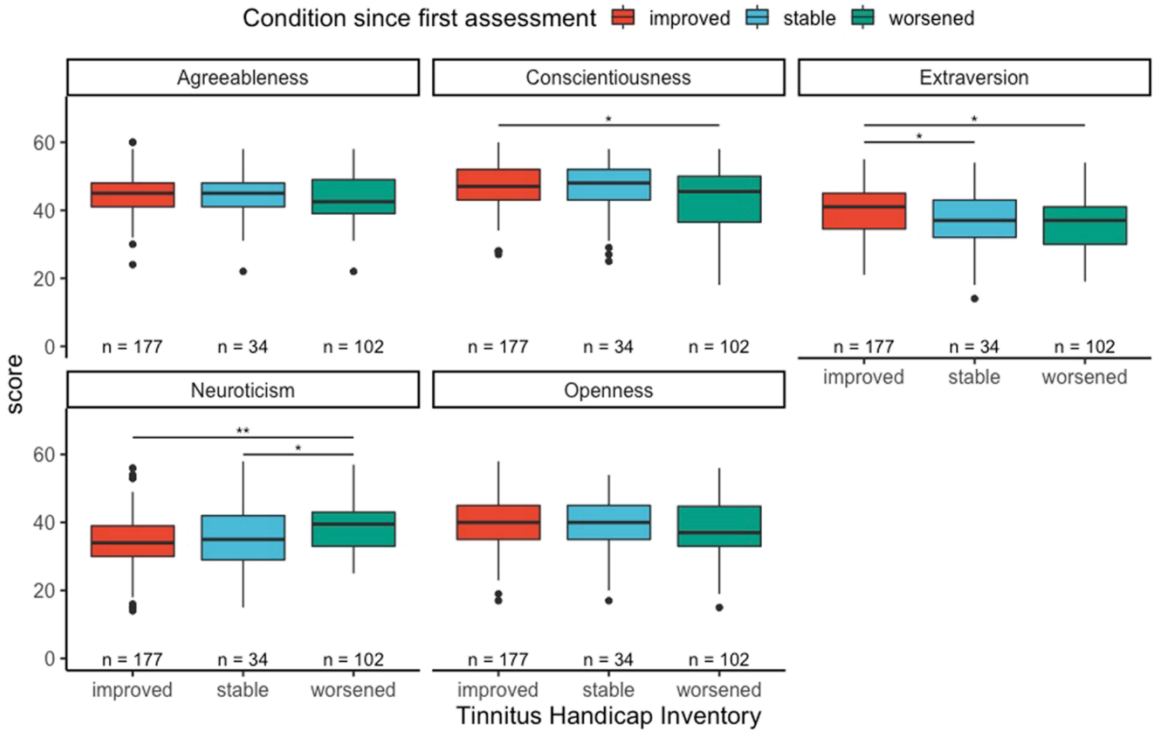

Figure 2.2 THI change grades and personality traits.

We could not observe a significant effect of any of the five personality traits on tinnitus distress over time in our multiple linear regression setup (except conscientiousness, which was at the margin of statistical significance in both models). On the other hand, the year of first assessment was a significant predictor of the difference in the THI and TQ in $T2 - T1$, suggesting that the longer the period between T1 and T2, the greater the decrease in tinnitus distress. To test for clinical relevance, which surpasses mere psychometric statistical analysis and therefore generate important practical insights for clinical routine in tinnitus, we grouped patients in three groups based on previous literature (111,112) : "clinically improved", "clinically stable", and "clinically worsened".

These differences reflected the difference in the THI and TQ between two time points. Patients grouped in the "worsened" group had higher levels of neuroticism than the other two groups in both the THI and the TQ, and extraversion was significantly higher in the "improved" group than in the other two for the differences in the THI, but not in the TQ. These differences in personality related to clinically relevant changes in tinnitus distress may have prognostic value, as they were able to statistically distinguish three clinically relevant groups of tinnitus patients. Similar effects were observed when we divided the three groups between patients who tried at least one clinical trial for their tinnitus and those who did not. Our results suggests that personality plays a role on the change of distress among patients who tried at least one treatment. There is an on going debate about the role of personality on placebo effects in clinical trials, and researchers are increasingly aware of its putative effects alongside other factors such as positive/negative expectations and patient-clinician relationship (117). *We recommend future tinnitus studies to measure and report personality traits in their clinical trials, as personality could either represent a cofounder in trials' outcomes or be used to identify efficient individual treatments.*

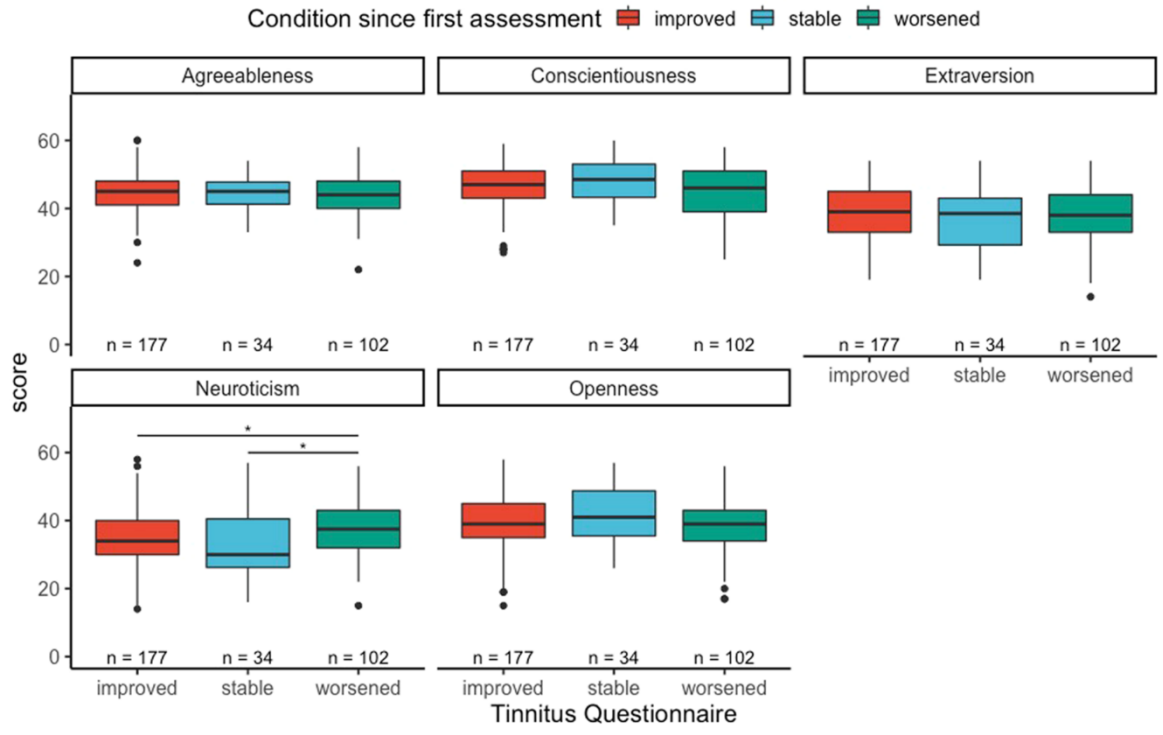

Figure 2.3 TQ change grades and personality traits.

Tinnitus heterogeneity has been implicated as a major obstacle to improving the condition's management, and thus tinnitus subtyping has been settled as a major objective in the research

community (56,78). Future research should further explore the role of personality on tinnitus heterogeneity and its implications on treatment outcomes. For instance, although the relation between personality and coping strategies is well characterized in the overall literature (118), little is known about it in tinnitus patients.

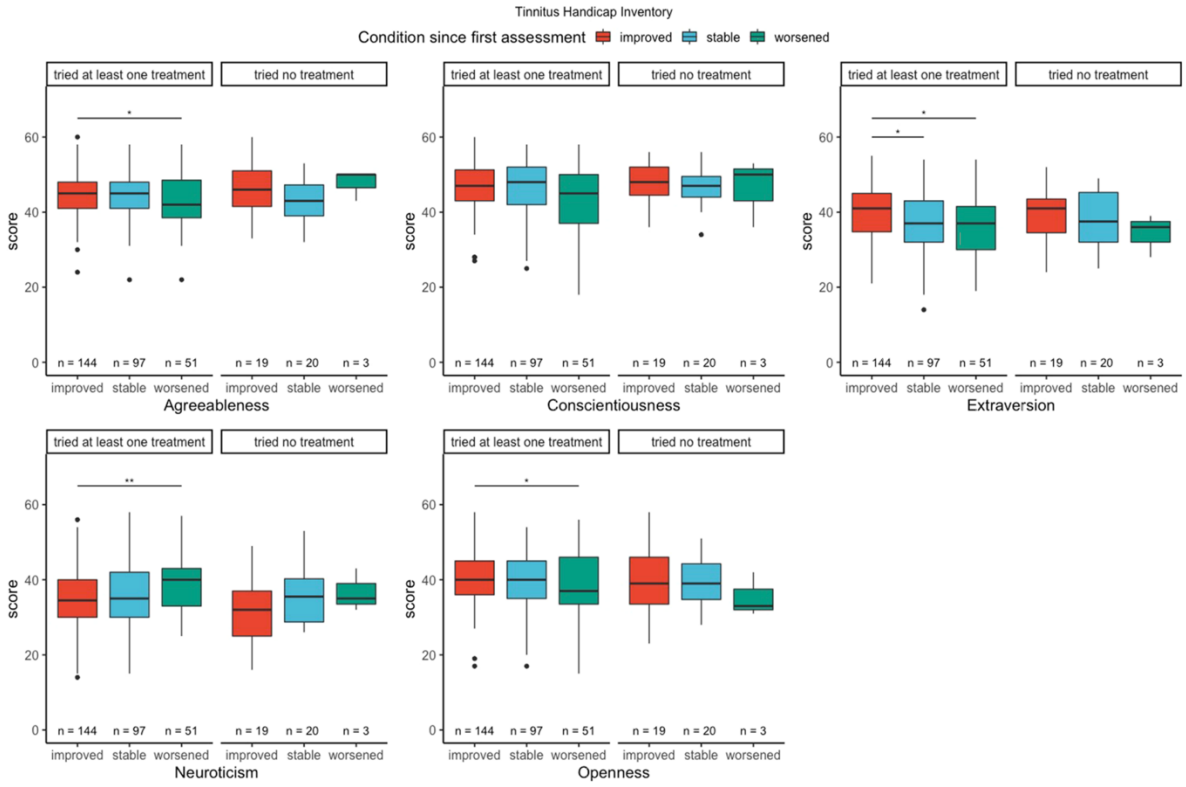

Figure 2.4 THI change grades and personality traits. Results are reported for patients who tried at least one treatment and patients who tried no treatment.

This study has inherent limitations. First, we collected the FFM at T2 and not at T1. Whether personality is a crystallized construct, i.e., it does not change over time, is debatable. For instance, it is possible to change FFM scores through experimental manipulation (119). *Conversely, Cost and Mccrae (103,104) reviewed the evidence for the stability of the construct longer periods of time. The stability of personality over time, in our cohort up to seven years to patients who visited our clinic in 2012, is an important assumption of our analysis (104). As proposed above, it would therefore be helpful to assess personality within standard psychometric tinnitus batteries at all time points in clinical trials or general longitudinal research. Second, we could not properly investigate the role of personality among patients who did not try any treatment due to small sample size. Whether clinically significant tinnitus habituation can be explained by personality remains a relevant, open question. Third, we could not discard a potential bias among those who responded to our survey at T2. To the best of our*

knowledge, no former study investigated whether patients participate in surveys and/or clinical trials. However, apart from a 2-point difference in the TQ, we could not find statistically significant differences between the sample which responded the survey and the sample which did not.

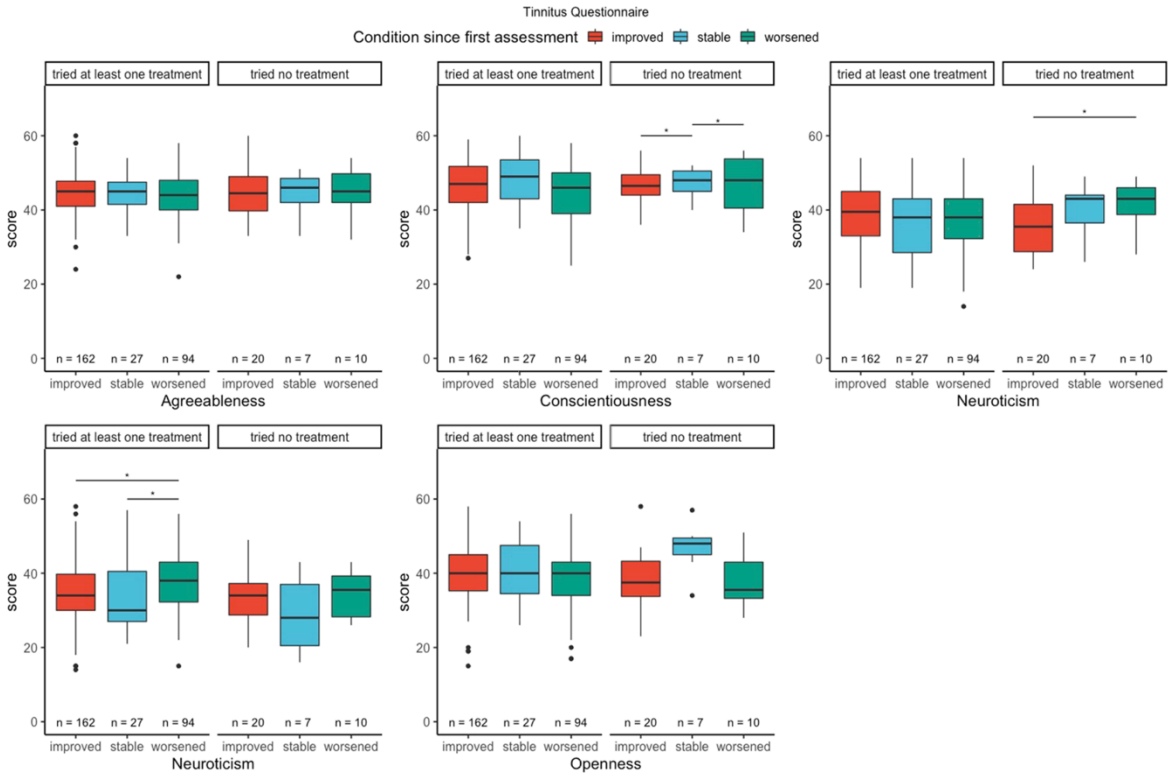

Figure 2.5 TQ change grades and personality traits. Results are reported for patients who tried at least one treatment and patients who tried no treatment.

In conclusion, our results suggest that personality traits, namely neuroticism and extraversion, can explain a large portion of the variance of tinnitus distress. Those two traits are relevant markers of tinnitus distress over time and can be used to statistically distinguish patient groups with clinically relevant changes of tinnitus distress. Personality assessments could provide valuable information to clinicians and researchers, and may eventually be used to deliver personalized treatments for tinnitus patients (120). Future studies would furthermore profit from assessing personality at several time points to further investigate interactions between personality and tinnitus.

Author contributions

P.N., D.F., W.S. and J.S. defned the study design and interpreted the results. B.L., P.N., M.S. and W.S. interpreted the results, and provided critical feedback during the manuscript preparation. D.F., M.S. and J.S. were responsible for data collection.

Competing interests

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Chapter III

The Progression of Chronic Tinnitus Over the Years*

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This manuscript is being peer-reviewed in Scientific Reports[8]

Abstract

Introduction

Little is known about the trajectory of tinnitus over time. This study addressed 1) how often tinnitus remitted in patients with chronic tinnitus; 2) how subjective reported tinnitus characteristics, such as loudness, laterality, and type and measures of burden, such as tinnitus distress, depression, and quality of life, changes over time; 3) how often tinnitus-specific treatments were undertaken and the prevalence of comorbidities, 4) if the number of treatments and comorbidities were associated to changes in tinnitus distress over time.

Methods

Data from 388 patients with chronic tinnitus who visited a tertiary tinnitus clinic between 2012 and 2017 were interrogated via a mail survey in 2018. Tinnitus characteristics were measured with the Tinnitus Sample Case History Questionnaire (TSCHQ) and numeric rating scales; tinnitus distress with Tinnitus Handicap Inventory (THI) and the Tinnitus Questionnaire (TQ), depression with the Major Depression Inventory and Quality of life with the World Health Organisation Quality of Life BREF at both time points and the clinical global impression scale. Comorbidities experienced and undertaken treatments were assessed with an in-house survey.

Results

Three participants (0.8% of the sample) reported tinnitus remission between both assessments. A decrease in the THI and TQ, and numeric ratings for tinnitus severity, annoyance,

unpleasantness, and discomfort was observed, but no differences in tinnitus characteristics, depression, quality of life or overall health status. 64% presented at least one comorbidity, and 88% sought at least on tinnitus-specific treatment. Common comorbidities were psychological and sleeping problems, and the most common interventions were going to the dentist, taking medications, and wearing hearing aids.

Conclusion

Our results suggest that full remission of tinnitus is a rare condition, that tinnitus distress on average decreases over time, and that tinnitus characteristics, quality of life, and depression tend to remain unaltered. The high number of interventions and comorbidities displayed minimal association to the changes in tinnitus distress, highlighting the substantial and durable burden of tinnitus sufferers.

Introduction

Tinnitus can be described as the perception of sounds, usually in the form of ringing or hissing, without an external source (19,76). Although a considerable number of patients report little to no impact in their daily lives due to this condition, tinnitus can also be exasperating (18,76). Previous studies from 2005 and 2013 estimated that, at the time, 13 million tinnitus patients were actively seeking support in Europe and in in the United States (13,121). Furthermore, the costs associated with tinnitus were estimated at 750 million pounds per year in the United Kingdom (122). Overall, tinnitus can be described as a burdensome condition both at the individual and societal level.

The reasons why only a subset of patients are burdened by the condition are unclear. Moreover, evidence suggests tinnitus can change over time even when presented chronically (55). Based on clinical experience it is generally assumed that tinnitus becomes less burdensome over time, but systematic data supporting this assumption are scarce. One mechanism of amelioration of tinnitus over time may be related to tinnitus habituation, first described by Hallam (123). It is also a key component of the so-called neurophysiological tinnitus model, and it offers a potential explanation why the condition is so burdensome for a subset of patients (124). According to this model, distress originates from aberrant activation in areas of the brain other than the auditory pathway, such as the limbic and autonomic systems, which prevents that patients habituate to tinnitus by repeated emotional and stressful ratings of the condition

(124,125). This concept is supported by recent imaging data demonstrating the involvement of non-auditory brain areas such as the frontal cortex, the amygdala and the parahippocampal cortex in tinnitus pathophysiology (57).

Recent studies using ecological momentary assessment indicate that tinnitus distress fluctuates over time and that these fluctuations are related to emotional factors (51,52). However, very little is known about the course of tinnitus over several years and about the facets of tinnitus that might vary over time, even if this knowledge would be of exceptional interest for clinicians, researchers and patients (56,78).

In the following, some of the longitudinal studies, alongside their main findings and limitations are briefly discussed.

Griest and Bishop (126) conducted a 15-year longitudinal study on noise-exposed workers in which the authors identified tinnitus as an early indicator of hearing loss. In a seven-year longitudinal study, Andersson et al. (127) found that tinnitus severity shows signs of improvement over time after clustering patients in three groups based on different degrees of distress. However, the authors did not use any distress-specific, numeric questionnaire to compare baseline and follow-up values. Olderog and colleagues (128) conducted a study with 44 patients suffering from tinnitus for less than four weeks with a six-month follow-up survey. A stepwise regression with the predictors "sleep disturbance", "anxiousness", and "life satisfaction" collected at baseline could explain 56% of the variance (R2) of tinnitus distress measured with the Tinnitus Questionnaire (TQ) in the six-month follow up. It remains unclear, however, whether these effects would persist in a larger, chronic tinnitus sample. Erlandsson and Persson (129) found that the Beck Depression's Inventory (BDI) and the trait and state anxiety (quantified by Spielberger's State and Trait Anxiety Inventory) decreased over a period of 18 months only among patients without a personality disorder. Lastly, Folmer (130) measured sleep quality, depression (measured by the BDI), and tinnitus distress (measured by the Tinnitus Severity Index, TSI) in 190 patients. The author reported a decrease in the TSI, especially among patients whose sleep patterns improved and whose BDI decreased by at least 3 points between the two assessments. We investigated whether tinnitus changes over time in a large cohort of patients with chronic tinnitus from a tertiary clinic in a retrospective mail survey to further understand the development of tinnitus over time.

Our research questions were 1) how often tinnitus remits in patients with chronic tinnitus; 2) how tinnitus characteristics and burden caused by tinnitus (tinnitus distress, depression,

quality of life and health status) change over time; 3) how often patients enrolled in a tinnitus-related treatment protocol and which treatments were most often sought; 4) if number of treatments or comorbidities were associated with changes in tinnitus distress over time.

Methods

Participants

Our sample consisted of patients from the Tinnitus Center of the University of Regensburg. Participants were invited to this study via a letter containing questionnaires and a consent form. The letters were sent to 1213 out-patients who visited the clinic between 2012 and 2017. 388 letters were sent back, resulting in a 32% response rate. The study was approved by the ethical committee at the faculty of medicine of the University of Regensburg (study number 18-1041-101). All the protocols and guidelines of the institution were followed, and only patients from whom we obtained signed informed consent were included in the final analysis.

Data Collection

Henceforward, the patients' first visit to the clinic between 2012 and 2017 will be described as T1, and the assessment through mail conducted in 2018 will be described as T2.

The Tinnitus Handicap Inventory (THI), Tinnitus Questionnaire (TQ), Tinnitus Numeric Ratings Scales for severity, loudness etc., Major Depression Inventory (MDI), World Health Organization Quality of Life (131), health status according to Clinical Global Impression and the Tinnitus Sample Case History Questionnaire (132) were collected at T1 and T2, and an informal in-house questionnaire asking patients which treatments they tried, and which comorbidities they experienced since T1 was obtained at T2 (available in the supplementary material).

Statistical Analysis

Differences between T1 and T2 (T2-T1) were calculated and reported with a Δ symbol. All statistical analyses were conducted with R statistical software (version 3.4.4, (89), alongside the "tidyverse" package (90). After checking whether variables presented normal distributions and homogeneous variance, t-tests were used to compare mean differences in numeric items between T1 and T2; categorical items were tested with Pearson's Chi-Squared test. Two previous studies defined an improvement in tinnitus distress, measured by the THI, to be clinically significant if above 20 and 7 points (111,133). Differences in the THI between T1

and T2 were used to calculate the percentage of patients who clinically improved under these definitions. Missing observations in pairwise comparisons were excluded from the analysis.

Multiple comparisons were corrected with the Holm-Bonferroni method (134). Following convention, p values below the threshold 0.05 were considered statistically significant and p values below 0.1 were considered trend significant. Effect sizes were calculated with the Cohen's d using the "effsize" package (135,136). The package Igraph was used to represent the association between comorbidities and treatments tried as a network (137). In this context, the node's size represents the number of people who experienced a comorbidity or attempted a treatment protocol, and the link's thickness between two nodes represents the number of people who experienced a given pair of comorbidities or two attempted treatment protocols between T1 and T2.

Results

Three patients (0.8%) reported losing their tinnitus at T2. Table 3.1 summarizes the demographics of our sample compared to those three individuals. Overall, we did not observe any clear pattern that could explain why those patients lost their tinnitus.

	Mean [SD], N = 385	Patient #1	Patient #2	Patient #3
Gender[1]	146/242	female	female	male
Age (years) [SD]	55.9 [11.9]	51	64	63
Duration (months) [SD]	154.3 [104.1]	77	266	158
Type of Tinnitus Sound*	232/31/72/46	tone	crickets	tone
Laterality of Tinnitus**	50/62/88/57/85/41	right ear	both ears	left ear
Loudness (1-100) [SD]	68.2 [53.3]	20	90	70
MDI (mean total score) [SD]	15.3 [11.5]	NA	22	14
THI (mean total score) [SD]	49.5 [23.3]	54	72	52
TQ (mean total score) [SD]	42.2 [17.7]	33	64	49

*Table 3.1 Characteristics of our sample at T1. The characteristics of all three patients who reported losing their tinnitus between the two assessments is presented. 1: female/male ratio. * from left to right: Tonal, Noise, Crickets, Other. ** from left to right: right ear, left ear, both ears (worse in right), both ears (worse in left), both ears (equally bad), inside the head. NA: Non Available*

Table 3.2 presents the difference between T1 and T2. We observed significant differences between the two time points for the THI, TQ and for numeric ratings for tinnitus severity, its discomfort, its annoyance, and its unpleasantness. For all other variables we did not find a significant difference between T1 and T2. Regarding the THI, 87 participants (22% of the sample) reported a decrease greater than 20 points between the two time points, while 182 (47%) reported a decrease in the THI of at least 7 points. Appointment to the dentist was the

most frequent treatment patients sought for their tinnitus (32.7%), followed by medication (32.4%), and hearing aids (30.6%, Figure 1e), and most patients (88%) tried at least one treatment for their tinnitus (Figure 1f).

Domain	Subscore	Mean [sd] / Ratio at Baseline	Mean [sd] / Ratio at 2nd Assessment	Test [ci]	p Value	Adjusted p	Effect Size
Distress	Problem*	2.55 [0.9]	2.27 [1.1]	4.33 [0.2-0.4]	<0.001	<0.001	0.33
	Loudness*	6.73 [2.1]	6.37 [2.5]	2.3 [0.1-0.7]	0.02	0.13	0.17
	Loudness***	68.73 [58.28]	63.61 [22.05]	1.66	0.09	0.49	0.12
	Uncomfortableness*	7.4 [2.3]	6.72 [2.6]	4.02 [0.4-1.01]	<0.001	0.001	0.3
	Annoyance*	7.11 [2.4]	6.39 [2.7]	3.99 [0.4-1.1]	<0.001	0.001	0.29
	Ignore*	7.18 [2.6]	6.72 [2.9]	2.37 [0.1-0.8]	0.02	0.13	0.18
	Unpleasantness*	7.17 [2.3]	6.47 [2.7]	4.01 [0.4-1.1]	<0.001	0.001	0.3
	THI	49.54 [23.1]	41.98 [23.8]	4.38 [4.2-10.9]	<0.001	<0.001	0.32
	TQ	42.31 [17.7]	36.87 [19.1]	4.06 [2.8-8.1]	<0.001	0.001	0.3
Depression	MDI	15.28 [11.5]	13.51 [10.4]	2.07 [0.1-3.5]	0.04	0.19	0.16
Quality of Life	Physical Health**	12.72 [1.7]	12.89 [1.7]	-1.39 [-0.4-0.07]	0.16	0.59	-0.1
	Psychological**	13.72 [2.1]	13.73 [2.1]	-0.09 [-0.3-0.3]	0.93	1	-0.01
	Social relationships**	14.6 [3.3]	14.25 [3.3]	1.45 [-0.1-0.8]	0.15	0.59	0.11
	Environment**	16.7 [2.2]	16.6 [2.2]	0.62 [-0.2-0.4]	0.54	1	0
Tinnitus Characteristics***	Begin of perception[1]	175/185	175/185	0	1	1	0
	Pulsation[2]	43/36/287	35/42/289	1.29	0.53	1	0.06
	Laterality of Tinnitus[3]	48/59/80/55/78/38	34/59/80/53/82/50	4.16	0.52	1	0.11
	Intermittence[4]	41/336	63/314	5.4	0.03	0.66	0.12
	Loudness fluctuation[5]	236/136	237/135	0.01	1	1	0
	Tone/white noise[6]	220/27/64/44	214/44/65/32	6.06	0.11	1	0.13
	Tone frequency[7]	114/191/59/4	116/175/72/5	2.12	0.56	1	0.08
	React to positive sounds[8]	238/84/49	253/70/48	1.74	0.43	1	0.07
	React to negative sounds[9]	191/84	196/79	0.22	0.71	1	0.03
	Somatic component[10]	146/226	141/231	0.14	0.77	1	0.22
	Effect of nap[11]	60/30/258	56/40/252	1.64	0.44	1	0.07
	Effect of sleep[12]	77/121/157	89/125/141	1.79	0.4	1	0.07
	Effect of strees[13]	261/4/100	275/6/84	2.16	0.34	1	0.08
	Hearing problem[14]	232/137	241/128	0.48	0.54	1	0.04
	Wear hearing aids[15]	8/9/48/304	11/13/70/275	6.76	0.08	1	0.14
	Toleration to loudness[16]	38/47/152/69/69	21/61/131/85/77	10.37	0.03	0.73	0.17
	Hyperacusis[17]	185/117	203/99	2.34	0.15	1	0.09
	Headache problems[18]	158/212	119/251	8.78	0	0.08	0.15
	Dizziness/vertigo[19]	132/231	104/259	4.92	0.03	0.73	0.12
	TMJ[20]	93/275	91/277	0.03	0.94	1	0.01
	neck pain[21]	235/138	209/164	3.76	0.06	1	0.1
	Pain syndromes[22]	170/206	163/213	0.26	0.65	1	0.03
	Psychological treatment[23]	77/299	63/313	1.72	0.23	1	0.07
	Year of Visit (2012-2017)	70/96/70/33/57/62	-	-	-	-	-

*Table 3.2 Differences between T1 and T2. T-tests and chi-squared tests were used for numeric and categorical items, respectively. The last row shows the frequency of visits per year. Multiple comparisons were corrected with the Holm-Bonferroni method, and effect sizes were calculated with Cohen's d. Missing observations in pairwise comparisons were excluded from the analysis. * Items of the Tinnitus Numeric Rating Scale; ** Subscores of WHOQoL; *** Items of TSCHQ. From left to right: 1: gradual/abrupt; 2: yes, with the heart rate/yes, different from heart rate/no; 3: right ear/left ear/ both ears, worse on left/both ears, worse on right/both ears equally/inside the head/elsewhere; 4: intermitent/constant; 5: fluctuates/constant; 6: tone/noise/cricket/other sound; 7: very high freq./high freq./medium freq./low freq.; 8: yes/no/do not know; 9: yes/no; 10: yes/no/do not know; 11: worsens tinnitus/improves tinnitus/no effect; 12: no correlation between sleep and tinnitus/correlation between sleep and tinnitus/do not know; 13: stress influences tinnitus/stress does not influence tinnitus; 14: has hearing problem/does not have hearing problems; 15: right ear/left ear/both ears/none; 16: never/rarely/sometimes/usually/always; 17: suffers from hyperacusis/ does not suffer from hypearcusis; 18: suffers from headaches/does not suffer from headaches; 19: suffers from dizziness/does not suffer from dizziness; 20: suffers from tempomandibular disorders/does not suffer from tempomandibular disorder ; 21: suffers from neck pain/ does not suffer from neck pain; 22: suffers from pain syndrome/does not suffer from pain syndrome; 23: currently having psychological treatment/currently not having psychological treatment. THI: tinnitus handicap inventory; TQ: tinnitus questionnaire; MDI: major depression inventory; TMJ: transcranial magnetic stimulation.*

Most patients (64%) reported having at least one comorbidity, with psychological and sleeping problems being the two most often reported (Figures 1a and 1b). Visiting the dentist and taking medication was the two most common treatments tried by patients between T1 and T2 (Figures 1e), and most patients (88%) tried at least one treatment for their tinnitus (Figure 1f). Figure 2 shows a network representation of the relation between treatments (Figure 2a) and comorbidities (Figure 2b) experienced by patients between T1 and T2. Interestingly, the two

most common comorbidities, psychological and sleeping problems, showed the strongest association (Figure 2b, as depicted by the link's thickness). Next, we investigated whether the number of comorbidities experienced, and the number of treatments tried between T1 and T2 influences tinnitus distress changes over time, measured as ΔTHI and ΔTQ (Figure 1).

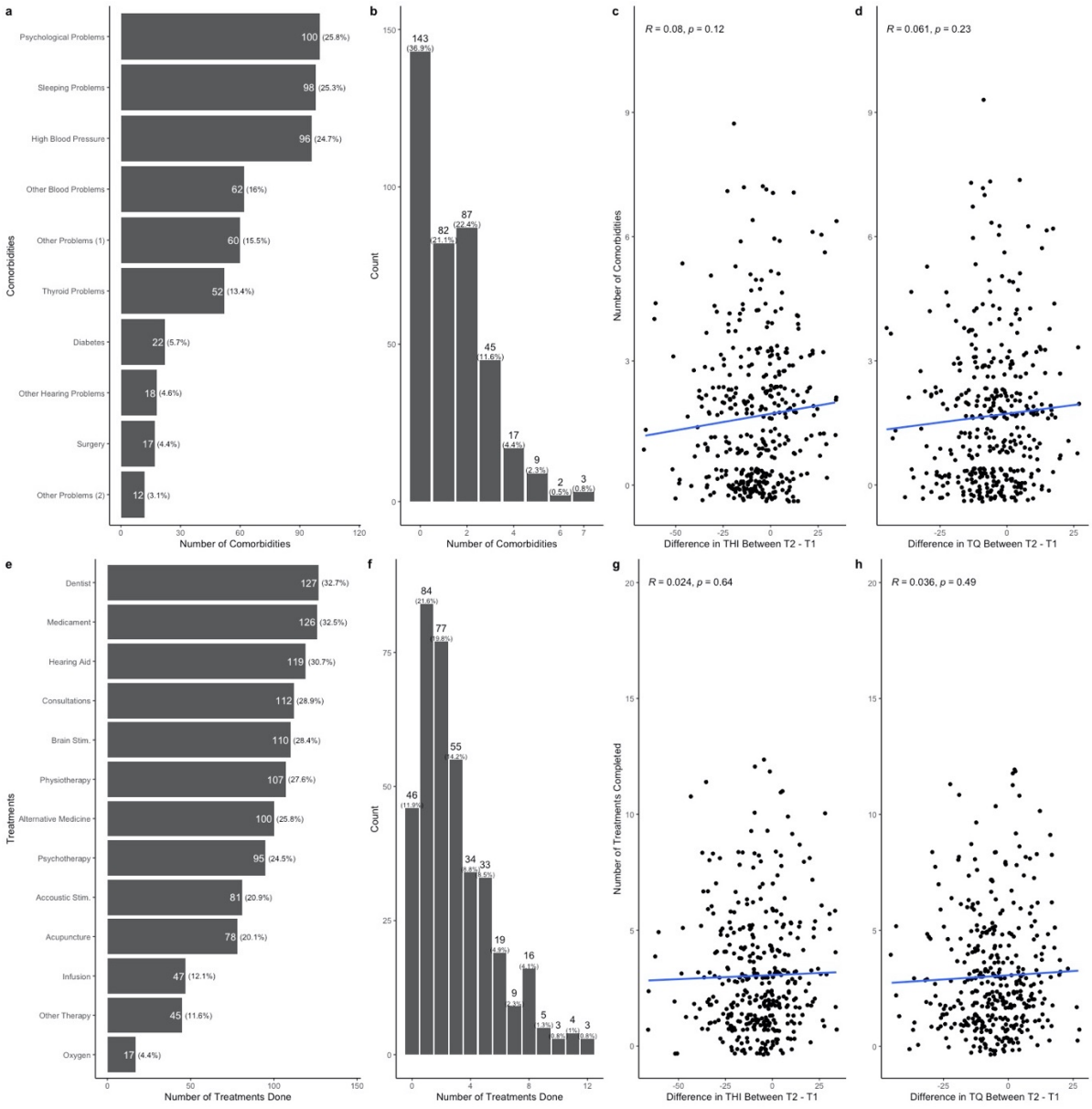

Figure 2.1 Relation between the number of comorbidities experienced, treatments tried, THI and TQ over time.

Figures 1g and 1h show a correlation between the number of treatments tried and ΔTHI (r = 0.08, p = 0.12) and ΔTQ (r = 0.06, p = 0.23) respectively, whereas Figures 1c and 1d show no

significant correlation between the number of comorbidities experienced by patients between T1 and T2 and ΔTHI (r = 0.024, p = 0.64) and ΔTQ (r = 0.04, p = 0.49) respectively.

Discussion

We analyzed retrospective longitudinal data of patients with chronic tinnitus from a tertiary tinnitus clinic. 388 of the 1213 contacted patients responded to the mail, resulting in a response rate comparable to a previous study with a cohort from the same clinic (138). Three patients (0.8% of our sample) reported full remission of tinnitus at T2. No common factors or characteristics were identified distinguishing those patients from the whole sample (Table 3.1). It is often suggested that tinnitus remits especially in its acute presentation (18,139)*. Our results suggest that, albeit rare, tinnitus may also disappear in chronic patients suffering from the condition for years or even decades. These numbers, however, may be underestimated as other patients who also lost their tinnitus may have not responded to the survey. We were not able to further investigate potential factors associated with remission as patients did not agree to be further contacted. Future studies could focus on this select subgroup of patients with prospective follow-up studies from large cohorts. If investigators choose to focus on remission per se, then patients with acute tinnitus, in which the remission rate is higher, could be studied* (139)*.*

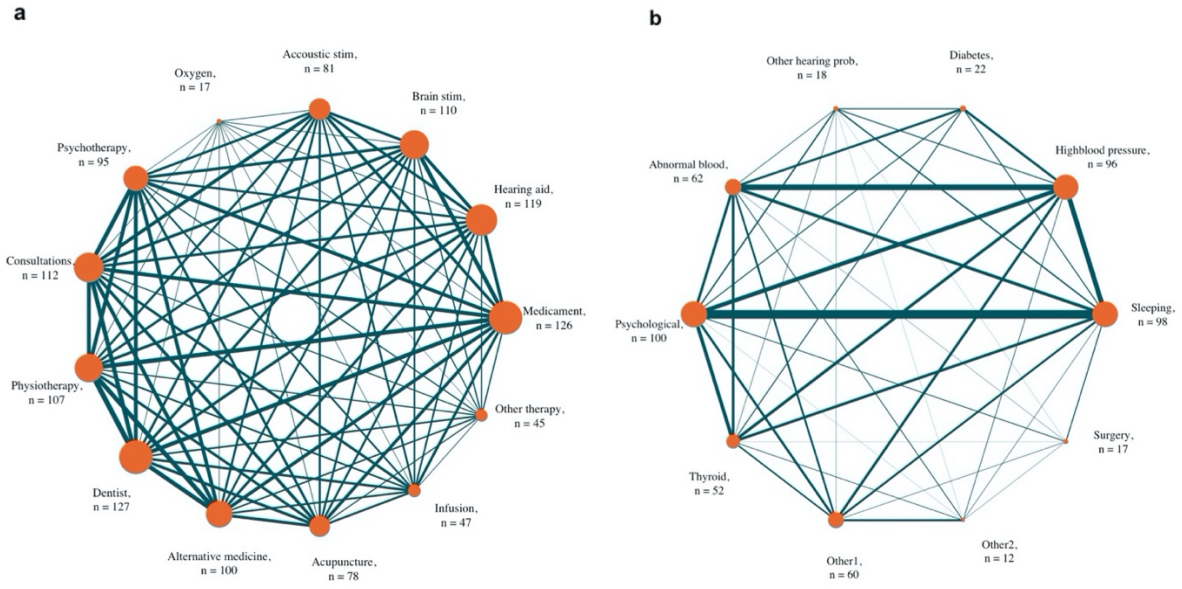

Figure 3.2 Network depiction of the relation between treatments (a) and comorbidities (b). The prevalence of comorbidities and the number of treatments undertaken by patients are represented by the size of the node. The link represents a pair of comorbidities

Tinnitus distress when measured using the THI and TQ, and the tinnitus severity items regarding the condition as troublesome, uncomfortable, annoying and unpleasant decreased over time (Table 3.2). Regarding the THI, 22.4% of patients reported a decrease of 20 or more points between the two time points, and 46.9% reported a decrease of 7 or more points.

Those two cut-off points have been previously suggested to represent "clinical meaningful improvements" of tinnitus (111,133), but empirical evidence supporting their usage is scarce. Other measures of burden, such as depression, quality of life or overall health status did not change between the time points. If changes in tinnitus distress do not impact the daily life of the patients, it is to discuss in what way the reported changes are meaningful. There is increasing discussion in the field of tinnitus and other conditions that quality of life should have more awareness in tinnitus trials (140). Future studies could evaluate the clinical relevance of these two definitions of "clinical improvement" from the THI based on whether they can distinguish improvements in quality of life and/or depression, for example.

Additionally, there was no difference in tinnitus characteristics, such as loudness, type of perceived sound, and laterality between the two time points after controlling for multiple comparisons. These results suggests that the acoustic perception remains largely stable over time, but the distress diminishes, e.g., by habituation. In this context, an important aspect of future research is the identification of factors that facilitate distress reduction. A previous study using the same cohort as the one from this study indicated that the personality traits neuroticism and extraversion are respectively negatively and positively related to ΔTHI and ΔTQ (66).

The high number of treatments patients sought, and the high number of comorbidities experienced highlight the burden tinnitus may cause (122). However, we observed no linear relation between number of treatments and tinnitus distress. It has been proposed that tinnitus treatment should be based on precision medicine, as not all treatments are equally beneficial to patients (66,141). Both clinicians and patients have indicated the lack of a universal treatment for tinnitus as one of their biggest complaints (142)x. However, these results may be confounded by a selection bias, as patients not severely affected by tinnitus may have improved after a first treatment or no treatment whatsoever. Since patients were not randomized into treatment or no treatment groups, our study cannot quantify the potential effects of treatments on the longitudinal trajectory of tinnitus distress. The same considerations apply when interpreting the relation between comorbidities and tinnitus distress.

Our analysis was limited to factors such as demographics, tinnitus distress and tinnitus characteristics, quality of life and depression. However, other confounding variables such as socio-demographics, coping strategies, life history, and personality (143) *could be of central interest for the longitudinal trajectory of tinnitus. Another limitation of our study was the variability of the time point when patients were first assessed (i.e., between 2012 and 2017) and the variability of treatments and comorbidities included in this analysis. Only a subset of patients reported to our mail survey; therefore, the possibility of a selection bias must be considered. Additionally, the observed improvement might reflect the tendency to the mean, that is, patients visit the clinic when they are severely impaired, and a later improvement may reflect spontaneous fluctuations. Future studies should assess both subjective and objective (e.g., minimum masking level, tinnitus matching, etc.) tinnitus characteristics at all time points.*

Conclusion

We investigated the longitudinal trajectory of tinnitus characteristics, tinnitus distress, depression and quality of life among chronic patients from a tertiary tinnitus clinic. Tinnitus disappeared from three chronic patients, suggesting that, albeit rare, remission is possible even after years of having tinnitus. Future research should further investigate which factors are associated with tinnitus remission. Our findings should also encourage future research to focus not only on tinnitus management but also on interventions to suppress it, as tinnitus remission may be possible also in the chronic manifestation of the condition.

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Chapter IV

Nomothetic and Idiographic Dimensions of Tinnitus Loudness, Distress, Mood, and Concentration Using Ecological Momentary Assessment

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This chapter has not been submitted yet to a peer-reviewed journal

Background:

Ecological momentary assessment (EMA) is an increasingly popular method in mental health research. EMA involves the repeated collection of behavioral and symptom-related data in real time. This is particularly relevant to tinnitus research because of the potentially recollection bias when data is collected retrospectively. The Track Your Tinnitus (TYT) mobile app provides a platform to collect ecologically valid, time-series data of tinnitus users. Such data can be used to address questions such as how variables like mood, concentration, tinnitus distress, and loudness relate over time.

Objectives:

To assess whether behavioral and symptom-related data of tinnitus patients cross-correlate in different time lags, both at the individual (idiographic) and group (nomothetic) levels.

Methods:

Anonymized data from 488 users of TYT who used the either the iOS or Android apps between 2015 and 2020 was collected. Tinnitus-related distress and overall stress, tinnitus loudness, overall mood, and concentration levels were assessed with a 10-point self-assessment manikin through a daily survey. A 10-day lagged cross-correlation was used to investigate the dynamics of those items over time at the group level, followed by linear regressions with elastic net regularization. Then, unified structural equation modeling (uSEM) was used to retrieve individualized models from 32 patients with at least 60 days of sequential app use.

Results:

No auto- or cross-correlation was observed at the group level between the variables assessed. However, elastic net regularization was able to uniquely predict tinnitus loudness and distress for a majority of participants. The models included both contemporaneous and lagged information from the previous day. uSEM models had on average adequate fits; both contemporaneous and lagged coefficients were obtained for most individuals, indicating that variables are uniquely interconnected.

Discussion:

Our results suggest that novel insights can be obtained from conducting analysis at the idiographic level using elastic net regularization and uSEM from EMA. Those findings are particularly important considering current strives to individualize tinnitus care.

Introduction

Tinnitus is a condition in which phantom sounds are perceived without a corresponding external stimulus. Those sounds usually take the form of ringing, hissing, or buzzing, but other less common types of perceptions have also been reported (19,76). The underlying causes of tinnitus are not fully clear, but it is believed that deafferentation of the auditory path plays a major role in the etiology of tinnitus (9,11). Although tinnitus is usually a benign condition, its bothersome manifestation, which is estimated to affect 1% of the population (23), can be debilitating (22). Tinnitus may be subdivided into two categories: acute and chronic. The first describes a somewhat common phenomenon, usually lasting a few seconds or minutes, where the phantom sounds are perceived after some insult to the auditory system (e.g., listening to loud music). The second category refers to uninterrupted perception for at least 6 months. In its chronic presentation, tinnitus is unlikely to disappear, but recent evidence suggests that chronic tinnitus may indeed disappear, but such occurrences are rare (Chapter 3, (144). No currently available treatment can reliably and effectively suppress the phantom perception, and therefore most strategies seek to reduce tinnitus-related distress (18).

There is a growing consensus that tinnitus is a heterogeneous condition, and that it may have an important effect on treatment response (66,67). For example, the heritability of tinnitus differs depending on its laterality (i.e., whether the sounds are perceived in one or both ears) and the patient's gender. Using data from the Swedish Twin Cohort, Maas and colleagues showed that tinnitus heritability among males suffering from bilateral tinnitus was 68%, whereas the heritability for unilateral tinnitus was 27% disregarding gender (65). Those

findings indicate that etiological factors of tinnitus may differ depending on the type of tinnitus. Overall, it is of great interest to identify which markers are relevant for treatment response. For instance, evidence suggests that personality traits may explain treatment response from internet-delivered cognitive behavior therapy (68), but not acoustic stimulation (69). The discrepancies in those results have been accredited to tinnitus heterogeneity, which would account for the uniqueness of each individual experiences the phantom perception (56,67).

Modeling data at the individual level, often referred to as idiographic modelling, increased in popularity in the field of psychopathology with the advent of ecological momentary assessment (EMA) and newer statistical techniques to extract individualized information from intensive, longitudinal data (49). Unified structural equation modeling (uSEM, 48) is an example of such technique. uSEM combines structural equation modelling and vector autoregression, which, in turn, can be used to extract autoregressive and cross-lagged effects from time series. As a result, uSEM has been widely used in psychological and medical science to estimate contemporaneous and lagged effects from time series data (e.g., brain activity from functional magnetic resonance imaging and behavioral/emotional fluctuations recorded by EMA), both at the individual and group levels. The validity and reliability of idiographic methods from ambulatory data (e.g., EMA, experience sampling methodology, ambulatory psychophysiology, daily diaries, passive sensing) has been previously discussed (A. G. C. Wright & Woods, 2020). These techniques have been used for a series of psychopathological conditions, including personality and internalizing disorders (39,42,145), but not in tinnitus.

Conversely, EMA has been used in the tinnitus field with nomothetic study designs, that is, studies focusing on group-level analysis. Examples of such include the ones conducted by Probst and colleagues (52), who modeled patterns on daily fluctuation in tinnitus, who identified a mediation role of tinnitus loudness on stress (51), and Pryss and colleagues (53) who showed that patients often have recollection bias with regards to tinnitus fluctuation throughout the day. However, studies extracting insights at the individual level using EMA methodology remains underexplored.

We used EMA from the Track Your Tinnitus mobile app to investigate two research questions. In the first study, we investigated whether states such as tinnitus loudness, distress, and mood impact auto- or cross-correlates throughout subsequent days at the group level (i.e., nomethetic dimension). For this analysis, auto- and cross-lagged correlations were used (146). Second, we modeled data at the individual level using linear regressions with elastic net regularization for each unique time-series with both tinnitus distress and tinnitus loudness as dependent variables.

Last, we used uSEM to obtain unique models for each participant on the contemporaneous and lagged effects between the variables collected with EMA.

Methods

Data preparation

The data analyzed in this study was collected from the TYT app between 2014 and 2020. The app is freely available on both Android and iOS mobile devices (available as TrackYourTinnitus). Although providing daily information about tinnitus could increase the distress from users by driving their attention repeatedly to their tinnitus, a previous study showed that using the TYT does not have a negative impact on the user (55). Informed consent was obtained from users to have their data anonymously used for scientific purposes. The study was approved by the ethics committee of the Faculty of Medicine, University of Regensburg (Study approval number 15-101-0204).

During the registration, users had to fill in two questionnaires, the Mini-Tinnitus Questionnaire (147) and the Tinnitus Sample Case History Questionnaire, TSCHQ (132), plus a question about the user's worse tinnitus-related symptom. The Mini-TQ is usually used in clinical trials and ambulatory assessment as a screening tool for tinnitus-related distress. The questionnaire possesses good psychometric properties (correlation > 0.9 with the original 52-item Tinnitus Questionnaire, a test-retest reliability of 0.89 and Cronbach's alpha of 0.9) and consists of 12 questions. The second questionnaire is part of an international effort to standardize data collection and reporting in tinnitus research and is also a standard screening tool. The TSCHQ consists of 34 questions related to tinnitus characteristics (e.g., the type of perceived sounds, duration of tinnitus, subjective loudness), life history (e.g., whether family members also suffer from tinnitus), and common comorbidities (e.g., headaches, insomnia, hearing aids). Both questionnaires were used for describing our sample (Table 4.1).

Regarding the EMA, users could set push notifications on or off and were allowed to report their status at any time point and as much as they wanted. For the study 1, only time series data with at least 10 days of sequential observation were included in the analysis. More stringent cut-off points, such as 20 or 50 days of interrupted observations did not change the results obtained but decreased the sample size considerably (data not shown). If the same user had two sequences of observations lasting at least 10 days, those two sequences were analyzed separately. Different strategies were explored when dealing with multiple entries from a given user in the same day (i.e., calculating the mean, or median values, the maximum or minimum values for that specific day, or selecting the first or last observations). None of those methods

to account for multiple observations in the same day changed the results (data not shown). The results reported in this article were obtained by selecting the first observation of each day. Missing values from a given sequence were imputed using the "aregImpute" function from the Hmisc package with default settings (supplemental material Figure 4.1 shows the percentage of missing values per item).

Statistical Analysis

Auto- and Cross-correlation

Autocorrelation can be described as the correlation of a variable with itself at differing time lags. For this study, the time lag consisted of different calendar days (see above). Mathematically, the auto correlation, r_k, can be expressed as:

$$r_k = \frac{c_k}{c_0} \qquad Equation\ 1$$

Where C0 represents the autocovariance of a variable at lag 0, and Ck represents the autocovariance for lag k, which can be mathematically described as:

$$c_k = \frac{1}{n}\sum_{t-1}^{n-k}(x_t - \bar{x})(x_{t+k} - \bar{x}) \qquad Equatio\ 2$$

Where k represents a lag (each lag representing one day), t, represents the t^{th} variable and $\bar{x}$ represents the mean of variable x . In a similar vein, cross-correlation can be described as the correlation between two variables at different lags. It, it can be mathematically expressed as:

$$r_k^{x\,y} = \frac{g_k^{xy}}{\sqrt{\sigma_x \sigma_y}} \qquad Equation\ 3$$

Where sigma represents the standard deviation of variables x and y, and g represents cross-correlation function, which can be represented as:

$$g_k^{xy} = \frac{1}{n}\sum_{t=1}^{n-k}(y_t - \bar{y})(x_{t+k} - \bar{x}) \qquad Equation\ 4$$

Where n represents the sample size, k represents the lag, t represents the t^{th} variable, and both $\bar{x}$ and $\bar{y}$ represents the mean of variables x and y. Auto- and cross-correlation were used to investigate whether the variables presented at table 4.2 were associated with one another at the group level.

Elastic net regularization

Elastic net is an increasingly popular method that accounts for datasets with large numbers of variables, especially when those may be correlated, which, in turn, may lead to overfitting of statistical models. The method combines two penalizing terms, L1 and L2, and can be mathematically described as:

$$\sum_{i=1}^{n} \frac{(y_i - x_i^J)^2}{2n} + \lambda\left(\frac{1-\alpha}{2} + \sum_{j=1}^{m} \hat{\beta}_j^2 + \alpha \sum_{j=1}^{m} |\hat{\beta}|\right) \qquad Equation\ 5$$

Where n is the sample size, i represents the i^{th} observation, j represents the j^{th} predictor, beta hat represents the estimated coefficients, lambda is the penalizing coefficient, and alpha is a tuning parameter: if set to 0, a ridge term is obtained, if set to 1, a lasso term is obtained. The first term represents the commonly used ordinal least square (OLS) regression, the second represents a L1 penalization (also known as ridge regression) and the third term represents a L2 penalization (also known as lasso). If lambda is estimated as 0, the output is a regular OLS regression. If not, lambda must assume a positive value in which the estimates from the regression are constrained. If a ridge penalization is used, the coefficients of regression are shrunk to values different than 0. Conversely, if a lasso regularization is used, coefficients may be set to 0, which functions as feature selection method. This powerful feature of elastic net to automatically select variables by setting some of them to 0 was used to build individualised models for each sequence of observations to predict both LO and TD.

All the variables in regression were modeled as linearly related to the outcome measure. A 10-fold cross-validation was computed to estimate lambda with the default settings using the cv.glmnet function. The final model was selected based on the lambda one standard error from the minimum for parsimonious results (70).

Unified Structural Equation Modelling

uSEM estimates contemporaneous and lagged relations (of order Q) with the following formula:

$$\eta_t = A\eta_t + \sum_{q=1}^{Q} \emptyset_q \eta_{t-q} + \zeta_t \qquad Equation\ 6$$

Where η_t the time-series of length t, A and φ_q contain a the (p, p)-dimension matrix of contemporaneous and lagged (at lag q) relations. Estimates are obtained from the R package GIMME (48)

All analyses were conducted in R (version 4.0.1, R Core Team, 2018) and supporting packages (90,148–156). Auto- and cross-correlations were conducted with an in-house script adapted by JB from the functions “acf” and “ccf” available in R.

	Analysis 1 (N=488)	Analysis 2 (N=32)
Age		
Mean (SD)	53.6 (13.0)	55.4 (7.09)
Median [Min, Max]	52.5 [2.00, 83.0]	54.0 [40.0, 65.0]
Missing	294 (60.2%)	18 (56.2%)
Tinnitus Onset (Months)		
Mean (SD)	17.4 (13.3)	17.6 (11.9)
Median [Min, Max]	15.0 [1.20, 67.9]	15.0 [6.00, 47.0]
Missing	154 (31.6%)	17 (53.1%)
Gender		
Female	360 (73.8%)	28 (87.5%)
Male	113 (23.2%)	4 (12.5%)
Missing	15 (3.1%)	-
Subjective Tinnitus Loudness		
Mean (SD)	49.2 (29.4)	49.5 (29.8)
Median [Min, Max]	52.0 [0, 100]	52.0 [0.5, 94.0]
Missing	91 (18.6%)	7 (21.9%)
Type of Perceived Sound		
crickets	39 (8.0%)	3 (9.4%)
noise	90 (18.4%)	8 (25.0%)
other	20 (4.1%)	1 (3.1%)
tone	318 (65.2%)	19 (59.4%)
Missing	21 (4.3%)	1 (3.1%)
Tinnitus Onset		
Abrupt	253 (51.8%)	19 (59.4%)
Gradual	220 (45.1%)	13 (40.6%)
Missing	15 (3.1%)	-
Mini-TQ		
Mean (SD)	13.9 (5.63)	13.9 (4.90)
Median [Min, Max]	15.0 [0, 24.0]	12.5 [3.00, 23.0]
Missing	18 (3.7%)	-

Table 4.1 Sample demographics during registration.

Results

Table 4.1 summarizes the demographics of the sample from both studies. From the original dataset, 57% of the data was excluded from the analysis as data was not obtained from that

sequence for at least 10 days uninterrupted (supplementary Figure 4.2). Thus, the sample of study 1 consisted of 488 unique sequences from 278 users). Following the guidelines of the GIMME package authors, only sequences with at least 60 days of uninterrupted usage were included in the analysis for study 2. The sample size consisted of 32 sequences, all from unique users. Table 4.2 shows how EMA questions were formulated (translated to English from German), with their abbreviations which are used henceforward. Two questions, namely questions 1 and 8, were excluded from the analysis as they were dichotomous.

Item	Translation of the German Question	Abbreviation
Question 2	How loud is the tinnitus right now?	LO
Question 3	How stressful is the tinnitus right now?	TD
Question 4	How is your mood right now?	MO
Question 5	How is your arousal right now?	AR
Question 6	Do you feel stressed right now?	ST
Question 7	How much did you concentrate on the things you are doing right now?	CO

Table 4.2 Questions of TYT included in the study. Question 1 ("Do you perceive your tinnitus right now?") and question 8 ("Do you feel irritable right now?") were excluded as their answers were dichotomous

Auto- and/or cross-correlated between tinnitus loudness, distress, and variables related to mood

First, we investigated whether the 6 variables were auto-correlated (Figure 4.1). None of the lagged were outside the 95% confidence interval (red dashed lines), suggesting no autocorrelation. Auto-correlations at lag 0 were always 1, as the nominators and denominators were identical in those cases (Equation 1). Next, we investigated whether there was cross-correlation between variables (Figure 4.2). Similar to the previous results, no correlation at lags > 0 were observed. However, corroborating previous findings, we observed contemporaneous correlations (i.e., at lag 0) between LO & TD, TD & MO, LO & ST, TD & ST, MO & AR, MO & ST, and AR & ST.

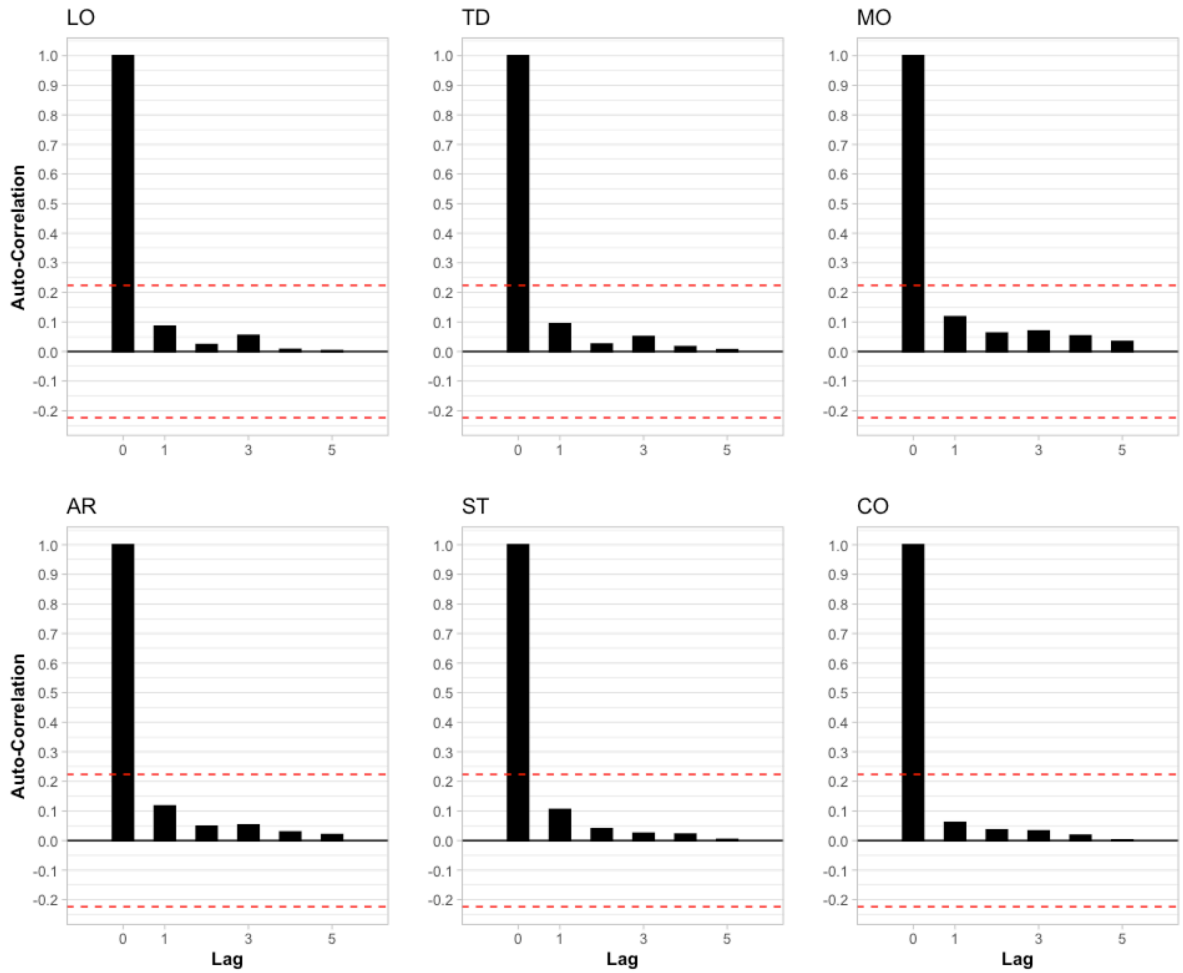

Figure 4.1 Auto correlation of the six variables included in the analysis. Each lag represents a different day of usage. Red dashed lines represent the 95% confidence interval. LO: Loudness; TD: Tinnitus Distress; MO: Mood; AR: Arousal; ST: Stress; CO: Concentration

Variance explained by elastic net regressions

Next, we investigated whether elastic net could be used to make individualized inferences about LO (Figures 4.3a-c) and TD (Figures 4.3d-f). For this analysis, contemporaneous variables and lagged variables from the previous days (acronyms ending with "1" in Figures 4.3a, 4.3c, 4.3d and 4.3f) were used as independent variables in regression setups. For 27% and 31% of the sample, no predictors of LO and TD were found (Figures 4.3a and 4.3d, respectively). For the remaining the sample, the R^2 for each time-series varied considerably (Figures 4.3b and 4.3e). Figures 4.3c and 4.3f present those findings with boxplots. Whereas certain variables were almost only positively associated with the outcome measure (e.g., LO, TD and ST), other variables interestingly presented both positive and negative valence across the sample (e.g., CO and LO).

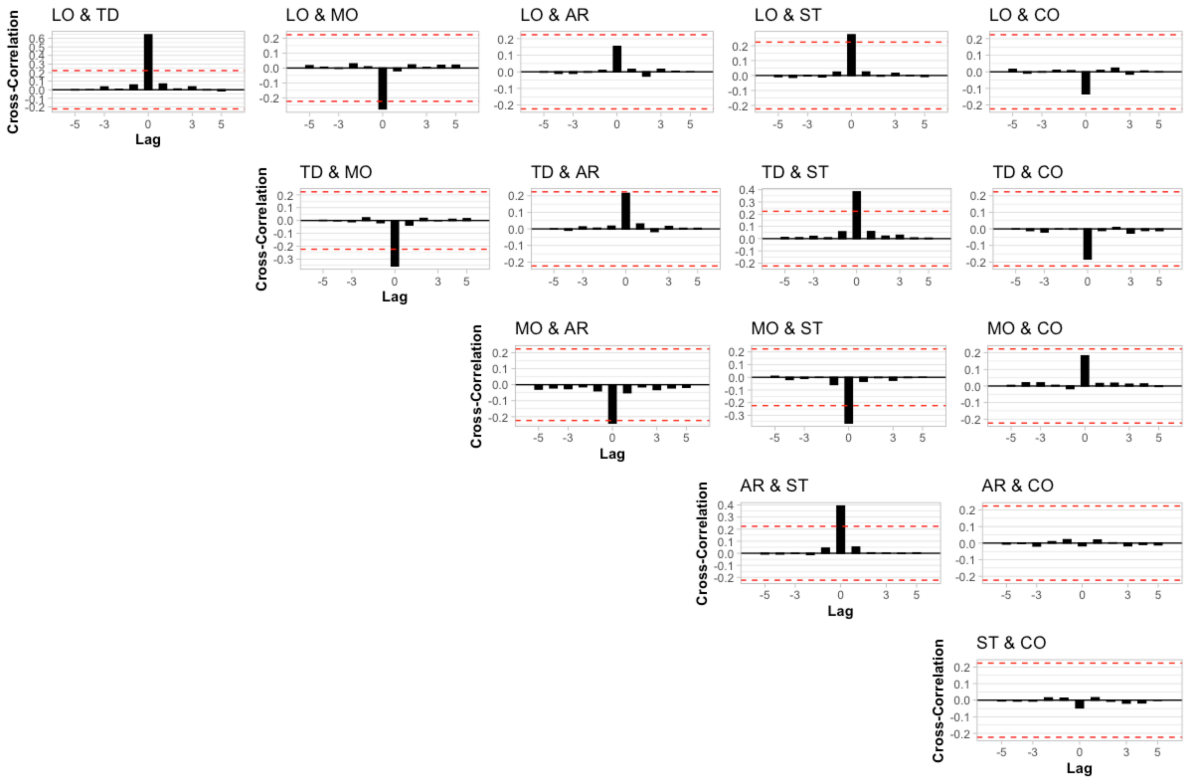

Figure 4.2 Cross correlation of the potential combinations of the six variables included in the analysis. Each lag represents a different day of usage. Red dashed lines represent the 95% confidence interval. LO: Loudness; TD: Tinnitus Distress; MO: Mood; AR: Arousal; ST: Stress; CO: Concentration

Idiographic modelling with uSEM

The left column of Figure 4.3 shows the mean values and their dispersion with kernel plots; the middle column shows the fluctuation of those variables through time with time-series plots; the right column depicts the contemporaneous relation between variables with correlational heat maps. Overall, those four examples highlight how symptoms are uniquely burdensome, how they fluctuate over time, and how they interact with each other. Moreover, the figures highlight the high within and between variability across the sample, which is leveraged by uSEM during estimation.

Following current guidelines (48), only time-series with at least 60 sequential observations were included in this analysis. By using this cut-off, individual time-series from 32 users were included in the analysis. Data from four users were arbitrarily selected to highlight how heterogeneously those variables manifest themselves over time.

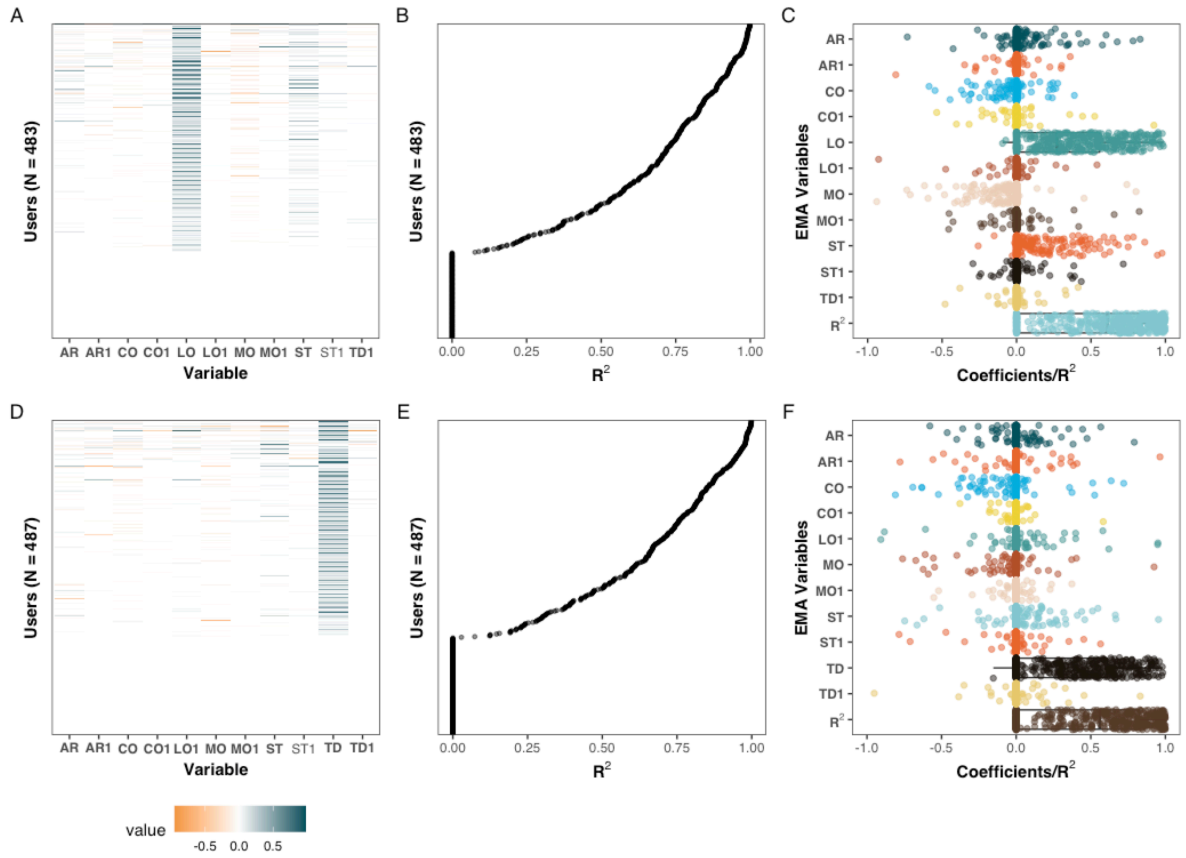

Figure 4.3 Elastic net models with TD (A-C) and LO (D-F) as dependent variable. Sequences which the dependent variable had no variability were excluded from this analysis. The users on the Y axis of figures 4.3 A-B, and D-E are aligned. Left column: standardized coefficients uniquely estimated for each sequence (user). Middle column: amount of variance explained, measured with R^2, for each unique sequence. Right column: Standardized coefficients from A and D, and R^2, from B and E are presented with box and dot plots.

Figure 4.5 shows the models estimated by uSEM of the same four individuals from Figure 4.4. The model failed to converge in three cases, and therefore those cases were not included in the remaining analysis. Apart from those cases, the models had adequate fit: (average: chi-square: 80.2, df = 44, CFI = 0.94, RMSEA = 0.07, NNFI = 0.9, SRMR = 9,95). The variable "Day", that is, the position in the time series was encoded as an exogeneous variable, meaning that the variable could predict any other variables, but not the other way and had regression paths retrieved for all the four cases (Figure 4.5). Both contemporaneous (solid) and lagged (dashed) paths were obtained across all cases. Although some paths were shared across subjects, e.g., the effect of TD on LO, other dynamics were idiographic (e.g., whereas ST had a positive contemporaneous effect on TD for user A, the relationship was inversed for user D, and no relationship was seen for the other two users).

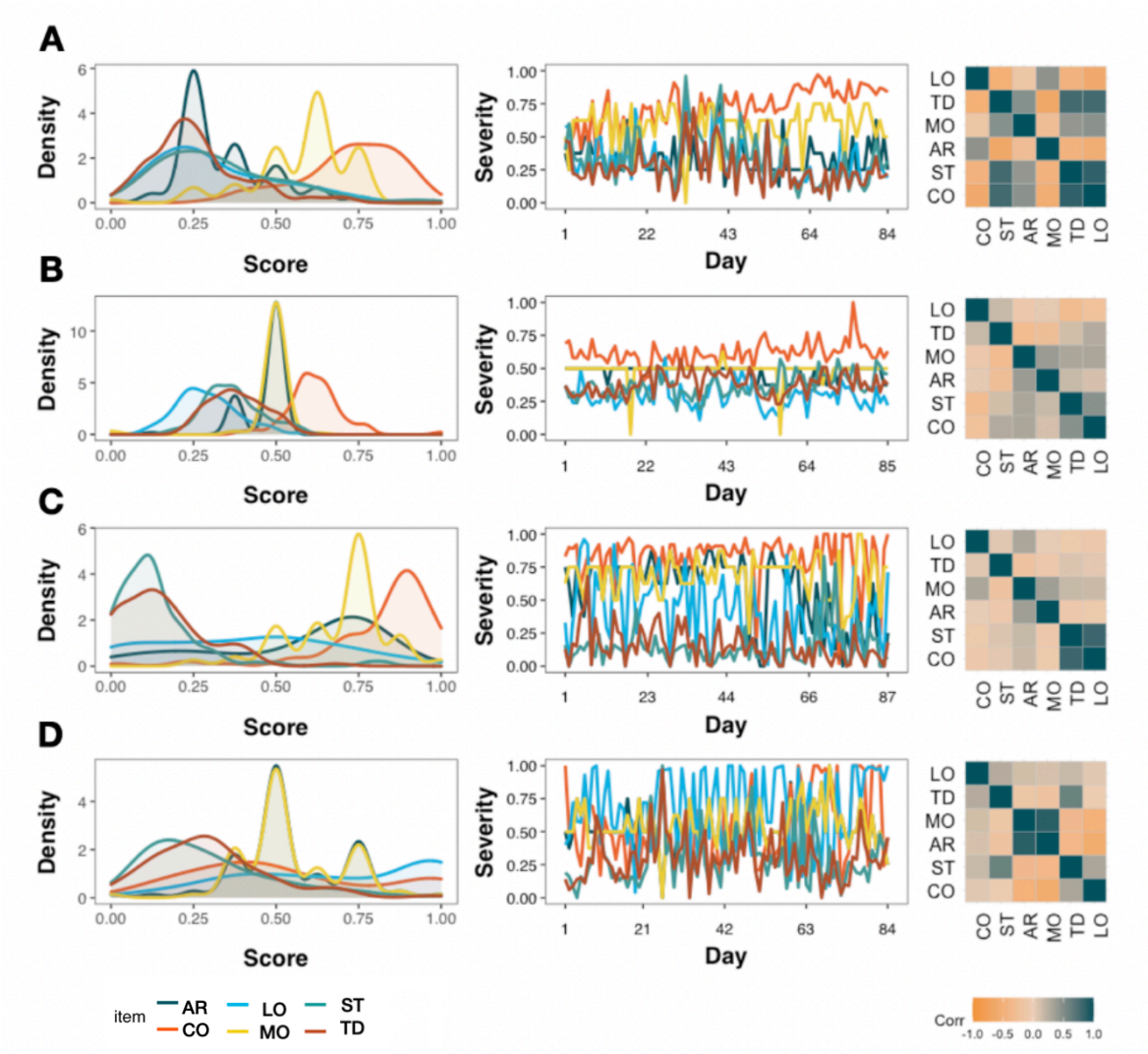

Figure 3.4 Variability across four TYT user, each represented in one row (A-D) who completed around 85 days of continuous EMA. Density plots (left), time series (middle) and correlation heatmaps (right) highlight how uniquely arousal (AR), concentration (CO), loudness (LO), mood (MO), stress (ST), and TD (tinnitus distress) interact with each other.

Discussion

In this study, we investigated the nomothetic and idiographic dimensions of tinnitus. We started by showing that at the group level no evidence for auto- or cross-correlation between six variables, namely loudness, tinnitus distress, concentration, mood and arousal could be observed. However, modelling data at the individual level revealed that LO and TD was auto- and cross-lagged from one day to another for several individuals. Figure 4.4 highlights the complex, intricate relationship between those variables in 4 individuals. Lastly, we used uSEM to highlight the unique interplay of those variables, effectively modelling how heterogeneously tinnitus manifests itself over time.

Our results provide a template on how to model LO and TD at the individual level (Figures 4.3, 4.4, 4.5). The interplay between those variables constitutes a complex mosaic on how tinnitus is experienced; although the uniqueness of subjective experiencing of tinnitus has been widely acknowledged (18,56,67), empirical studies demonstrating this complex relation were missing. Additionally, by using uSEM, we were able to incorporate the effect of time in the models, a critical component of experiencing tinnitus (52).

Corroborating previous findings, we showed a positive association between stress, loudness, and tinnitus loudness (51,157). Interestingly, we also observed that emotional arousal and concentration had ambivalent associations with both loudness and distress (figures 4.3c and 4.3f). Tinnitus is known to have potential negative consequences on cognition (158,159), but this is the first time that a positive association between CO and TD/LO is shown. Future studies should further investigate this seemingly paradoxical relation.

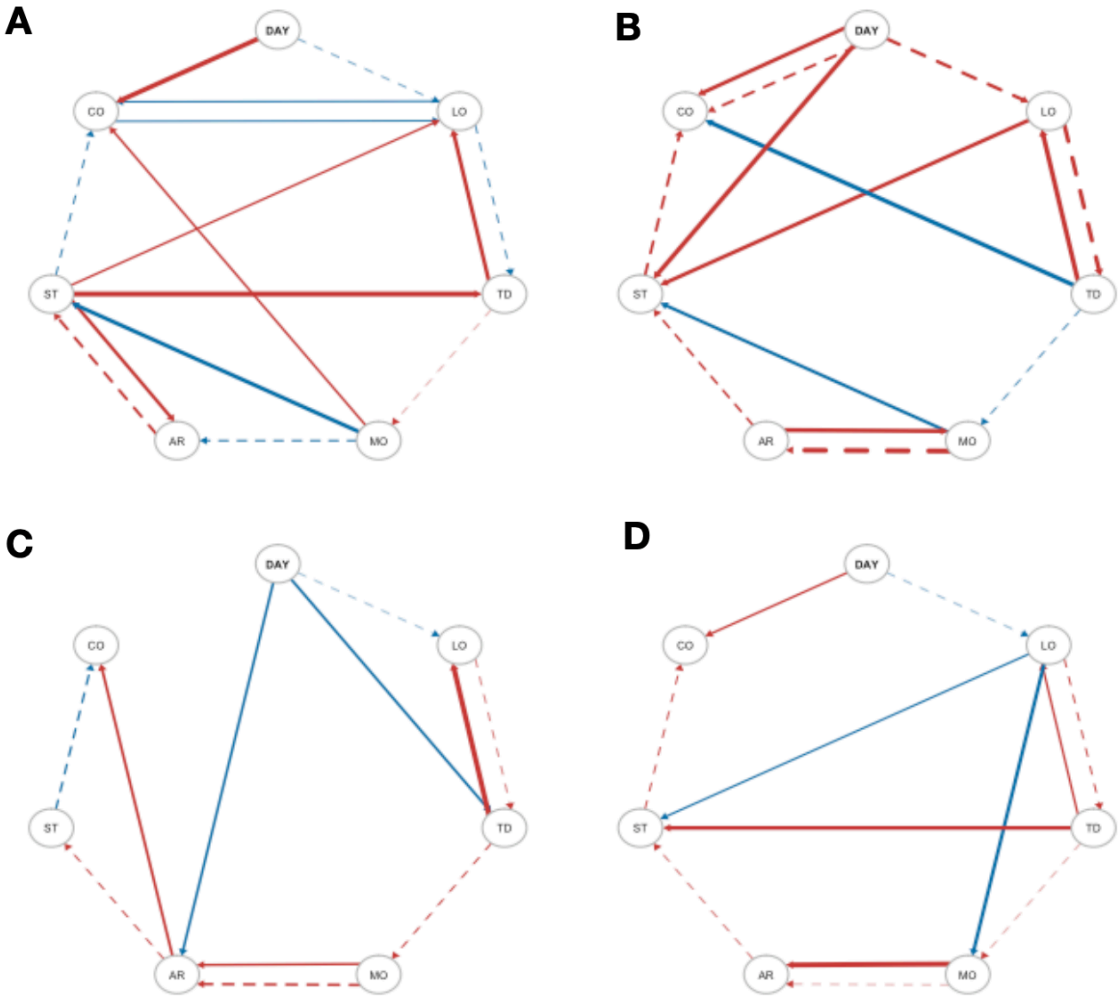

Figure 4.5 Model estimated by uSEM. Solid lines represent contemporaneous effect (lag = 0), and dashed lines represent lagged effects (lag >= 1). Circles represent the variables included in the study, plus the exogeneous variable "day". As an exogeneous variable, "day", that is, the day in the sequence of observations, could predict

other variables, but not be predicted from them. Arrows indicate the direction of the relationship. Red arrows indicate positive regression paths, and blue lines indicate negative regression paths. The same 4 individuals from Figure 4.4 are displayed.

Another potential future line of research may investigate the benefits from just-in-time adaptive intervention (JITAI) (160). JITAI uses mobile sensing to deliver tailored interventions based on the unique fluctuations recorded by EMA. Such system has been used in several fields, including, physical health, addiction and mental care research, but not in tinnitus (161). For example, tailored interventions could be delivered for patients whose LO and/or TD are auto- or cross-correlated across days: once the algorithm detects a potential spike in LO or ST in the next day, an intervention could be administered. Such interventions could include psychoeducation tips for tinnitus coping (162), sound therapy (163), internet-delivered cognitive behavior techniques (164), or meditation techniques (165). Future studies could include variables such as coping, positive, and negative affect (166) on quality of life using EMA (167,168).

Methodological aspects should be considered when interpreting these results. Missing values constitute a main challenge for researchers, including those using EMA. A recent study investigated the causes for discontinuing app usage (169), but no clear predictors of adherence to app usage on the long run were found. Biased results cannot be discarded as only a fraction of users used the app for more than 10 days (supplemental material). In this article we used a popular, robust method for data imputation, but empirical evidence that this is the optimal method for imputation is not available.

In summary, we provide evidence that the variables collected with EMA had both a contemporaneous and lagged effect, but the interplay between those variables was unique across subjects.

Discussion

This thesis comprised four articles that advance the current understanding of tinnitus heterogeneity. In the first study (Chapter 1), I showed that variables such as demographics, tinnitus characteristics, and treatment characteristics could partially predict the outcome of 26 different tinnitus-related treatments. One of the main strengths of this study was to assess heterogeneity in terms of treatment response (71). Future studies could add to those results by evaluating transdiagnostic markers as predictors of treatment response (170–173).

Next, we showed that personality traits are also relevant factors of heterogeneity, as they contribute to the course of tinnitus over the years (Chapter 2). Several other factors that may explain tinnitus suffering remain under-investigated; Genitsaridi and colleagues (71) conducted a literature survey on what characteristics are often used to subtype tinnitus. The authors found that usually researchers tend to mainly focus on tinnitus characteristics and basic demographics (e.g., age, gender), whereas psychopathological profiles are seldom investigated (see section *heterogeneity in context*). Furthermore, modelling environmental stressors empirically (as opposed to self-reported through surveys/questionnaires, such as perceived loudness at the workplace) remains heavily understudied. Variables such as noise and environmental pollution may interplay with subjective factors (e.g., stress, sleep), which, in turn could affect tinnitus. It is increasingly common for studies to combine information from environmental databases with phenotypes from biobanks with geographic information (see section *future directions for future research* below), which may in the future prove itself as a critical component to understand the heterogeneous manifestation of bothersome tinnitus.

A significant finding from the third study (Chapter 3) was that tinnitus may remit, even in chronic individuals suffering from the condition for years. While previously known from anecdotal reports, these results adds to the emerging evidence that tinnitus may remit also in its chronic manifestation (144). We also found that tinnitus characteristics such as subjective loudness, laterality, type of perceived noise, loudness fluctuation throughout the day, and pitch frequency usually remain stable over the years. Lastly, we found that distress tends to reduce over time, but no factors promoting or deterring tinnitus habituation were identified in this study.

However, habituation was not associated with alterations in quality of life. Therefore, more work is recommended to evaluate to which extent tinnitus distress as a construct should be used as an outcome measure for treatment response. Such a recommendation is particularly relevant

given the importance quality of life has gained as a main outcome measure for clinical trials (173), and given the fact that clinically available treatments cannot suppress tinnitus in the long term. Lastly, future studies should investigate other potential factors that may contribute to (non)habituation, as they may deem relevant for prognosis.

In the fourth study (Chapter 4), I showed how the experiencing tinnitus may vary across individuals, and how null effects at the group level may be misleading. No auto- or cross-correlation among six different variables (Figures 4.1 and 4.2) collected from an intense sampling longitudinal study design was seen. The results demonstrate that tinnitus may be experienced differently. Although that was known from a clinical standpoint, scientific articles were restricted to conceptual arguments for unique patterns of experiencing (56,67).

Future directions for tinnitus research

Simoes and colleagues (in preparation) identified some of the main challenges hindering progress towards a cure for tinnitus and proposed solutions for those challenges. The review summarizes the main challenges in key areas of tinnitus research, including epidemiology, risk factors, neurophysiological mechanisms, assessment, treatment development, and heterogeneity. From those areas, four suggestions are provided, namely:

1) The establishment of multidisciplinary, multicenter collaborations such as ESIT (78), TIN-ACT (174), TIGER (175), and UNITI (176);

2) Increased efforts to systematically synthesize existing knowledge. This could be accomplished through systematic literature reviews, such as the recently published review by Genitsaridi and colleagues systematically assessing what variables are usually included in models of tinnitus heterogeneity (71);

3) Co-joint efforts to standardize data collection, analysis, reporting and outcome measures. For instance, Hall (177) provides suggestions on how to design clinical trials to increase the evidence of their findings, whereas the TRI database provides a platform for standardizing data collection and analysis (178);

4) The collection and analysis of large datasets with thorough phenotyping could drive the field of tinnitus towards new insights. Biobanks like the UK Biobank (61) contain data from dozens of thousands of tinnitus bearers, including comorbidities, demographics, genetic data and neuroimaging, but remains underexplored.

In the following paragraphs, some additional potential directions for future research are offered, with a special focus on untangling tinnitus heterogeneity. One recurring topic in the social sciences, including psychology, is the often the misplaced convolution between statistical models and theoretical models (Fried, 2020). In this context, a theoretical model

provides a framework that can be understood and applied effectively and coherently (180). Following this definition, Cima (22) is one of the few in the psychological sciences proposing a formal model for tinnitus with the so-called fear-avoidance framework. This framework is mostly guided by insights from cognitive behavior therapy and aims to explain why tinnitus may be bothersome and how to treat it. Such formal model is necessary for falsifying hypothesis, a critical step of the scientific method. Without it, researchers may be led to heavily rely on statistical methods to support their claims. Such unaccounted reliance on statistical methods may unintendedly lead to the publication of null findings (Fried, 2020), which, in turn, leads to several shortcomings (181).

For instance, none of the studies using data-driven methods to subtype tinnitus identified by Genitsaridi and colleagues (71) validated internally or externally, a critical step in evaluating the robustness of the models. In other words, it is likely that none of those results are replicable. An inpiring succesful alternative example on how to combine theory and data-driven statistical methods is provided by Blanken and colleagues (182). Prior to conducting the analysis itself, the authors identified in a literature survey all the potentially relevant variables for subtyping insomnia, and only then collected the identified variables in a large (i.e., more than 10,000 participants) sample. Additionally, the authors made sure to test their model robustness by replicating their findings in a second, independent clinical sample.

From a neurophysiological standpoint, there are diverse models explaining the neurophysiological substrates of tinnitus (141). Although no consensus has been reached yet on the neural mechanisms of tinnitus, those models can be evaluated, further developed or rejected based on the results from empirical testing. The study conducted by Demarchi and colleagues (183), in which tonotopic information is shown to be predicted by the brain even without bottom-up auditory input – a feature speculated from previous findings in different brain areas and from the free-energy principle (15), but never empirically shown – exemplifies a successful combination of data-driven methods and formal theoretical theories. As a potential bridge between psychiatry and neurosciences, Huys and colleagues (184) proposed a new discipline called Computational Psychiatry, which would leverage developments of computational and statistical methods, such as elastic net regularization (Chapter 4, Equation 4.5), and combine with formal theory testing to improve understanding, prediction and treatment of mental illness.

The ongoing shift in psychopathology towards a more quantitative field represents another opportunity for tinnitus research. This shift has been led by two movements: one relying on factor analysis to compose a hierarchical structure of psychopathology, and the second one

relying on graph theory to describe associations between symptoms, behaviors, emotions, etc. through network metrics (47). In the following, a brief description of those two perspectives is given alongside prospects for future research.

Motivated by the inconsistencies of traditional diagnoses in mental health, researchers have been applying factor analysis of mental health comorbidities to reveal a hierarchical structural of mental phenomena. Those efforts culminated in the Hierarchical Taxonomy of Psychopathology (HiTOP) model (39,40,185), which aims to replace traditional, and to a large degree arbitrary, nosological categories of mental health with a validated, empirical-driven nosology of psychopathology. This hierarchical model has been proposed to have 6 levels, each identified consistently with factor analysis (40). Those levels are: (1) symptoms/signs/maladaptive behaviors (e.g., tinnitus-related avoidance, tinnitus-related distress), (2) symptom components and maladaptive traits, which bundles symptomatic behavior together (recent articles have combined the first two levels into one level (186), (3) dimensional syndromes (or empirical syndromes, such anxiety, personality psychotic syndromes, etc.), (4) dimensional syndromes (e.g., fear or distress dimensions), (5) broad spectra (e.g., internalizing and externalizing), and (6) super-spectra (the psychopathological factor, p) (40). Importantly, all those factors/subfactors are compiled based on current evidence, and updates are constantly made in light of new findings (187). A visual representation of this hierarchy is provided in Figure 6.1. In this context, bothersome tinnitus symptoms and its commonly co-occurring comorbidities (e.g., anxiety, insomnia, depression, etc.) would occupy the lower tiers of the hierarchical structure, which, in turn, would be explained quantitatively by higher-order phenomena unique to each individual in its intensity. Importantly, the HiTOP model can integrate biomarkers across different fields, such as neuroimaging (145) and genetics (188). Given the initial reliability and validity shown by the HiTOP model (42), alike to the reliability and validity shown by the empirically-driven five-factor model of personality (73,101), mapping the psychopathological structure of tinnitus patients should be encouraged. Guidelines for implementing the HiTOP model into clinical and research settings are also available (187).

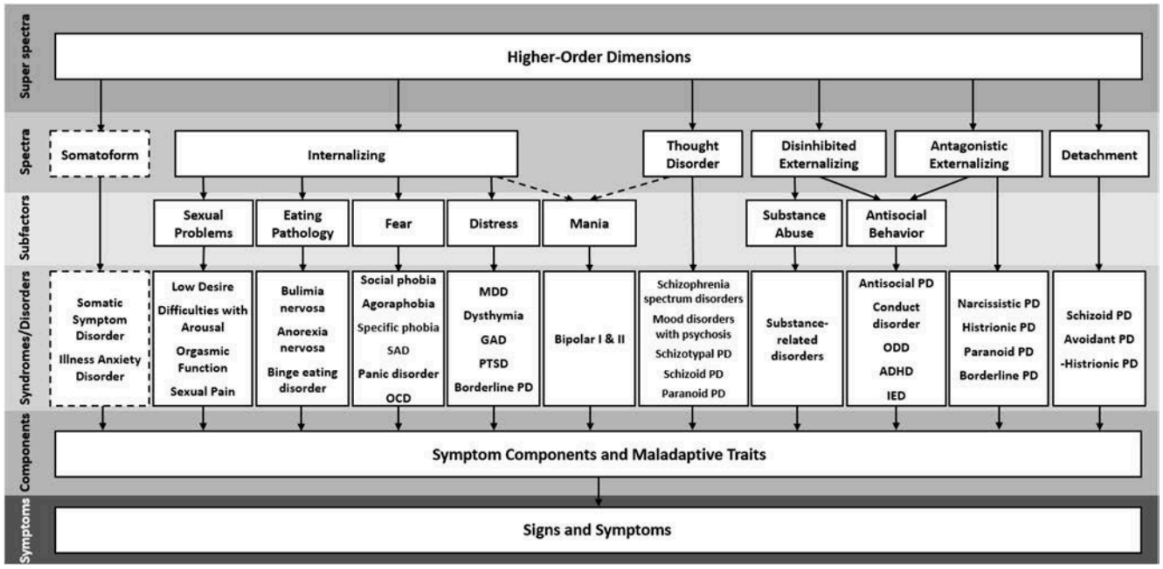

Figure 5.1 Hiearhical Taxonomy of Psychopathology. Dashed lines represents paths/components currently under investigation. Figure extracted from Kotov et. al 2017[9] (40).

Parallel to the developments from the HiTOP, researchers have leverageg graph theory to incorporate network science into psychopathology (189). In this context, mental phenomena are causally modeled as the interplay between symptoms. An example of a network model is provided with data from tinnitus patients in Figure 5.2. This modelling technique has been used in clinical trials, where it has been shown that variables with high centrality, that is, with many input and output connections, to be preferential targets to decrease symptoms in major depression patients (42). For example, Figure 5.2 suggests that aspects quality of life, emotional and cognitive aspects of tinnitus to be preferred targets for interventions for improving tinnitus-related distress (albeit an empirical analysis would be necessary to evaluate the centrality of those nodes). There is an active discussion between researchers and clinicians on the promises and limitations of using network analysis in the context of psychopathology (42). Those discussions are important given the novelty of those methods, and refinements, standardizations and validations are expected as a result.

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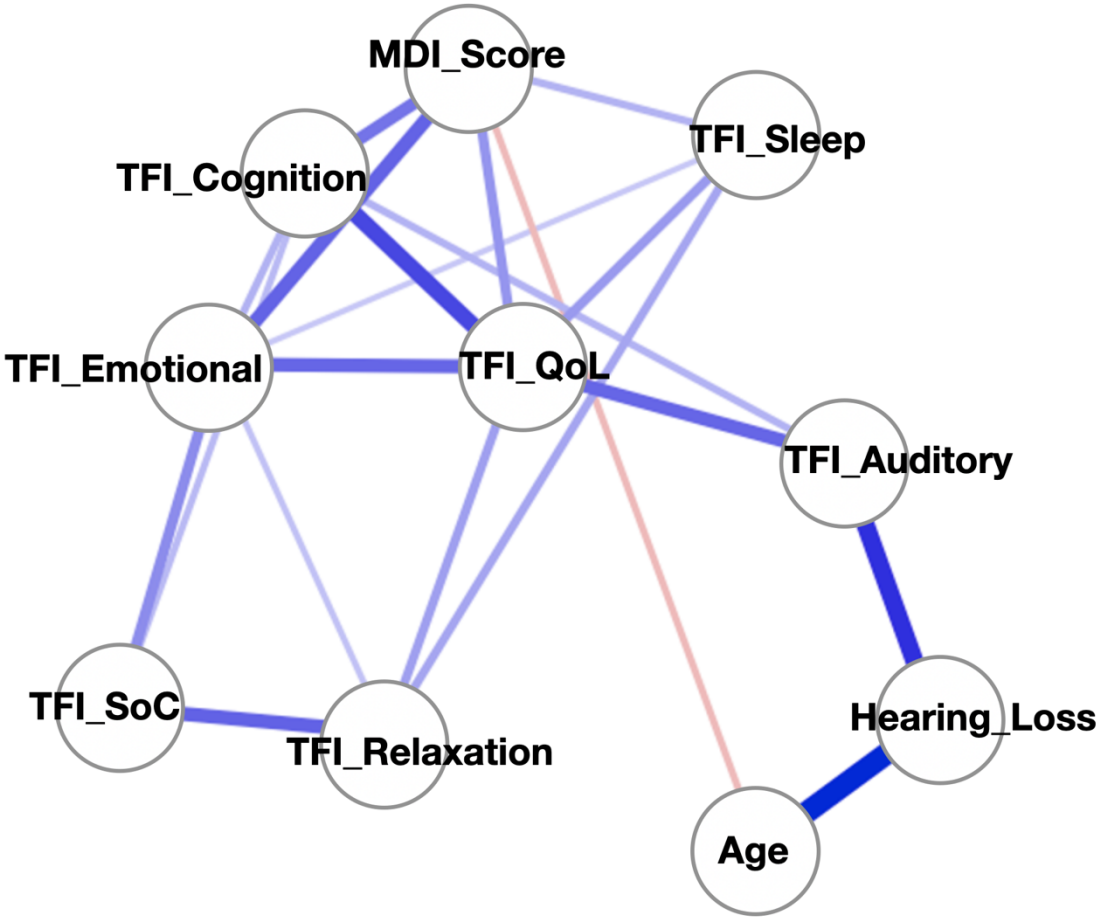

Figure 5.2 Network analysis of 454 tinnitus patients from the TRI database. Ambulatory data from patients from the Tinnitus Center Regensburg was analysed with the bootnet and qgraph packages (190,191). Nodes represent variables (hearing loss, age, depression as measured by the Major Depression Inventory, and the subfactors of the Tinnitus Functional Index). Blue and red lines represent positive and negative associations. Line thickness and saturation represent the strength of the association. Quality of Life (TFI_QoLl) presents the highest centrality in the symptomatic network. TFI_SoC: Sense of Control. This data has not been published yet.

However, tinnitus researchers remain absent from those important methodological and conceptual discussions. Standardized multiple clinical trials (176) could investigate the stability of such networks across different samples. Additionally, network models provide an attractive way that incorporates covariates to evaluate the outcome of clinical trials by assessing how the relation between variable changes over time with graph-related measures.

Another important aspect worth considering is the quality and the quantity of the data being used for modeling tinnitus heterogeneity. For instance, stratification plays an important on the genetic makeup of the condition (65), and large samples such as the ones seen in public datasets and biobanks are necessary to detect such phenomena. Tinnitus researchers should feel encouraged to use data from biobanks. Indeed, the call to do so has already been made, but the

pace of articles using this rich data remains meager (192). An informal consortium was formed in 2020 with members of the University of Nottingham, University of Regensburg (including the author of this dissertation), the British Tinnitus Association, and of the self-help web platform TinnitusTalk to map and publish which biobanks have tinnitus-related data. Furthermore, the consortium aims to identify other variables that may be of interest to epidemiologists and geneticist such as phenotypes (e.g., common comorbidities, neuroimaging data, genetic markers, dietary habits, etc.) and descriptors of available data, such as sample size, presence of twin data and/or longitudinal data, etc.

An equally important objective to better understand heterogeneity is to design studies in which the specificities of different samples are taken into account. An important paper from Probst and colleagues (82) showed that different samples of tinnitus patients are not representative of one another. For example, users of mobile phone apps to monitor their tinnitus were demographically different from patients seeking clinical support in a specialized, tertiary clinic, and the demographics of both samples were different from a third sample of tinnitus bearers from a self-help online platform. Researchers seldom pay attention to whether their results could be extrapolated to other subpopulations (also known as external validation). In psychological research for example, most of the published scientific studies recruit participants from a homogenous sample of Western, Educated, Industrialized, Rich, Democratic (also known as WEIRD) (193) background. The relation between tinnitus and depression is a prime example of this phenomenon: although the relationship between the two is well characterized (113), it is debatable to what extent it extends to other populations other than the clinical subpopulation.

In other words, one conclusion from one sample must not necessarily generalize to other subsamples. Unfortunately, results from the tinnitus literature are seldom externally validated, and it is understandable that researchers are often constrained by the subpopulation of tinnitus bearers that seek medical support, which are estimated to be only a fraction of the overall tinnitus population (23) . The previously mentioned study from Blanken and colleagues (182) exemplifies a noteworthy attempt to address the heterogeneity of insomnia patients, first collected from an online sample and later validated in a clinical sample, and future tinnitus research should aim to conduct robust studies in a similar vein.

Online platforms where users can fill in questionnaires to leverage Big Data have been successfully used in several cases, such as the one mentioned above or as the ones used in the

study of moral psychology (194). The yourmorals.org platform[10] is an example where hundreds of thousands of surveys have been filled in for dozens of peer-reviewed studies. Although the ESIT has been developed to streamline clinical research (and it has shown considerable efficacy to that end, e.g., 194), adding a webpage in which different types of studies can be designed and conducted with (large) online samples would represent a paradigm-shift for tinnitus research. Although such practice is increasingly popular (196), similar initiatives in tinnitus research remain underexplored. One of the main objectives pursued during this doctoral work was to establish the ESIT database as a platform to streamline research. That goal was successful: although a base database (TRI) was already available, the progress made during the last three years permitted the conduction of studies such as the one conducted by Schlee and colleagues (195)[11] in a couple of months to evaluate the effects of COVID-19 on tinnitus patients. The progress obtained with the ESIT database harmonizing data collection and analysis are also being utilized for on-going clinical trials (176). Current developments are underway to add an online self-test platform using the architectural backbone of the ESIT database, where any internet user could fill in questionnaires related to their tinnitus for free, and where studies can be designed aiming towards the big sample sizes required to untangle heterogeneity.

Conclusion

This doctoral work advanced the current understanding of tinnitus heterogeneity by:

1) Including treatment response as a dimension as a heterogeneity and indicating that tinnitus characteristics and demographics can partially explain (non-)treatment response.
2) Demonstrating that personality factors play a role on the progress of tinnitus over the years.
3) Suggesting that tinnitus may disappear even in its chronic format, albeit not being able to identify factors leading to tinnitus remission.
4) Incorporating state-of-science methodology to retrieve individual and group-level models of tinnitus experience. By doing so, the work in this thesis is one of the first to empirically model the high variability in the subjective experience of tinnitus.

However, a theoretical framework to generate hypotheses to untangle tinnitus heterogeneity in its multiple levels of complexity (i.e., pathophysiological, psychopathological, etiological, etc.) remains missing. I propose incorporating the HiTOP into clinical and research work, which has

[10] Due to GDPR regulations, the platform is not available to users from the European Union
[11] The dissertation's author also co-authors this article

been established by psychologists, psychiatrists and psychometricians to tackle similar challenges in other domains of psychopathology as the ones faced by tinnitus researchers. Figure 5.3 provides an example on how the HiTOP model could be used in the tinnitus field:

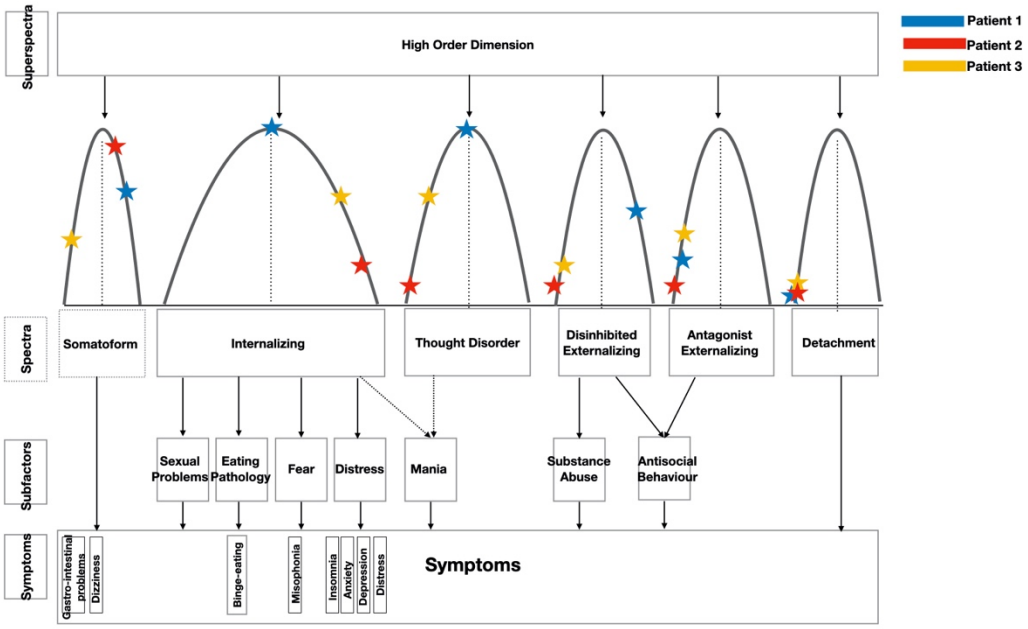

Figure 5.3 Simplified Schematic representation of the HiTOP model (a complete version is available, Figure 5.1). Dashed arrows and boxes represent provisional elements of the model. The bottom level, symptoms, is comprised of thousands of symptoms that patients may suffer from; here only a selection of co-occurring symptoms (e.g., gastro-intestinal complaints, dizziness, binge-eating, insomnia, anxiety, depression and distress) are depicted for illustration purposes. Density plots convey the central idea of the model that psychopathological phenomena should be understood as a continuum: each patient comprises a unique mosaic of symptoms, subfactors, and spectra. Together, the interplay between those structures comprises the uniqueness of how individuals experience their mental health.

In this example, three hypothetical patients are presented with different symptoms (bottom layer) which, in turn, correspond to different expressions of latent variables in higher levels of the hierarchy. In this example, the focus is on the spectra level for illustration purposes. The three patients would have different psychopathological profiles: whereas the profile of patient 1 would be related to somatoform spectrum (197), the internalizing spectrum would be more pronounced in patients 2 and 3 (107). Importantly, those profiles could be assessed quantitatively through questionnaires, and therefore avoid well-known drawbacks from the established categorical nosology of mental health (briefly discussed in the introduction section) (40–42,145). Suggestions on how to quantitively assess the HiTOP are available (187), including a suggested questionary battery (198).

Additionally, proposals have been made to identify the neurobiological underpinnings of higher structures in the HiTOP model (145). A previous study used the concepts of the HiTOP to identify (199) novel genetic loci related to mood instability using data from the UK Biobank, highlighting the potential benefits of a quantitative understanding of psychopathology (see previous section for a discussion on the role of biobanks for untangling tinnitus heterogeneity). Another important step towards this goal is to sample data from the general population experiencing the clinical phenotype of interest (as opposed to sampling solely from clinical populations) to better account for heterogeneity. To that end, an online self-test platform (see previous section) would be able to sample a more heterogeneous, and perhaps more representative stratum of the tinnitus population. A main advantage of such platform compared to using data from a biobank would be the flexibility to design a specific research hypothesis (Blanken and colleagues (182) provides an example on how a specific research hypothesis could be used in this context by linking information from clinical and online samples.

In conclusion this doctoral thesis not only identified novel aspects of tinnitus heterogeneity, but it also incorporated state-of-the-art methodological techniques to the field of tinnitus research to retrieve individualized models of tinnitus heterogeneity. Lastly, a proposal is made to incorporate the HiTOP framework as a way to integrate different dimensions of heterogeneity alongside practical suggestions for future clinicians and researchers on how to use the said framework. Altogether, this thesis shows novel ways to untangle heterogeneity, alongside prepositions for future projects. Ultimately, I expect that those insights will help clinicians and researchers reach the ultimate goal of delivering evidence-based, personalized interventions to better care for tinnitus patients.

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Supplemental Material (Chapter 1)

Acoustic Neuromodulation							
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.017	0.001	1.498	1.033	0.359	0.633	3
Age	0.071	0.022	1.482	1.440	0.206	0.633	7
Onset	0.113	0.049	1.461	1.762	0.092	0.598	9
Noise reactivness	0.096	0.048	1.462	1.998	0.072	0.574	7
Hyperacusis	0.028	-0.006	1.502	0.836	0.505	0.633	5
Somatic	0.012	-0.005	1.502	0.684	0.507	0.633	3
Jaw/neck problems	0.078	0.054	1.457	3.269	0.024	0.253	4
Hearing loss	0.024	-0.001	1.499	0.962	0.413	0.633	4
Laterality of Hearing loss	0.056	0.042	1.520	3.861	0.054	0.430	2
Frequency of Tinnitus	0.054	-0.024	1.571	0.690	0.633	0.633	6
Laterality of Tinnitus	0.028	-0.006	1.503	0.823	0.513	0.633	5
Fluctuation of Tinnitus	0.062	0.037	1.470	2.542	0.060	0.478	4
Duration of treatment	0.080	0.039	0.652	1.974	0.088	0.598	6
Sum	-	0.249	-	-	-	-	-

Table S1.1. summary of statistical models with the outcomes of the treatment ”Acoustic Neuromodulation” as dependent variable

Acupuncture							
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.023	0.018	1.283	4.792	0.003	0.029	4
Age	0.005	-0.008	1.300	0.386	0.928	0.928	9
Onset	0.017	0.004	1.292	1.311	0.235	0.928	9
Noise reactivness	0.003	-0.007	1.299	0.322	0.925	0.928	7
Hyperacusis	0.012	0.005	1.291	1.851	0.117	0.780	5
Somatic	0.002	-0.001	1.296	0.594	0.552	0.928	3
Jaw/neck problems	0.029	0.025	1.279	6.217	0.000	0.004	4
Hearing loss	0.007	0.002	1.293	1.446	0.228	0.928	4
Laterality of Hearing loss	0.002	-0.001	1.277	0.777	0.379	0.928	2
Frequency of Tinnitus	0.010	-0.003	1.279	0.791	0.557	0.928	6
Laterality of Tinnitus	0.012	0.005	1.291	1.806	0.126	0.780	5
Fluctuation of Tinnitus	0.009	0.005	1.293	1.952	0.120	0.780	4
Duration of treatment	0.087	0.079	0.524	11.651	0.087	0.627	6
Sum	-	0.124	-	-	-	-	-

Table S1.2. summary of statistical models with the outcomes of the treatment ”Acupuncture” as dependent variable

Antidepressants							
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF

Gender	0.001	-0.003	2.274	0.277	0.842	0.962	4
Age	0.031	0.021	2.247	3.067	0.002	0.021	9
Onset	0.022	0.012	2.257	2.197	0.026	0.180	9
Noise reactivness	0.014	0.006	2.263	1.852	0.087	0.346	7
Hyperacusis	0.022	0.017	2.251	4.357	0.002	0.017	5
Somatic	0.006	0.004	2.266	2.528	0.080	0.322	3
Jaw/neck problems	0.008	0.004	2.266	1.995	0.113	0.453	4
Hearing loss	0.001	-0.002	2.273	0.387	0.763	0.962	4
Laterality of Hearing loss	0.000	-0.002	2.218	0.002	0.962	0.962	2
Frequency of Tinnitus	0.032	0.022	2.191	3.247	0.007	0.061	6
Laterality of Tinnitus	0.014	0.009	2.260	2.833	0.024	0.166	5
Fluctuation of Tinnitus	0.022	0.018	2.255	5.693	0.001	0.008	4
Duration of treatment	0.063	0.057	0.878	10.485	0.000	0.000	6
Sum	-	0.163	-	-	-	-	-

Table S1.3. summary of statistical models with the outcomes of the treatment ”Antidepresssants” as dependent variable

	CBT						
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.037	0.029	1.860	4.683	0.003	0.035	4
Age	0.019	0.000	1.887	1.003	0.429	0.961	8
Onset	0.007	-0.015	1.901	0.312	0.961	0.961	9
Noise reactivness	0.011	-0.005	1.892	0.667	0.676	0.961	7
Hyperacusis	0.021	0.010	1.877	1.969	0.099	0.690	5
Somatic	0.007	0.002	1.885	1.380	0.253	0.902	3
Jaw/neck problems	0.007	-0.002	1.889	0.809	0.489	0.961	4
Hearing loss	0.006	-0.002	1.889	0.777	0.507	0.961	4
Laterality of Hearing loss	0.008	0.003	1.729	1.707	0.193	0.845	2
Frequency of Tinnitus	0.051	0.029	1.706	2.319	0.045	0.445	6
Laterality of Tinnitus	0.011	0.000	1.887	1.002	0.407	0.961	5
Fluctuation of Tinnitus	0.037	0.029	1.860	4.684	0.003	0.035	4
Duration of treatment	0.074	0.061	0.721	5.796	0.074	0.652	6
Sum	-	0.140	-	-	-	-	-

Table S1.4. summary of statistical models with the outcomes of the treatment ”Cognitive Behavior Therapy” as dependent variable

Chiropractor

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.001	-0.005	1.336	0.179	0.911	0.911	4
Age	0.008	-0.007	1.337	0.539	0.805	0.911	8
Onset	0.017	0.001	1.332	1.048	0.399	0.911	9
Noise reactivness	0.030	0.018	1.321	2.449	0.024	0.266	7
Hyperacusis	0.003	-0.005	1.336	0.406	0.804	0.911	5
Somatic	0.010	0.006	1.329	2.410	0.091	0.818	3
Jaw/neck problems	0.019	0.013	1.324	3.162	0.024	0.268	4
Hearing loss	0.002	-0.005	1.336	0.264	0.852	0.911	4
Laterality of Hearing loss	0.002	-0.002	1.316	0.528	0.468	0.911	2
Frequency of Tinnitus	0.023	0.007	1.310	1.388	0.229	0.911	6
Laterality of Tinnitus	0.004	-0.004	1.335	0.461	0.764	0.911	5
Fluctuation of Tinnitus	0.014	0.008	1.324	2.308	0.076	0.682	4
Duration of treatment	0.061	0.051	0.533	6.255	0.000	0.000	6
Sum	-	0.076	-	-	-	-	-

Table S1.5. summary of statistical models with the outcomes of the treatment ”Chiropractor” as dependent variable

Self-help book

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.005	-0.007	1.349	0.452	0.716	0.901	4
Age	0.017	-0.006	1.349	0.731	0.625	0.901	7
Onset	0.049	0.018	1.333	1.577	0.132	0.836	9
Noise reactivness	0.020	-0.003	1.347	0.861	0.524	0.901	7
Hyperacusis	0.024	0.008	1.339	1.516	0.198	0.895	5
Somatic	0.026	0.018	1.333	3.331	0.037	0.411	3
Jaw/neck problems	0.002	-0.010	1.351	0.194	0.901	0.901	4
Hearing loss	0.023	0.012	1.337	1.995	0.115	0.807	4
Laterality of Hearing loss	0.019	0.013	1.233	2.967	0.087	0.643	2
Frequency of Tinnitus	0.044	0.012	1.234	1.364	0.241	0.901	6
Laterality of Tinnitus	0.024	0.008	1.340	1.506	0.201	0.895	5
Fluctuation of Tinnitus	0.011	-0.001	1.346	0.908	0.438	0.901	4
Duration of treatment	0.052	0.033	0.551	2.743	0.020	0.243	6
Sum	-	0.094	-	-	-	-	-

Table S1.6. summary of statistical models with the outcomes of the treatment ”Self-Help books” as dependent variable

GABA

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.005	-0.004	2.419	0.531	0.589	0.589	3
Age	0.113	0.086	2.308	4.167	0.000	0.003	8
Onset	0.068	0.036	2.371	2.088	0.038	0.227	9
Noise reactivness	0.081	0.057	2.345	3.356	0.003	0.031	7
Hyperacusis	0.042	0.026	2.383	2.547	0.040	0.241	5
Somatic	0.012	0.003	2.410	1.375	0.255	0.589	3
Jaw/neck problems	0.071	0.059	2.341	5.971	0.001	0.007	4
Hearing loss	0.016	0.004	2.409	1.294	0.277	0.589	4
Laterality of Hearing loss	0.057	0.051	2.459	8.454	0.004	0.038	2
Frequency of Tinnitus	0.080	0.046	2.465	2.350	0.044	0.265	6
Laterality of Tinnitus	0.030	0.013	2.398	1.806	0.128	0.514	5
Fluctuation of Tinnitus	0.013	0.000	2.414	1.000	0.394	0.589	4
Duration of treatment	0.133	0.115	0.830	7.113	0.000	0.000	6
Sum	-	0.491	-	-	-	-	-

Table S1.7. summary of statistical models with the outcomes of the treatment ”GABAergic medication” as dependent variable

Hearing Aid

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.008	0.003	2.077	1.762	0.153	0.613	4
Age	0.014	0.003	2.077	1.318	0.239	0.820	8
Onset	0.038	0.026	2.053	3.273	0.001	0.011	9
Noise reactivness	0.027	0.019	2.061	3.142	0.005	0.038	7
Hyperacusis	0.015	0.010	2.070	2.631	0.033	0.234	5
Somatic	0.007	0.005	2.076	2.561	0.078	0.459	3
Jaw/neck problems	0.041	0.037	2.042	9.676	0.000	0.000	4
Hearing loss	0.040	0.036	2.043	9.441	0.000	0.000	4
Laterality of Hearing loss	0.000	-0.001	2.007	0.052	0.820	0.820	2
Frequency of Tinnitus	0.007	-0.001	2.006	0.877	0.496	0.820	6
Laterality of Tinnitus	0.022	0.017	2.063	3.890	0.004	0.031	5
Fluctuation of Tinnitus	0.002	-0.003	2.082	0.376	0.770	0.820	4
Duration of treatment	0.217	0.211	0.845	37.340	0.000	0.000	6
Sum	-	0.360	-	-	-	-	-

Table S1.8. summary of statistical models with the outcomes of the treatment ”Hearing Aid” as dependent variable

Homeopathics

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.022	0.015	1.264	3.113	0.026	0.236	4
Age	0.036	0.020	1.261	2.209	0.033	0.294	8
Onset	0.019	-0.000	1.273	0.985	0.447	0.909	9
Noise reactivness	0.057	0.043	1.245	4.177	0.000	0.005	7
Hyperacusis	0.004	-0.006	1.277	0.402	0.808	0.909	5
Somatic	0.003	-0.002	1.274	0.536	0.586	0.909	3
Jaw/neck problems	0.005	-0.002	1.274	0.715	0.543	0.909	4
Hearing loss	0.026	0.019	1.261	3.741	0.011	0.120	4
Laterality of Hearing loss	0.009	0.006	1.224	2.520	0.114	0.795	2
Frequency of Tinnitus	0.006	-0.013	1.235	0.306	0.909	0.909	6
Laterality of Tinnitus	0.007	-0.003	1.275	0.697	0.594	0.909	5
Fluctuation of Tinnitus	0.014	0.007	1.270	1.931	0.124	0.832	4
Duration of treatment	0.097	0.086	0.536	9.015	0.000	0.000	6
Sum	-	0.169	-	-	-	-	-

Table S1.9. summary of statistical models with the outcomes of the treatment ”Homeopathic Medication” as dependent variable

HBOT

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.066	0.022	1.578	1.511	0.232	0.802	3
Age	0.110	-0.054	1.638	0.672	0.694	0.802	8
Onset	0.404	0.275	1.359	3.137	0.008	0.099	9
Noise reactivness	0.183	0.058	1.549	1.460	0.217	0.802	7
Hyperacusis	0.063	-0.029	1.619	0.688	0.604	0.802	5
Somatic	0.038	0.016	1.583	1.746	0.193	0.773	2
Jaw/neck problems	0.091	0.026	1.575	1.398	0.257	0.802	4
Hearing loss	0.069	0.026	1.575	1.590	0.216	0.802	3
Laterality of Hearing loss	0.159	0.130	1.485	5.466	0.027	0.265	2
Frequency of Tinnitus	0.084	-0.099	1.668	0.461	0.802	0.802	6
Laterality of Tinnitus	0.182	0.103	1.512	2.288	0.076	0.458	5
Fluctuation of Tinnitus	0.213	0.157	1.466	3.783	0.017	0.172	4
Duration of treatment	0.067	-0.050	0.606	0.573	0.720	0.802	6
Sum	-	0.581	-	-	-	-	-

Table S1.10. summary of statistical models with the outcomes of the treatment ”Hyperbaric Oxygen Therapy” as dependent variable

	LLLT						
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.006	-0.026	1.844	0.177	0.838	0.988	3
Age	0.117	0.009	1.812	1.082	0.387	0.988	8
Onset	0.134	0.027	1.795	1.258	0.288	0.988	8
Noise reactivness	0.015	-0.086	1.898	0.151	0.988	0.988	7
Hyperacusis	0.067	0.005	1.816	1.078	0.375	0.988	5
Somatic	0.083	0.054	1.771	2.813	0.068	0.813	3
Jaw/neck problems	0.042	-0.006	1.826	0.883	0.455	0.988	4
Hearing loss	0.065	0.019	1.803	1.413	0.248	0.988	4
Laterality of Hearing loss	0.000	-0.022	1.622	0.014	0.907	0.988	2
Frequency of Tinnitus	0.078	-0.038	1.634	0.674	0.645	0.988	6
Laterality of Tinnitus	0.037	-0.010	1.830	0.780	0.510	0.988	4
Fluctuation of Tinnitus	0.032	-0.016	1.835	0.671	0.573	0.988	4
Duration of treatment	0.045	-0.035	0.768	0.562	0.729	0.988	6
Sum	-	-0.126	-	-	-	-	-

Table S1.11. summary of statistical models with the outcomes of the treatment ”Low level laser therapy” as dependent variable

	Sound Masker						
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.000	-0.004	1.870	0.043	0.958	0.960	3
Age	0.027	0.013	1.854	1.972	0.057	0.286	8
Onset	0.052	0.037	1.832	3.406	0.001	0.010	9
Noise reactivness	0.027	0.015	1.852	2.266	0.036	0.181	7
Hyperacusis	0.012	0.004	1.863	1.487	0.205	0.820	5
Somatic	0.020	0.016	1.852	5.011	0.007	0.062	3
Jaw/neck problems	0.022	0.016	1.851	3.704	0.012	0.094	4
Hearing loss	0.004	-0.002	1.869	0.599	0.616	0.960	4
Laterality of Hearing loss	0.017	0.014	1.904	6.140	0.014	0.109	2
Frequency of Tinnitus	0.003	-0.011	1.928	0.205	0.960	0.960	6
Laterality of Tinnitus	0.019	0.011	1.856	2.388	0.050	0.251	5
Fluctuation of Tinnitus	0.025	0.019	1.852	4.207	0.006	0.053	4
Duration of treatment	0.187	0.179	0.724	22.837	0.000	0.000	6
Sum	-	0.306	-	-	-	-	-

Table S1.12. summary of statistical models with the outcomes of the treatment ”Sound Masker” as dependent variable

Neurofeedback and meditation

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.010	-0.001	1.666	0.871	0.457	0.890	4
Age	0.019	-0.007	1.671	0.724	0.652	0.890	8
Onset	0.014	-0.017	1.679	0.450	0.890	0.890	9
Noise reactivness	0.017	-0.005	1.670	0.757	0.604	0.890	7
Hyperacusis	0.007	-0.008	1.672	0.444	0.776	0.890	5
Somatic	0.014	0.007	1.660	1.926	0.148	0.890	3
Jaw/neck problems	0.004	-0.007	1.671	0.377	0.770	0.890	4
Hearing loss	0.032	0.021	1.648	2.936	0.034	0.406	4
Laterality of Hearing loss	0.003	-0.004	1.603	0.439	0.509	0.890	2
Frequency of Tinnitus	0.038	0.007	1.595	1.227	0.299	0.890	6
Laterality of Tinnitus	0.007	-0.008	1.672	0.493	0.741	0.890	5
Fluctuation of Tinnitus	0.021	0.010	1.659	1.867	0.135	0.890	4
Duration of treatment	0.101	0.084	0.652	5.916	0.000	0.000	6
Sum	-	0.071	-	-	-	-	-

Table S1.13. summary of statistical models with the outcomes of the treatment ”Neurofeedback and Meditation” as dependent variable

Neuromonics

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.008	-0.003	1.810	0.705	0.403	0.991	2
Age	0.058	-0.018	1.823	0.767	0.616	0.991	8
Onset	0.070	-0.017	1.823	0.803	0.601	0.991	9
Noise reactivness	0.105	0.044	1.767	1.720	0.126	0.847	7
Hyperacusis	0.057	0.015	1.794	1.357	0.255	0.968	5
Somatic	0.000	-0.022	1.827	0.009	0.991	0.991	3
Jaw/neck problems	0.017	-0.015	1.821	0.522	0.668	0.991	4
Hearing loss	0.026	-0.006	1.813	0.799	0.498	0.991	4
Laterality of Hearing loss	0.002	-0.013	1.933	0.147	0.703	0.991	2
Frequency of Tinnitus	0.082	0.011	1.911	1.151	0.343	0.991	6
Laterality of Tinnitus	0.057	0.015	1.793	1.364	0.253	0.968	5
Fluctuation of Tinnitus	0.014	-0.018	1.833	0.438	0.726	0.991	4
Duration of treatment	0.063	0.011	0.760	1.201	0.315	0.968	6
Sum	-	-0.017	-	-	-	-	-

Table S1.14. summary of statistical models with the outcomes of the treatment ”Neuromonics Treatment” as dependent variable

Notched Music

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.035	0.026	1.310	4.000	0.020	0.177	3
Age	0.012	-0.020	1.340	0.387	0.910	0.982	8
Onset	0.013	-0.024	1.343	0.353	0.944	0.982	9
Noise reactivness	0.032	0.005	1.324	1.202	0.307	0.982	7
Hyperacusis	0.013	-0.005	1.331	0.737	0.568	0.982	5
Somatic	0.000	-0.009	1.333	0.018	0.982	0.982	3
Jaw/neck problems	0.009	-0.004	1.330	0.697	0.555	0.982	4
Hearing loss	0.014	0.001	1.327	1.053	0.370	0.982	4
Laterality of Hearing loss	0.060	0.053	1.335	8.694	0.004	0.041	2
Frequency of Tinnitus	0.093	0.059	1.331	2.715	0.023	0.205	6
Laterality of Tinnitus	0.003	-0.015	1.337	0.187	0.945	0.982	5
Fluctuation of Tinnitus	0.057	0.044	1.301	4.396	0.005	0.055	4
Duration of treatment	0.120	0.099	0.543	5.904	0.000	0.001	6
Sum	-	0.212	-	-	-	-	-

Table S1.15. summary of statistical models with the outcomes of the treatment ”Notched Music” as dependent variable

Off label medication

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.002	-0.008	1.411	0.156	0.926	0.926	4
Age	0.020	-0.006	1.409	0.775	0.625	0.926	9
Onset	0.017	-0.009	1.411	0.672	0.716	0.926	9
Noise reactivness	0.012	-0.007	1.410	0.631	0.705	0.926	7
Hyperacusis	0.006	-0.007	1.410	0.494	0.740	0.926	5
Somatic	0.003	-0.004	1.407	0.448	0.639	0.926	3
Jaw/neck problems	0.022	0.013	1.396	2.333	0.074	0.741	4
Hearing loss	0.007	-0.003	1.407	0.735	0.532	0.926	4
Laterality of Hearing loss	0.012	0.007	1.373	2.364	0.126	0.864	2
Frequency of Tinnitus	0.019	-0.007	1.382	0.739	0.595	0.926	6
Laterality of Tinnitus	0.009	-0.004	1.408	0.686	0.602	0.926	5
Fluctuation of Tinnitus	0.028	0.019	1.392	2.992	0.031	0.374	4
Duration of treatment	0.165	0.151	0.548	12.082	0.000	0.000	6
Sum	-	0.137	-	-	-	-	-

Table S1.16. summary of statistical models with the outcomes of the treatment ”Off-Label Medication” as dependent variable

Psychiatrist							
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.013	0.003	2.033	1.285	0.280	0.874	4
Age	0.025	-0.002	2.038	0.941	0.483	0.874	9
Onset	0.063	0.037	1.998	2.414	0.015	0.139	9
Noise reactivness	0.038	0.018	2.017	1.921	0.077	0.541	7
Hyperacusis	0.045	0.032	2.004	3.418	0.009	0.085	5
Somatic	0.012	0.005	2.031	1.723	0.180	0.874	3
Jaw/neck problems	0.006	-0.004	2.041	0.567	0.637	0.874	4
Hearing loss	0.003	-0.007	2.043	0.335	0.800	0.874	4
Laterality of Hearing loss	0.041	0.036	2.018	7.601	0.006	0.064	2
Frequency of Tinnitus	0.010	-0.018	2.074	0.362	0.874	0.874	6
Laterality of Tinnitus	0.022	0.008	2.028	1.628	0.167	0.839	5
Fluctuation of Tinnitus	0.040	0.030	2.007	4.043	0.008	0.077	4
Duration of treatment	0.016	-0.001	0.762	0.945	0.452	0.874	6
Sum	-	0.136	-	-	-	-	-

Table S1.17. summary of statistical models with the outcomes of the treatment ”Psychiatrist” as dependent variable

Psychologist							
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.016	0.008	1.895	2.078	0.103	0.513	4
Age	0.035	0.014	1.889	1.694	0.098	0.499	9
Onset	0.006	-0.015	1.917	0.264	0.977	0.977	9
Noise reactivness	0.030	0.015	1.888	1.989	0.066	0.398	7
Hyperacusis	0.017	0.007	1.896	1.701	0.149	0.729	5
Somatic	0.002	-0.003	1.905	0.480	0.619	0.977	3
Jaw/neck problems	0.005	-0.002	1.905	0.690	0.559	0.977	4
Hearing loss	0.022	0.014	1.889	2.871	0.036	0.299	4
Laterality of Hearing loss	0.005	0.001	1.737	1.118	0.292	0.875	2
Frequency of Tinnitus	0.035	0.013	1.726	1.582	0.166	0.729	6
Laterality of Tinnitus	0.017	0.007	1.896	1.673	0.155	0.729	5
Fluctuation of Tinnitus	0.047	0.040	1.866	6.351	0.000	0.004	4
Duration of treatment	0.046	0.034	0.736	3.695	0.003	0.034	6
Sum	-	0.132	-	-	-	-	-

Table S1.18. summary of statistical models with the outcomes of the treatment ”Psychologist” as dependent variable

Retigabine

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.106	0.089	2.359	6.070	0.017	0.206	2
Age	0.147	0.036	2.427	1.320	0.268	0.956	7
Onset	0.152	-0.002	2.474	0.988	0.459	0.956	9
Noise reactivness	0.173	0.085	2.364	1.964	0.102	0.709	6
Hyperacusis	0.007	-0.054	2.538	0.107	0.956	0.956	4
Somatic	0.083	0.047	2.413	2.275	0.113	0.709	3
Jaw/neck problems	0.046	-0.012	2.487	0.787	0.507	0.956	4
Hearing loss	0.079	0.023	2.443	1.401	0.254	0.956	4
Laterality of Hearing loss	0.000	-0.040	2.805	0.003	0.955	0.956	2
Frequency of Tinnitus	0.270	0.175	2.499	2.833	0.061	0.510	4
Laterality of Tinnitus	0.116	0.062	2.393	2.153	0.105	0.709	4
Fluctuation of Tinnitus	0.069	0.012	2.457	1.212	0.315	0.956	4
Duration of treatment	0.114	0.020	1.016	1.210	0.319	0.956	6
Sum	-	0.439	-	-	-	-	-

Table S1.19. summary of statistical models with the outcomes of the treatment ”Retigabine Administration” as dependent variable

Self Administered Sound Therapy

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.010	0.008	1.423	5.375	0.001	0.010	4
Age	0.006	0.000	1.428	1.089	0.368	0.497	9
Onset	0.005	-0.000	1.429	0.922	0.497	0.497	9
Noise reactivness	0.049	0.046	1.396	13.487	0.000	0.000	7
Hyperacusis	0.011	0.008	1.423	4.253	0.002	0.018	5
Somatic	0.002	0.001	1.428	1.617	0.199	0.497	3
Jaw/neck problems	0.004	0.002	1.427	2.110	0.097	0.389	4
Hearing loss	0.004	0.002	1.427	1.955	0.119	0.462	4
Laterality of Hearing loss	0.004	0.003	1.443	3.640	0.057	0.340	2
Frequency of Tinnitus	0.007	0.002	1.443	1.375	0.231	0.497	6
Laterality of Tinnitus	0.004	0.001	1.428	1.435	0.220	0.497	5
Fluctuation of Tinnitus	0.015	0.013	1.421	7.700	0.000	0.000	4
Duration of treatment	0.099	0.096	0.653	34.203	0.000	0.000	6
Sum	-	0.182	-	-	-	-	-

Table S1.20. summary of statistical models with the outcomes of the treatment ”Self Administered Sound Therapy” as dependent variable

SoundCure							
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.004	-0.003	1.797	0.634	0.427	0.959	2
Age	0.042	-0.015	1.808	0.743	0.653	0.959	9
Onset	0.119	0.067	1.734	2.284	0.025	0.277	9
Noise reactivness	0.059	0.018	1.779	1.425	0.209	0.959	7
Hyperacusis	0.009	-0.020	1.813	0.305	0.874	0.959	5
Somatic	0.003	-0.011	1.805	0.228	0.796	0.959	3
Jaw/neck problems	0.031	0.010	1.786	1.488	0.221	0.959	4
Hearing loss	0.002	-0.019	1.812	0.101	0.959	0.959	4
Laterality of Hearing loss	0.020	0.009	1.800	1.811	0.182	0.959	2
Frequency of Tinnitus	0.206	0.159	1.658	4.370	0.001	0.017	6
Laterality of Tinnitus	0.025	-0.003	1.798	0.896	0.468	0.959	5
Fluctuation of Tinnitus	0.027	0.006	1.789	1.301	0.277	0.959	4
Duration of treatment	0.182	0.152	0.750	6.140	0.000	0.000	6
Sum	-	0.352	-	-	-	-	-

Table S1.21. summary of statistical models with the outcomes of the treatment ”SoundCure” as dependent variable

Steroids							
	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.001	-0.008	1.681	0.063	0.979	0.979	4
Age	0.018	-0.002	1.676	0.890	0.515	0.979	8
Onset	0.020	-0.003	1.677	0.876	0.537	0.979	9
Noise reactivness	0.033	0.016	1.661	1.915	0.078	0.690	7
Hyperacusis	0.012	0.001	1.674	1.070	0.371	0.979	5
Somatic	0.010	0.004	1.671	1.749	0.176	0.878	3
Jaw/neck problems	0.016	0.007	1.668	1.856	0.137	0.806	4
Hearing loss	0.011	0.003	1.672	1.292	0.277	0.979	4
Laterality of Hearing loss	0.003	-0.002	1.701	0.613	0.435	0.979	2
Frequency of Tinnitus	0.007	-0.016	1.714	0.315	0.904	0.979	6
Laterality of Tinnitus	0.011	-0.000	1.675	0.963	0.428	0.979	5
Fluctuation of Tinnitus	0.013	0.005	1.670	1.543	0.203	0.895	4
Duration of treatment	0.017	0.002	0.776	1.167	0.325	0.979	6
Sum	-	0.006	-	-	-	-	-

Table S1.22. summary of statistical models with the outcomes of the treatment ”Steroids Administration” as dependent variable

Supplements and Herbal

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.002	-0.001	1.178	0.603	0.613	0.640	4
Age	0.008	0.001	1.177	1.103	0.359	0.640	9
Onset	0.009	0.002	1.176	1.340	0.219	0.640	9
Noise reactivness	0.016	0.010	1.171	3.029	0.006	0.061	7
Hyperacusis	0.003	-0.001	1.178	0.804	0.523	0.640	5
Somatic	0.003	0.001	1.177	1.577	0.207	0.640	3
Jaw/neck problems	0.003	-0.000	1.178	0.968	0.407	0.640	4
Hearing loss	0.002	-0.001	1.178	0.692	0.557	0.640	4
Laterality of Hearing loss	0.020	0.019	1.165	14.271	0.000	0.002	2
Frequency of Tinnitus	0.010	0.002	1.175	1.340	0.245	0.640	6
Laterality of Tinnitus	0.002	-0.001	1.178	0.632	0.640	0.640	5
Fluctuation of Tinnitus	0.022	0.020	1.166	8.804	0.000	0.000	4
Duration of treatment	0.101	0.097	0.515	25.821	0.000	0.000	6
Sum	-	0.149	-	-	-	-	-

Table S1.23. summary of statistical models with the outcomes of the treatment ”Supplements and Herbal Administration” as dependent variable

Transcranial Magnetic Stimulation

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.003	-0.020	2.376	0.130	0.720	0.832	2
Age	0.118	0.005	2.347	1.046	0.405	0.832	6
Onset	0.177	0.022	2.327	1.140	0.360	0.832	8
Noise reactivness	0.051	-0.070	2.434	0.421	0.832	0.832	6
Hyperacusis	0.274	0.221	2.076	5.167	0.004	0.047	4
Somatic	0.063	0.019	2.331	1.422	0.253	0.832	3
Jaw/neck problems	0.035	-0.036	2.395	0.490	0.691	0.832	4
Hearing loss	0.235	0.179	2.132	4.189	0.011	0.101	4
Laterality of Hearing loss	0.207	0.177	2.215	6.806	0.015	0.134	2
Frequency of Tinnitus	0.400	0.296	2.048	3.838	0.016	0.141	5
Laterality of Tinnitus	0.184	0.124	2.202	3.078	0.038	0.304	4
Fluctuation of Tinnitus	0.032	-0.039	2.398	0.455	0.715	0.832	4
Duration of treatment	0.161	0.054	0.736	1.499	0.212	0.832	6
Sum	-	0.931	-	-	-	-	-

Table S1.24. summary of statistical models with the outcomes of the treatment ”Transcranial Magnetic Stimulation” as dependent variable

Tinnitus Retraining Therapy

	R^2	Adj. R^2	Sigma	statistic	p val	Adj. p val	DF
Gender	0.008	-0.000	1.969	0.962	0.411	0.664	4
Age	0.065	0.047	1.922	3.607	0.001	0.010	8
Onset	0.040	0.019	1.950	1.888	0.061	0.425	9
Noise reactivness	0.035	0.019	1.951	2.173	0.045	0.315	7
Hyperacusis	0.016	0.005	1.964	1.491	0.204	0.613	5
Somatic	0.005	-0.000	1.969	0.934	0.394	0.664	3
Jaw/neck problems	0.034	0.026	1.943	4.285	0.005	0.055	4
Hearing loss	0.042	0.034	1.935	5.357	0.001	0.014	4
Laterality of Hearing loss	0.004	0.000	1.872	1.044	0.308	0.616	2
Frequency of Tinnitus	0.060	0.039	1.835	2.936	0.014	0.123	6
Laterality of Tinnitus	0.007	-0.004	1.973	0.598	0.664	0.664	5
Fluctuation of Tinnitus	0.011	0.003	1.966	1.348	0.259	0.616	4
Duration of treatment	0.144	0.132	0.781	12.225	0.000	0.000	6
Sum	-	0.319	-	-	-		-

Table S1.25. summary of statistical models with the outcomes of the treatment ”Tinnitus Retraining Therapy” as dependent variable

Supplemental Material (Chapter 3)

Questionnaire Developed in-House for the Article "The Progression of Chronic Tinnitus Over the Years"

- **Please answer each questionnaire, even if you filled it out during your last visit.**
- **Please do not change the question or answer option!**
- **Please tick the appropriate answer (☒) or fill in empty fields.**

1. **A.) Do you still have tinnitus (although you may find it easier to distract yourself or ignore tinnitus)?**

   ☐ YES NO☐

2. **Please compare your current state of health with your condition during your first visit to our office in Regensburg on XX.XX.XXXX and estimate how much your tinnitus has improved?**

   1. Very much better ☐
   2. Much better ☐
   3. Somewhat better ☐
   4. No change ☐
   5. Slightly worse ☐
   6. Much worse ☐
   7. Very much worse ☐

3. **Do you feel informed about tinnitus?**

   ☐ YES NO☐

4. **Treatments for your tinnitus**. Please tick the appropriate box.

What treatment did you experience in the time after your initial consultation on XX.XX.XXXX?	**Specify the type of therapy, e.g. if you have been given a medication, which medication is it?**	**Does this treatment last?**	**Please evaluate the effect of treating your tinnitus.** **1. very much worse** **2. worse** **3. no effect** **4. better** **5. very much better**
☐ drug therapy		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ hearing aid		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Brain stimulation such as TMS/magnetic stimulation		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Acoustic stimulation, noise therapy with hearing aids, music therapy, mask		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Oxygen therapy		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Psychotherapy/behavioral therapy		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Counseling sessions regarding tinnitus		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ physiotherapy		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Dental treatment		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ alternative medicine (alternative practitioner, osteopathy, chiropractor)		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Acupuncture		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐

☐ Infusions		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ other therapy: _____		☐ YES NO☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐

5. **Other diseases.** Please tick as appropriate.

Has any other condition (other than tinnitus) been treated between your first presentation at the Regensburg Tinnitus Center and the present time?	**Are you receiving or have you been receiving drug treatment?**	**Please evaluate the effect of treating your tinnitus.** **1. very much worse 2. worse 3. no effect 4. better 5. very much better**
☐ Insomnia	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ high blood pressure	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Diabetes	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ other hearing disorders	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ elevated blood values, e.g. cholesterol	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ mental illness, e.g. depression, anxiety disorder	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Thyroid gland disease	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ other disease: _____	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ other disease: _____	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ other disease:	☐ YES NO ☐	1.☐ 2.☐ 3.☐ 4.☐ 5.☐

_____		
☐ Operation: _____		1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Operation: _____		1.☐ 2.☐ 3.☐ 4.☐ 5.☐
☐ Operation: _____		1.☐ 2.☐ 3.☐ 4.☐ 5.☐

6. **Have there been any changes in your life situation in the time since your first performance on XX.XX.XXXX?**

   6.1 Professional changes YES ☐NO☐

   6.1.1 If YES, this change was POSITIVE ☐NEUTRAL ☐NEGATIVE☐

   6.2 Private changes YES ☐NO☐

   6.2.1 If YES, this change was POSITIVE ☐NEUTRAL ☐NEGATIVE☐

7. **How is the tinnitus compared to your initial presentation?**

_____

_____

_____

_____

8. **Did you apply some of the treatments from question 4 at the same time? If so, which treatments were they?**

_____

_____

_____

9. **Are there factors that you think influence the tinnitus? Does it make the tinnitus better or worse?**

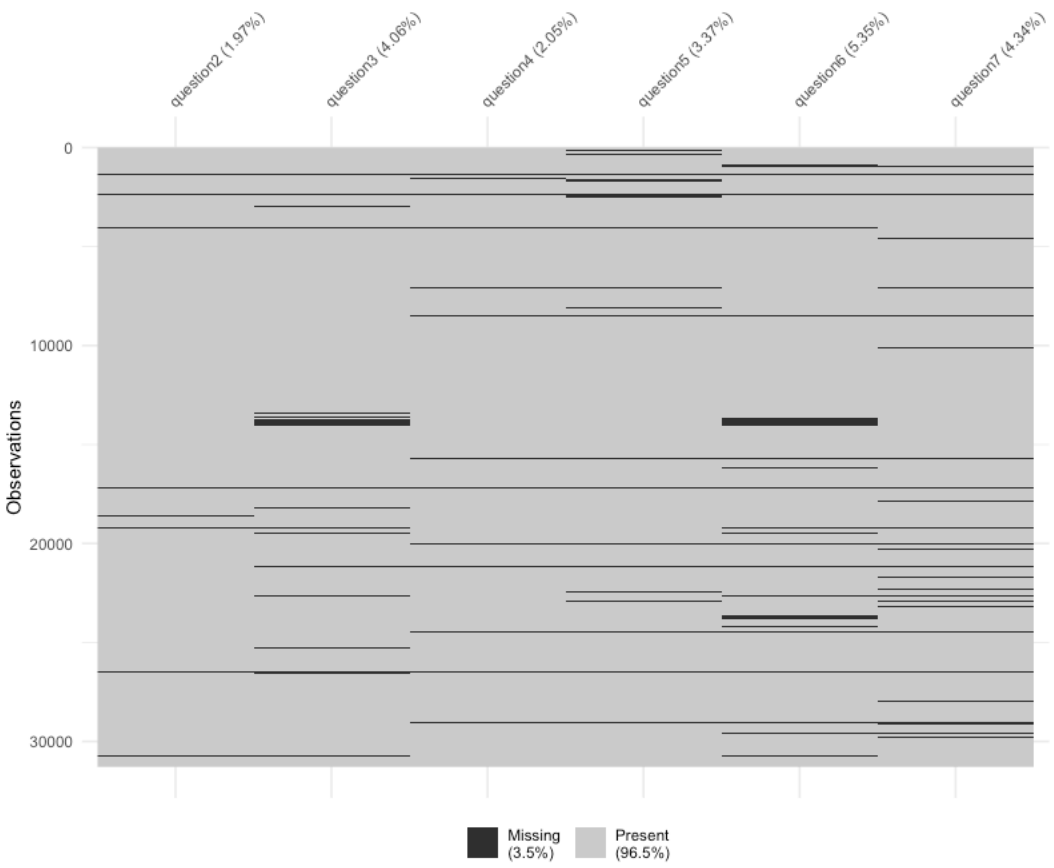
_____

_____

_____

_____

Supplemental Material (Chapter 4)



Sup. Figure s4.1 Missing values for each of the 6 variables included in the analysis. Table 4.2 describes each of the items. The function "vis_miss" from the "visdat" package was used to generate the plot

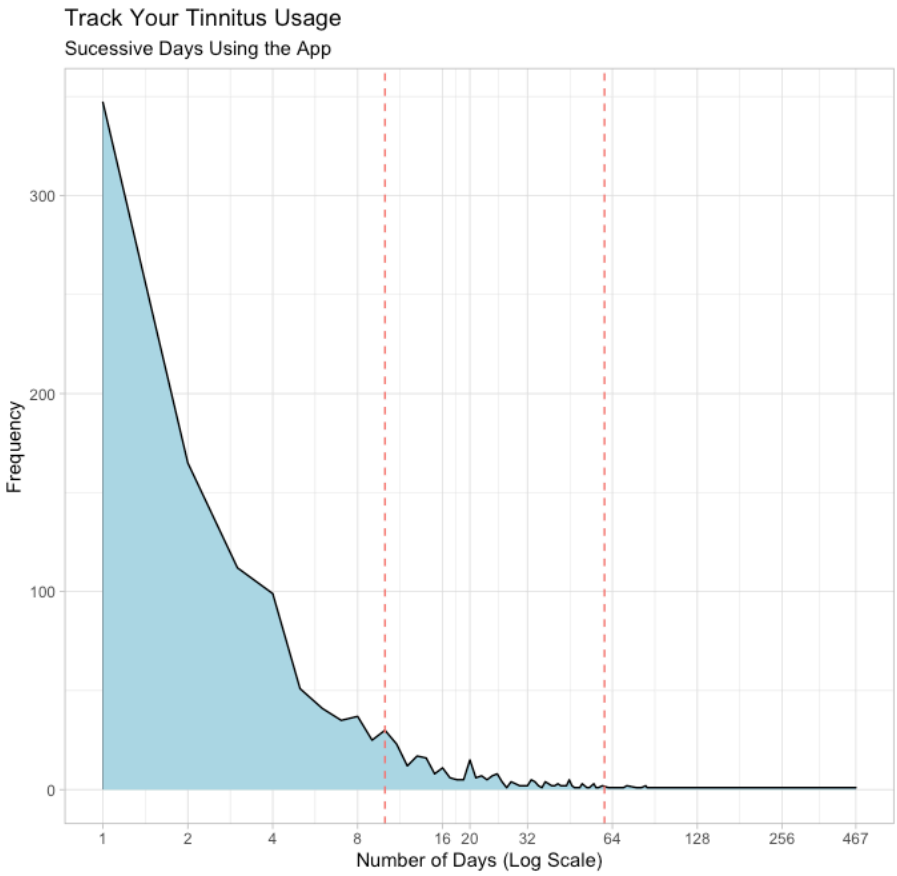


Figure s4.2 Y-axis represents the number of unique entries with sequential observations (x-axis) from 2584 unique users. Red lines represent the cut-off points for inclusion in the first analysis (Left, n = 10) and second analysis (Right, n = 60).

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I dedicate this thesis to my son Tristan.

Jorge Piano Simões,
Regensburg, 18.01.2021

Affidavit

I hereby declare, that this submitted thesis entitled **Tinnitus profiling to guide personalized therapeutic decisions - diagnosis improved with large- scale, longitudinal data** is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given. I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

Regensburg, 15.01.2021 _____