Aus dem

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Looking Beyond – Psychosomatic Characteristics of Chronic Tinnitus-Related Distress

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Is this a triangle?
No, that's a shoe
Is this a triangle?
No, that's you
So I'm a triangle?
What? No!
One, two, three, six, eight, three
Go!

Rachel Bloom, The Math of Love Triangles

Acknowledgements

Acknowledgements are a marvellous part of a thesis – as they shine a light on all colleagues and, most importantly, friends whom I was fortunate to encounter and spend my life with during this time.

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Abstract

Chronic Tinnitus denotes the longstanding, conscious awareness of a tonal or composite noise for which there is no identifiable external acoustic source. Depending on the psychological makeup of affected individuals, tinnitus can be highly distressing. Current guidelines view the symptom together with its cognitive-emotional processing as a psychosomatic phenomenon – and suggest (1) medico-audiological treatment for underlying medical influences – if known, and (2) psychological treatment for highly distressed individuals. Anchored within a psychosomatic vulnerability-stress-coping framework, the present thesis sets out to examine chronic tinnitus-related distress. It asks two questions:

1. In how far do direct or indirect psychological factors – that may or may not correlate with 'somatic' variables – influence individuals' experience of a tinnitus symptom as distressing? And:
2. In how far are psychosomatic (i.e. psychologically or medico-audiologically anchored) treatment approaches effective in ameliorating tinnitus-related distress?

Chapter 1 [**Introduction**] briefly reviews evidence on vulnerability-stress-coping contributors to chronic tinnitus symptomatology and related distress-reactions. **Chapter 2** [**Vulnerability**] presents the first two studies of the thesis, which examine chronic tinnitus-related distress at the junctions of (1) biological markers of tinnitus symptom vulnerability or perceived stress experiences and (2) psychological vulnerability-stress interactions. **Chapter 3** [**Stress**] presents the third study, which investigates, whether transdiagnostically relevant psychological variables underlie chronic tinnitus- and pain-related distress experiences. **Chapter 4** [**Coping**] examines the efficacy of psychosomatic treatment approaches. The final three studies of this thesis examine (1) whether a transdiagnostic psychological treatment approach ameliorates different functional symptom clusters, (2) whether a 'somatic' treatment approach (hearing amplification) bears psychological benefit, and (3) psychological effects on hearing amplification via hearing aid use-time. **Chapter 5 [General Discussion]** summarizes the presented papers and discusses theoretical and clinical implications.

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Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
ACTH	Adrenocorticotropic hormone
BOLD	Blood-Oxygenation-Level Dependent
CAS	Central auditory system
CRP	C-reactive protein
DMN	Default-Mode-Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
fMRI	functional Magnetic Resonance Imaging
FPI-r	Freiburger Persönlichkeitsinventar – revised version
HA	Hearing aid
HADS_a	Hospital Anxiety and Depression Scale - Anxiety subscale
HADS_d	Hospital Anxiety and Depression Scale - Depression subscale
HL	Hearing loss
ICD	International Statistical Classification of Diseases and Related Health Problems
IHC	Inner hair cells
IL	Interleukin
ISR	ICD-10 Symptom Rating
MPV	Mean Platelet Volume
NLR	Neutrophil/lymphocyte ratio
OHC	Outer hair cells
OSI	Oxidative stress index
PSQ	Perceived Stress Questionnaire
RCT	Randomized Controlled Trial
SES	Pain Experience Scale
SOD	Superoxide dismutase
TAS	Total antioxidant status
TFI	Tinnitus Functional Index
THI	Tinnitus Handicap Inventory
TNF	Tumor necrosis factor
TOS	Total oxidant status
TQ	Tinnitus Questionnaire - German version
TRD	Tinnitus-related distress
TRNA	Tinnitus-related neural activity

The men who were able to establish themselves on the oceans had to be effective with the sword upon both land and sea. They had also to have anticipatory vision, ship designing capability, and original scientific conceptioning, mathematical skill in navigation, and exploration techniques for coping in fog, night, and storm with the invisible hazards of rocks, shoals, and currents. But as they went on their sea ventures, they gradually found that the waters interconnected all the world's people and lands.

Richard Buckminster Fuller, Operating Manual for Spaceship Earth

Chapter 1 [Introduction]

Prologue

Psychosomatic phenomena; i.e. interactions between emotional experiences and somatic symptoms are complex [1]. The term 'psychosomatic' can refer to

1. **medical disorders** that are caused or negatively influenced by psychological factors [2],
2. **psychological phenomena** that are caused or negatively influenced by medical factors [3],
3. the **branch of medicine**, which deals with the unity of body and mind [4,5],
4. the **interdisciplinary research field** that deals with the influence of psychological experience and behaviour on the human body [6], or
5. **symptom groups** such as conversion, health-anxious or dissociative phenomena.

In psychosomatic research and practice, two overarching principles apply:

1. **psychological = physiological** (human experiences have a physiological equivalent) and
2. **physiological = psychological** (physiological states are psychologically *experienced*).

It is thus helpful to view psychosomatic interactions within a 3 x 2 matrix wherein 'somatic' or 'psychological' *risk factors* can trigger or maintain 'somatic' or 'psychological' *symptoms* - each of which can further be operationalized and described from a 'somatic' or 'psychological' *perspective*. **Table 1** illustrates this idea and assigns the dissertation's papers to the relevant areas.

Table 1. Psychosomatic perspectives and the present dissertation's studies.

	Risk factors		**Phenomenon / 'Symptom'**	
	'somatic' physical changes e.g. hearing loss	**'psychological'** events with emotional [symbolic] meaning e.g. „negative life events'	**'somatic'** anchored in physical changes e.g. tinnitus *symptom* [ringing/noise]	**'psychological'** anchored in cognitive /or emotional meaning e.g. appraisal of the tinnitus symptom / tinnitus-related *distress*
'somatic perspective' [psycho-] physiological correlates	(neuro)physiological correlates of hearing loss (e.g. hair cell damage[7])	(neurophysiological) correlates of negative life events (e.g. changes in neurophysiological stimulus processing patterns, vegetative reactions, hormonal influences, etc.[8])	(neuro)physiological influences that may contribute to the development or maintenance of the tinnitus sound (e.g. changes in peripheral auditory stimulus processing or "salience networks"[9])	(neuro)physiological correlates of the distress experience (e.g. changes in neurophysiological stimulus processing patterns, vegetative reactions, hormonal influences, etc.[10])
	Paper 1, Part 1 **Boecking B**, Klasing S, Walter M, et al. Vascular–Metabolic Risk Factors and Psychological Stress in Patients with Chronic Tinnitus. *Nutrients*. *2022;14(11):2256*			**Paper 1, Part 2** **Boecking B**, Klasing S, Walter M, et al. Vascular–Metabolic Risk Factors and Psychological Stress in Patients with Chronic Tinnitus. *Nutrients*. *2022;14(11):2256*
'psychological perspective' cognitive-affective correlates	Perception, appraisal and experience of these (neuro)physiological correlates[11]	Perception, appraisal and experience of these (neuro)physiological correlates (the psychological effects of negative life events[12])	Perception, appraisal and experience of these (neuro)physiological states or influences[13]	Perception, appraisal and patterns of experience (e.g. investigation of possible correlations between 'tinnitus-related distress' and other psychological constructs such as 'aggression inhibition', or 'stress'[14])
			Papers 5-6 **Boecking**, et al. Hearing Therapy Improves Tinnitus-Related Distress in Mildly Distressed Patients with Chronic Tinnitus and Mild-to-Moderate Hearing Loss: A Randomized-Controlled Cross-Over Design. *J Clin Med. 2022;11(7):1764.vel* **Boecking**, et al. Hearing Aid Use Time Is Causally Influenced by Psychological Parameters in Mildly Distressed Patients with Chronic Tinnitus and Mild-to-Moderate Hearing Loss. *J Clin Med. 2022;11(19):5869.evel 3.*	**Papers 2-4** **Biehl, Boecking**, et al. Personality Traits, Perceived Stress, and Tinnitus-Related Distress in Patients With Chronic Tinnitus: Support for a Vulnerability-Stress Model. Front Psychol. 2020;10 **Boecking**, et al. Tinnitus-related distress and pain perceptions in patients with chronic tinnitus–Do psychological factors constitute a link? *PLOS ONE. 2020;15(6):e0234807* **Boecking**, et al. Two birds with one stone.–Addressing depressive symptoms, emotional tension and worry improves tinnitus-related distress and affective pain perceptions in patients with chronic tinnitus. *PLOS ONE. 2021;16(3):e0246747*

A third relevant assumption refers to the impossibility to deduce a cause-and-effect relationship between two variables solely on the basis of an observed correlation ([3] **correlation ≠ causation**; see **Figure 1**). For example, the distress some individuals may experience upon 'perceiving' a tinnitus symptom does not have to be 'caused' by it.

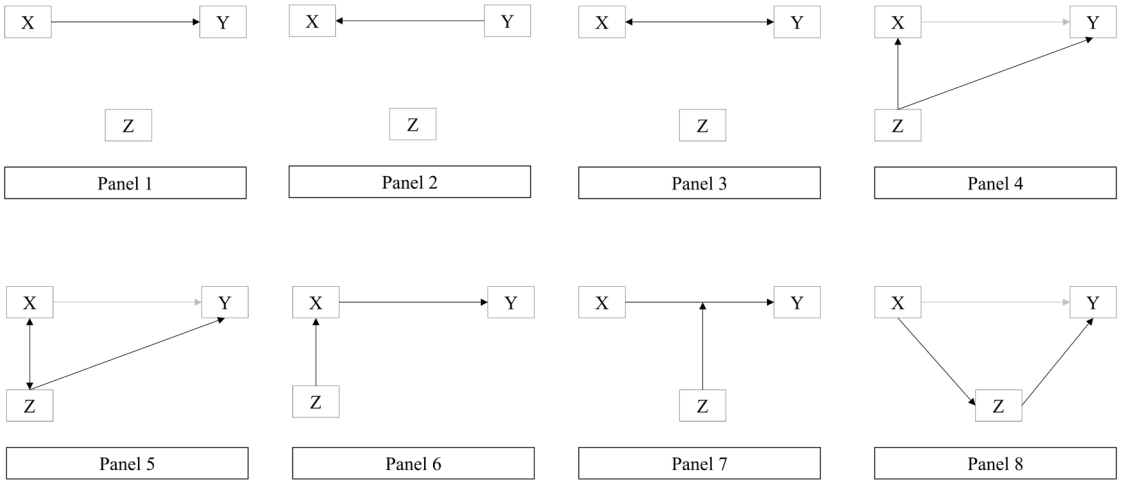

Figure 1. External variables and an X → Y relationship (adapted from [15[p562]]) and common causal influences that can underlie an observed X → Y association [16]. *Example*: X = 'tinnitus sound'; Y = 'tinnitus-related distress'; Z = 'pre-existing distress'. **Panel 1**: X causes Y. **Panel 2**: Y causes X. **Panel 3**: X and Y cause each other. **Panel 4**: Z causes both X and Y. **Panel 5**: Z causes Y, but correlates with X. **Panel 6** ('Moderation''): Z causes X and X causes Y. **Panel 7** ('Moderation''): Z causally influences the strength of the X → Y relationship. **Panel 8** ('Mediation'): Z mediates the X → Y relationship (X causes Z, and Z causes Y). Light gray arrows indicate a spurious X → Y relationship.

Chronic Tinnitus: Phantom Sound and Phenomenon

Tinnitus denotes '*the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source*' [17(p1)]. The tinnitus symptom can differ in its (1) perceived localisation [unilateral or bilateral in the ear; in the head]; (2) onset [spontaneous vs. gradual]; (3) duration (acute [< 3 months] vs. chronic [> 3 months] [18]); (4) (its perception's) course [intermittent vs. constant]; and (5) quality [such as hissing, ringing, crackling, humming, whistling or hissing] [19].

The clinical and research literature does not always define 'tinnitus' equivocally – and uses the term to describe different phenomena. These include, for example, tinnitus-related neural activity, patients' self-report of the tinnitus symptom, patients' degrees of hearing loss (HL), questionnaire measures assessing tinnitus-related distress (TRD), or *general* emotional distress that is attributed to a contemporaneous tinnitus symptom. Linked to this definitional ambiguity and heterogeneous study quality, prevalence estimates of 'tinnitus' vary widely and range from 8.7 – 28.3 % in Europe [20].

The majority of people habituate to the symptom [21]**,** however, a substantial proportion of patients experience psychological distress – which can reach clinical levels in about 1 - 2.4% of patients presenting to medical services [22].

It is this (pre-existing, resultant or exacerbated) distress which likely facilitates and constitutes symptom chronification [23]**.** Due to the strong conceptual overlap between chronic tinnitus and psychological phenomena, most notably depression [24], it has been argued that 'chronic tinnitus' is a centrally represented, 'genuine' psychosomatic phenomenon [17] – which has to be distinguished from acute, often medically mediated tinnitus presentations.

Pathogenesis of Chronic Tinnitus: It's in the Inner Ear – Is It?

Various theories link HL and tinnitus symptom onset [25–27]. Whilst early theories suggested that tinnitus-related neural activity (TRNA) originated peripherally (i.e. in the cochlea), later theories postulated that the tinnitus sound was in fact *centrally* generated in the auditory system - even if it may have been triggered by peripheral damage in the inner ear or cochlea [25,28].

Amongst many theories about the origin of TRNA and its subsequent cognitive-emotional processing, Hallam's 'discordant dysfunction theory' and Jastreboff's linked 'neurophysiological model' [25] have been very influential (cf. **Figure 2**). In short, the model postulates that

'*the tinnitus signal – the generation of which is typically linked to the periphery of the auditory system – is detected and processed by subconscious centers of the auditory pathways and finally interpreted at the highest level of the auditory system (probably the secondary auditory cortices). If a person just perceives tinnitus without having a negative reaction induced by it, the tinnitus signal may be constrained within the auditory pathways. If, however, this activity spreads to the limbic and autonomic nervous systems by activation of specifically the sympathetic part of the autonomic system, it evokes several negative reactions such as annoyance, anxiety, and panic and triggers survival reflexes resulting in a decreased ability to enjoy life activities. This last mentioned effect has a profound impact on a person's life*' [29(p579)]

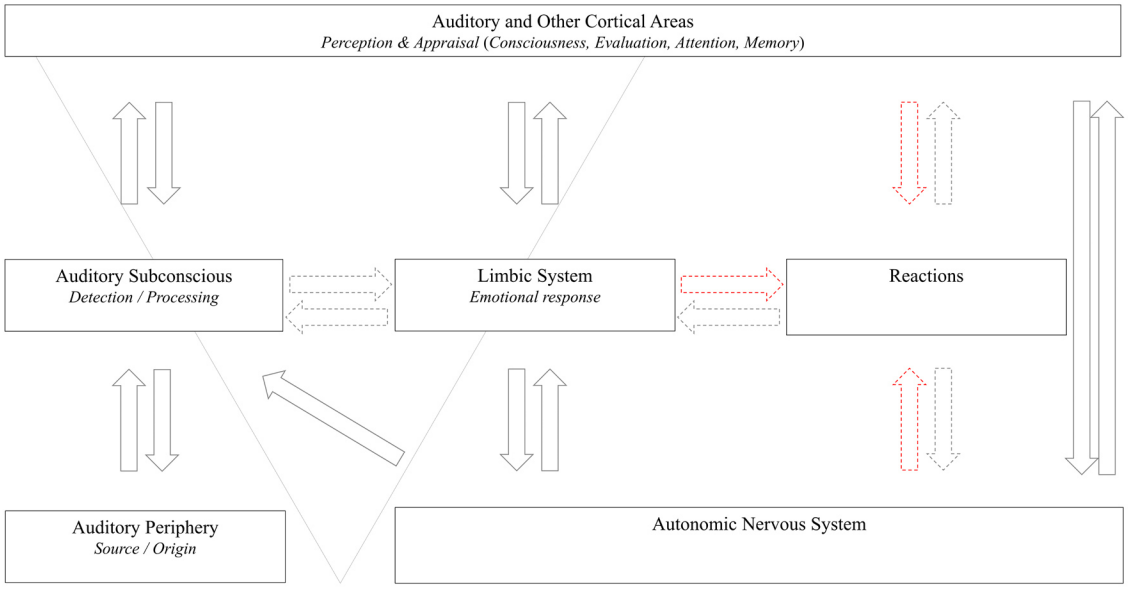

Figure 2. Jastreboff's Neurophysiological Model of Tinnitus (adapted from [29]).

In more detail, the theory postulates that outer hair cell damage in the cochlea causes pathological changes in type II auditory nerve fiber signals. These changes effect disinhibition in the dorsal cochlear nucleus – thereby generating tinnitus-related neural activity (TRNA) as a function of regular discharge patterns of afferent cochlear nerve fibers [30] (other authors, however, argue for centralized generation of TRNA [28]). Cochlea pathology may then lead to reduced auditory nerve activity that results in increased or bursting compensatory neural activity within central auditory structures [31]. Once the tinnitus symptom reaches consciousness and is appraised as 'distressing', limbic pathways exacerbate the quality of the auditory signal. TRD is then represented across sympathetic and limbic systems (the tinnitus symptom is experienced as anxiety provoking and emotionally significant), attentional systems (individuals struggle to ignore the 'threatening' tinnitus symptom), and frontal-executive systems (individuals struggle to shift attention away from the tinnitus symptom towards other stimuli).

Indeed, chronic tinnitus – particularly if experienced as distressing – correlates with various non-auditory neural networks [32,33]. For example, various studies reported differences in the so-called default-mode network (DMN) [34] in resting-state functional connectivity between healthy controls and individuals with tinnitus symptomatology and concomitant HL [35], emotional distress [36], or cognitive dysfunction [37,38]. Due to the as-yet unmeasurable nature of the tinnitus symptom 'as such', however, the functional nature of the measured differences remains somewhat elusive and future, well-controlled studies ought to stratify included participants based on degrees of cognitive dysfunction and distress.

Generally, neuroimaging studies report chronic-tinnitus-related findings across auditory, attention-related, and emotion-related neural networks. For an overview of findings, please be referred to Husain et al. [39]. It is essential to emphasize, however, that most neuroimaging is correlational in nature – thus disallowing for any conclusions about cause-effect relationships. All reported effects may be causes, consequences or correlates of the tinnitus-symptom, TRD, general emotional distress or other factors that occur in context of any given tinnitus symptomatology. To date, research suggests an interplay of audiologically mediated

genesis of the tinnitus symptom somewhere alongside the auditory pathway. Once entering consciousness, the symptom is interpreted in context of an individual's dynamic inner world, which leads to a variety of cognitive, emotional and behavioural consequences – that are conversely reflected in dynamically interlinked neural networks involved in attention, emotion, memory, motivation and stimulus interpretation.

Tinnitus and Tinnitus-Related Distress: Brothers or Distant Cousins?

As mentioned previously, the heterogeneity of tinnitus concepts led to a suggested distinction between 'Tinnitus' and 'Tinnitus Disorder'. Whilst the former is said to reflect 'the auditory or sensory component' of a tinnitus presentation; the latter aims to reflect 'associated suffering'; defined as 'emotional distress, cognitive dysfunction, and/or autonomic arousal that leads to behavioural changes and functional disability' [17].

Beyond, this important distinction, it can sometimes be challenging to decide, (1) if existing psychological models [40,41] explain *chronic tinnitus*-related distress or chronic tinnitus-related *distress* and (2) if the reported emotional distress is in fact 'tinnitus-related' or linked to other influences in any given patient's life [42].

To address this issue, it might be helpful to use formulation-based psychological frameworks, which do not require distinctions between 'general' and 'tinnitus-related' distress. 'Formulation' denotes the integration of psychologically relevant information (including self-reported information, observations, feelings and interpersonal dynamics [43]) into a coherent, theory-based narrative that allows for problem understanding as well as flexible treatment planning. The literature offers a wealth of formulation approaches [44–47] - spanning cognitive-behavioural [48–50], psychodynamic [51,52], or humanistic treatment approaches [53,54]. All perspectives share the application of psychological theory under the primacy of giving *meaning* to current distress experiences [55] on the basis of a trusting therapeutic relationship [56,57]. Indeed, some theorists have postulated that the joint construction of meaning lies at the core of the psychotherapeutic process [58–62].

Formulation models conceptualize feedback loops between biographical experiences (**vulnerability**), current factors influencing emotional distress ('**stress**' – including, but not limited to the tinnitus symptom), and intrapersonal or interpersonal behavioural **coping** strategies, that are also biographically anchored; i.e. learned [63]. Moreover, based on seminal work by Lazarus and Folkman, 'stress' is not a function of stressor or resource characteristics 'per se' (e.g. 'unemployment', 'friends', or 'tinnitus'), but of individuals' *appraisal*s, i.e. any given stressors' or resources' *meaning* for an individual's sense of belonging, needs, identity, emotions, and self-image [64,65]. Because the tinnitus sound is evaluated in context of both (1) concurrent limbic and sympathetic arousal (i.e. contemporaneous emotional distress linked to the respective individuals' life contexts) and (2) previous experiences (i.e. memories that contribute to the evaluation of stimuli as threatening [66]), vulnerability-stress-coping models constitute a useful transdiagnostic psychological framework. Importantly, whilst the model may suggest a separability of vulnerability, stress and coping-variables – this somewhat mechanistic distinction primarily aids structuring purposes, as all processes actively interact with each other simultaneously and at any given time. **Figure 3** illustrates a simple psychological vulnerability-stress-coping model.

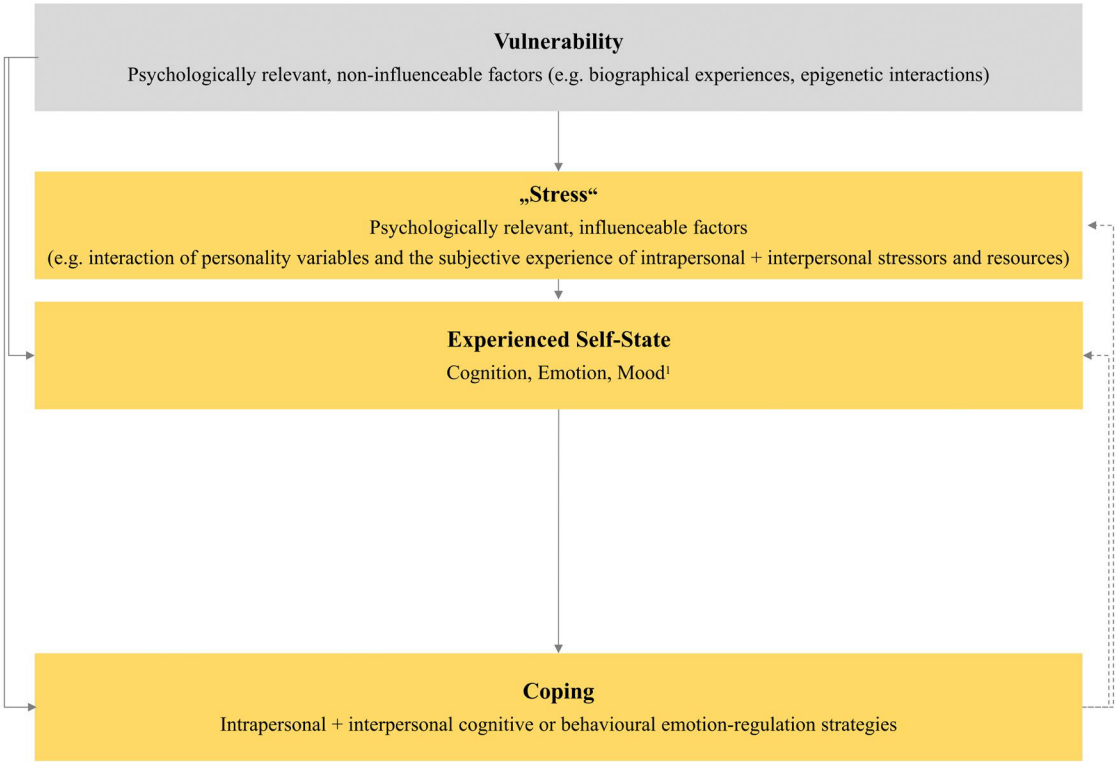

Figure 3. Psychological Vulnerability-Stress-Coping Model (*Figure by the author*).

Viewed in synopsis, the two models[2] suggest, that predisposing **vulnerability** factors for chronic tinnitus may comprise both *'somatic' components [and their associated psychological impact]* such as HL or inner-ear disorders and *'psychological' components [and their associated physiological correlates]* such as personality variables or maladaptive lifestyle behaviours that can increase the likelihood of symptom onset or distress-related stimulus processing.

Similarly, precipitating **stress** can comprise *'somatic' components [and their associated psychological impact]* such as HL or acoustic trauma and *'psychological' components [and their associated physiological correlates]* such as individuals' inner 'cognitive-emotional landscape'. In this context, the tinnitus symptom is appraised in context of personality factors and other current distress experiences.

Last, **coping reactions** can comprise *'somatic' components [and their associated psychological impact]* such as peripheral or central healing- or adaptation processes and, perhaps more overtly, *'psychological' components [and their associated physiological correlates]* such as intrapersonal and interpersonal reactions including cognitive (e.g. attentional focusing) or behavioural factors (e.g. emotional avoidance, maladaptive lifestyle behaviours, or help-seeking).

The following sections follow the vulnerability-stress-coping framework and briefly review chronic-tinnitus-related evidence from 'somatic' and 'psychological' perspectives.

[1] Cognition refers to all forms of cognition and knowledge (e.g. paying attention, remembering, judging, imagining, anticipating, planning, deciding, problem solving, and mental representation [67]). Emotions refer to a psychophysiological state of arousal. Mood refers to longer-lasting emotional states [68].

[2] The neurophysiological and vulnerability-stress-coping models.

Vulnerability

Somatic Risk Factors of Tinnitus-Symptom Onset

Hearing loss

The most important risk factor for many – though not all – tinnitus presentations is HL [69–71]. The evidence base for other somatic risk factors remains weak [72]. The likelihood of HL increases with age [73–75] as well as the presence and degree of behavioural or cardio-vascular risk factors such as noise exposure [76], smoking, or hypertension [77]. In individuals with normacusis and tinnitus, researchers also demonstrated some evidence of initial auditory damage in the cochlea [78] or elevation of hearing thresholds (i.e. lower hearing ability) [79] in the tinnitus frequency range (often > 8000 kHz). The frequency regions that are affected by HL often match individuals' subjective ratings of their respective tinnitus [80] suggesting a link between HL, frequency-specific deafferentiation patterns and quality of the tinnitus symptom [81].

Hearing loss and tinnitus-related distress.

Whilst HL is a reliable predictor of tinnitus onset, its relation to TRD is much less clear – with the latter being likely unrelated to objective characteristics of HL. Examining the effect of HL on TRD, Wallhäusser-Franke et al. [23,82] reported that the degree of HL in the acute phase of tinnitus onset predicted tinnitus loudness but *not* TRD in the chronic phase – further highlighting the distinction between tinnitus characteristics and distress as largely independent constructs [17]. Deklerck et al. [83] as well as Kleinstäuber and Weise [84] summarized prospective studies in the field and conclude that the majority of studies did ***not*** find associations between HL (and its degree or characteristics) and TRD across various follow-up intervals.

Psychological Risk Factors

Only few longitudinal studies investigated psychological vulnerability factors for chronic tinnitus or TRD respectively. A recent review summarized these studies and emphasized the crucial roles of psychological factors in mediating shifts from acute to chronic tinnitus symptomatology [84].

Modifiable behavioural risk factors that increase the likelihood of hearing loss

Because the onset of tinnitus is likely linked to HL, behavioural risk factors (primarily noise exposure) are relevant for tinnitus onset. Variables that were found to be associated with noise exposure comprised general risk-taking propensity [85], lifestyle behaviours [76] (such as smoking [86] or lack of exercise, poor diet, diabetes, and cardiovascular disease [87]) as well as underestimations of noise-related risk and hesitant use of hearing protection devices [88,89].

Overall, noise exposure as well as cardio-vascular influences constitute the main groups of modifiable risk factor for developing HL. Psychological functions that facilitate maladaptive noise exposure (i.e. individual cognitive, affective or motivational reasons for voluntary noise exposure or maladaptive lifestyle behaviours) are likely complex and remain largely uninvestigated at present.

Pre-existing psychological vulnerability

Pre-onset psychiatric diagnoses.

Psychological factors that heighten the risk of tinnitus onset mainly centre on pre-existing emotional distress. For example, some studies reported histories of psychiatric diagnoses in some individuals with chronic tinnitus [90,91] – likely linked to negative appraisals of the tinnitus sound in context of pre-existing psychological vulnerability [92].

Salviati et al. [93] examined a cross-sectional sample of $N = 239$ patients to investigate possible psychiatric vulnerability to tinnitus onset. Whilst no causal conclusion could be drawn, 25% of the sample had been diagnosed with a psychiatric disorder prior to the onset of tinnitus and 48% at the time of assessment. From a dimensional point of view, patients with psychiatric diagnoses showed higher expressions of depression, somatization, obsession, and anxiety compared to those that did not meet diagnostic criteria for a psychiatric disorder. The authors reported that TRD was moderate and directly correlated with the observed levels of psychopathology and stress. Moreover, approximately two thirds of the sample (66.66 %) reported 'a stressful event' during a 6-month period prior to tinnitus onset. Whilst these events involved areas such as 'work', 'finances', 'health', 'bereavement', 'change of residence', 'courtship-engagement-cohabitation', 'legal matters', 'family and social relations' or 'marriage', the specific <u>*meanings*</u> of these events within a biographically anchored psychological context were not examined.

Somatization tendency.

Whilst early studies had reported cross-sectional associations between somatization, i.e. '*a tendency to experience and communicate psychological distress as bodily and organic symptoms and to seek medical help for them* [94(p160)]' and TRD [95], several recent longitudinal studies confirmed this link. Examining Baseline, 5-year and 10-year follow-up data from the Netherlands Longitudinal Study on Hearing, Goderie et al. [86] reported that higher levels of somatization (and a history of smoking) predicted new-onset tinnitus 5 years later in a sample of 734 participants at baseline 137 of whom developed tinnitus 5 or 10 years later. This finding was confirmed in studies examining the transition from acute to chronic tinnitus at 6-month follow-up [23,82,96,97]

Noise sensitivity.

Vielsmeier et al. [98] examined several predictors of chronification of acute tinnitus presentations and reported that 'noise sensitivity' at the time of tinnitus onset (which is also associated with emotional factors [99]) predicted chronic TRD at 6-months follow-up.

Stressful life events.

Only one study investigated the common clinical observation, that tinnitus onset was associated with stressful life events. Yildirim et al [100] asked $N = 200$ patients with chronic tinnitus, whether stressful life events had coincided with the onset of their tinnitus symptomatology. Results indicated that 13.5% of the sample reported previous stressful life events pertaining to 'loss or serious illness of a family member', 'other family related problems', and 'work related problems'. Group comparisons further revealed that patients with a history of reported stressful life events that coincided with symptom onset further reported significantly higher rates of TRD as measured by the Tinnitus Handicap Inventory (THI).

Negative appraisal of the tinnitus symptom.

Research has examined several non-specific psychological risk factors that may influence a habitually negative appraisal of stimuli in general and the tinnitus symptom in particular. Amongst these, childhood trauma and personality factors featured prominently.

Childhood trauma.

Some studies investigated childhood trauma as a risk factor for emotional distress in patients with chronic tinnitus. Here, cross-sectional evidence suggested an association between self-reported childhood trauma and TRD. For example, Altintas et al. [101] reported that, compared to $n = 45$ healthy controls, $n = 45$ patients with chronic tinnitus reported significantly higher rates of anxiety, depression, dissociative experiences and childhood trauma. However, direct associations between childhood trauma and TRD were not investigated. This gap was addressed by Belli et al. [102] who found a significant correlation between childhood trauma and TRD. Overall, childhood trauma likely poses a risk factor for interpreting stimuli in a threatening way; however, research on specifically trauma-informed interpretations of the tinnitus symptom is limited to date.

Personality factors.

Numerous studies investigated associations between personality characteristics and TRD. A recent review concluded that (1) evidence on any such associations was largely inconclusive; however that (2) there is some evidence for an association between 'neuroticism' and TRD [103]. Neuroticism has been defined as '*the trait disposition to experience negative affects, including anger, anxiety, self-consciousness, irritability, emotional instability, and depression*'[104(p144)]. Individuals with high expressions of neuroticism struggle to respond adequately to environmental stress, interpret stimuli as threatening, and can experience minor obstacles as overwhelming [104]. The definition of neuroticism suggests that individuals high in neuroticism may interpret the tinnitus sound in a threatening manner – with elevated reactive levels of anxiety likely heightening the risk for the aforementioned feedback loop to close. However, a 'neurotic' personality predisposition is not sufficient to explain TRD; and vulnerability-stress interplays are likely better suited to account for the heterogeneity of findings in the personality risk-factor literature.

Somatic Correlates of Tinnitus (-Related Distress?)

The majority of available biomedical studies examine saliva or blood level cortisol as biomarkers of 'stress'. A thorough review of physiological correlates of all eligible psychological or somatic vulnerability factors exceeds the scope of this thesis. Focusing on 'chronic tinnitus' as index symptomatology, however, a recent review [105] highlighted difficulties in biomarker research that arise from the absence of objective diagnostic marker for chronic tinnitus. The authors thus aimed to summarize studies about biomarkers for 'a diagnosis' or 'the pathophysiology' of tinnitus. Importantly, it cannot be ruled out that the measured constructs may reflect contemporaneously present psychological (such as distress) and/or somatic phenomena respectively. The following sections briefly paraphrase the review's findings.

Metabolic parameters.

Kim et al. [105] conclude that there is some evidence for a link between tinnitus diagnosis and hyperlipidaemia as indexed by higher levels of total cholesterol and low-density lipoprotein as well as lower levels of high-density lipoprotein compared to healthy control subjects. Whilst the authors argue that metabolic parameters might form a risk factor for tinnitus onset due to rendering microcirculatory disturbance in the inner ear more likely, some studies also reported associations between metabolic parameters and TRD. To this regard, associations of metabolic parameter expressions with psychological constructs including perceived stress were not investigated at the behavioural level.

Platelet activity.

Examining haemostatic parameters (most importantly Mean Platelet Volume, MPV) some studies identified differences in haemostatic variables across patients with vs. without chronic tinnitus and normal hearing or HL respectively (summarized in Kim et al. [105]). Overall, whilst research studies are far, few and mixed, there is some evidence for elevated MPV rates or heightened platelet activity in patients with chronic tinnitus and high frequency HL [105]. At present, this biomarker appears to index non-specific inflammatory processes that can be observed across many other different conditions as well [106]. How and why platelet activity may potentially affect the inner ear and increase the risk for TRNA or TRD remains unknown at this stage.

Inflammatory parameters.

The authors conclude that some, but not other studies identified heightened levels of inflammatory markers such as C-reactive protein (CRP) or Neutrophil/lymphocyte ratio (NLR) in individuals with chronic tinnitus and high frequency HL. However, results are highly inconclusive – and it is unclear at present whether inflammatory markers actually reflect inner ear inflammation (i.e. factors relevant for tinnitus symptom onset) or stress-related, psychological processes [107].

Endocrine responses.

Reviewing studies on endocrine parameters such as serum cortisol, adrenocorticotropic hormone (ACTH), or 5-hydroxyindoleacetic acid (5-HIAA), Kim et al. [105] conclude that there is some evidence for hormonal conspicuities in patients with chronic tinnitus. However, any such effects are likely attributable to psychological experiences of distress – and less to inner-ear damage, HL, or the tinnitus symptom 'per se'.

Immunologic parameters.

Similar to the previous paragraph, evidence regarding immunological markers is mixed (e.g Interleukin [IL]-1α, 1β, 2, 6, Tumor necrosis factor α [TNF α]) – with the available body of studies mainly interpreting immunological findings as biomedical correlates of emotional distress [105].

Oxidative parameters.

Summarizing studies on oxidative parameters [105] (e.g. Serum total oxidant status [TOS], total antioxidant status [TAS], oxidative stress index [OSI], superoxide dismutase [SOD], or Serum Zinc), there is some evidence suggesting that these factors may contribute to inner-ear pathology such as hair cell death. However, oxidative parameters have also been linked to TRD in some studies, but not others.

Overall, the concept of oxidative stress on 'tinnitus' warrants much more consistent construct operationalizations – which systematically distinguish between tinnitus symptom- and distress-related parameters.

Psychological Contributors to Tinnitus-Related Distress

'Stress' - One word, different concepts.

In a recent overview, Elarbed et al. [108] concluded that the relationship between tinnitus and stress was highly inconclusive. Part of this difficulty lies in definitions of 'stress', which can refer to

1. a **response-based** concept wherein stress is defined via biophysiological changes that occur in response to a demanding event [109],
2. a **stimulus-based** concept wherein stress is defined as a dysregulating event that an individual experiences and that requires an adaptation effort [110], or,
3. a **transaction-based** concept wherein stress is defined as the psychological result of an interaction between internal or external stressors and an individual's perception and interpretation of (a) these stressors, as well as (b) available resources for coping with them [65],

Concept '3' is most often 'meant' in context of chronic tinnitus symptomatology – as indexed by the content of common TRD-related self-report questionnaires. Conceptually, tinnitus-related or –accompanying psychological distress is commonly described using a variety of terms including tinnitus handicap [111], tinnitus-severity [112], tinnitus-related distress [113], tinnitus disability [114], tinnitus annoyance [115], tinnitus bother [116] or tinnitus distress [117]. Additionally, 'perceived stress', i.e. the degree to which people appraise situations as stressful [118] has also been associated - and found to considerably overlap - with TRD [119–122].

At present, the variety of terms, potential construct overlaps and likely circular relationships between primary (pre-existing) and secondary ('tinnitus-related') 'stress' render the identification of pathophysiological trajectories difficult – and longitudinal or high-quality studies are sparse. Psychological stress can facilitate symptom onset or chronification [123] – likely against a backdrop of pre-existing psychological vulnerability [103]. Moreover, some low-quality evidence suggests an etiological role of perceived stress in the development of some chronic pain conditions [124] – which appears to share some pathophysiological variance with chronic tinnitus presentations [120,125,126]. Concomitant to the tinnitus-symptom, perceived stress and/or TRD may further preclude habituation to the tinnitus-sound – thereby

facilitating symptom chronification and maintaining psychological distress [40]. Lastly, the tinnitus sound itself can act as a perceived stressor – possibly against a backdrop of pre-existing psychological vulnerability and cognitive-affective reactions following symptom onset [41,119,127] – therein closing a vicious feedback loop between perceived stress and tinnitus maintenance or exacerbation [128,129].

Concurrent emotional state.

High levels of pre-existing psychological stress may contribute to the onset, exacerbation or maintenance of tinnitus symptomatology [130–132]. Moreover, numerous cross-sectional studies identified links between TRD and anxiety, depression, or psychological stress (for an overview see Deklerck et al., [83 Table 4] or Elarbed et al. [108]). Available longitudinal studies also consistently demonstrate that general psychological distress at the time of tinnitus symptom onset predicted symptom chronification as well as appraisal of the tinnitus symptom as 'disabling' 6 months later [23,82,96,97]

Using an ecological momentary assessment design, Goldberg et al [133] demonstrated a direct link between individuals' moment-to-moment psychological stress experiences and TRD – likely owed to both construct overlap and an assessment of the latter in context of the overall context of a person's momentary situation and emotional state. The authors argued that these factors varied based on a common underlying factor – which is likely psychological in nature [134] and might be interpreted as 'psychological stress' [133].

Applying a similar design, Probst et al. [135] reported that individuals who showed greater variability in intensity and quality of their emotional states reported overall higher levels of subjective tinnitus loudness. Moreover, 'stress' mediated the association between tinnitus loudness and tinnitus distress.

Stressful life events.

Examining a sample of Navy and marine servicemen, Cliffort et al. [136], reported that stressful, traumatic events during combat (firing a weapon, witnessing an attack, or being attacked) predicted tinnitus progression 3 months after the end of military deployment.

Perceived stress levels.

Fifteen studies reported significant correlations between TRD and measurements of perceived stress [108 Table3] that ranged from 0.26 to 0.67. Overall, findings on possible links between tinnitus loudness, TRD or 'stress' are inconsistent – likely owed to numerous confounding factors in existing studies, varying definitions of stress (event, emotion, biological state or cognitive appraisal), as well as inconsistent operationalizations of 'tinnitus'. Whilst it is likely that emotional or psychological stress modulates the perception and experience of the tinnitus sound, exact pathways remain unidentified.

Negative appraisal of the tinnitus symptom at the acute stage.

Five longitudinal studies examined the question, whether a distress-related appraisal of the tinnitus sound facilitated centralized representations of chronic tinnitus phenomenology – and drove feedback-loops between emotional distress, attentional focus and a chronic tinnitus percept beyond inner-ear damage. Results demonstrated that TRD at the acute stage predicted tinnitus decompensation, i.e. high levels of TRD, either 6 [23,82,96,97] or 24 months later [137]. In addition, emotional disturbances 'due to tinnitus' predicted work-related disability 'due to tinnitus' at 18-month follow-up [138]. Last, symptoms of depression – which highly overlap with TRD – also predicted TRD at a 2-year follow-up in a multivariate analysis controlled for gender, age, and income [137].

Coping

Because there is no identified healing process for chronic tinnitus [139], the following review limits itself to psychological coping mechanisms. Various theoretical papers examine the construct of coping in terms of managing TRD [140,141]. Overall, the available evidence suggests that TRD (and, associated, help-seeking behaviour) is related much more strongly to personal reactions (influenced by personality factors and idiosyncratic functions of coping strategies) than to symptom characteristics or strategies 'per se' [142].

Cognitive appraisal of the tinnitus symptom

Early research on tinnitus-related coping styles differentiated between 'adaptive' and 'maladaptive' coping styles following tinnitus onset. Budd and Pugh [143] operationalized 'maladaptive' coping as (1) catastrophic thinking about the consequences of tinnitus ('Tinnitus might cause a nervous breakdown', 'I will not be able to cope with the "noises"', 'I wonder what I have done to deserve tinnitus') or (2) avoidance behaviours ('I attempt to get away from the tinnitus by going to bed and avoid social situations'). The contribution of 'catastrophizing' to TRD has also been highlighted elsewhere [144,145] and suggests that an anxiety-prone interpretation of the tinnitus symptom may, in context of high psychological vulnerability, facilitate symptom chronification.

By contrast, 'adaptive' coping styles comprised individuals' 'use of positive self-talk' to encourage themselves to cope with tinnitus, alongside various coping strategies such as 'distraction' or 'attention switching'. Interestingly, embracing these 'adaptive' coping styles did <u>*not*</u> predict lower levels of TRD – highlighting the possibility that *seemingly* adaptive coping strategies may serve an avoidance function or mask underlying emotional issues. Crucially, Budd and Pugh emphasized that '*the mere use of effective coping strategies does not necessarily mean that [they] will be useful*' [143(p334)]. This important idea was further corroborated by Beukes et al. [146], Dineen et al. [147] and Andersson and Willebrandt [141] all of whom suggested that mechanistically-conceptualised coping strategies 'per se' can<u>*not*</u> ameliorate TRD.

Overall, the available research highlights the importance of coping behaviours' *context*, *meaning* and *function* for understanding psychological appraisal-emotion-reaction patterns.

Behavioural Reactions to the Tinnitus Symptom

Emotion-regulating coping behaviours.

Few longitudinal studies include information on maladaptive coping behaviours. Vielsmeier et al. [98] reported that 'alcohol use' following acute tinnitus onset predicted symptom chronification at 6-month follow-up. Whether this effect may be better understood from psychological [148,149] or medical perspectives [150], however, has not yet been investigated. Moreover, 'lack of regular physical exercise' was found to predict work-related disability 'due to tinnitus' at 18-month follow-up [138].

Interestingly, allegedly 'positive' coping styles (active and problem-oriented coping styles, self-distraction and self-affirmation) predicted *increased* levels of TRD at 6-month post-onset follow-up [151] – suggesting a potentially maladaptive psychological *function* of these behaviours that may require more in-detail investigations as to their appraisal, meaning and contexts for different individuals. Spiritual coping responses such as 'religiousness' and 'search for meaning' or cognitive coping responses such as 'trivialization' did not influence tinnitus decompensation at 6-months follow-up post-tinnitus onset [151].

Help-seeking.

Owed to the common-though-not-necessary contributions of HL and psychological distress reactions to chronic tinnitus, current treatment guidelines suggest a combination of hearing aid (HA) provision for individuals with HL – and psychological interventions for individuals with high levels of psychological distress following symptom onset and wish for psychotherapeutic support [18].

Examining factors associated with tinnitus help-seeking, Scott and Lindberg [152] controlled participants' HL levels and compared the psychological profiles of n = 117 tinnitus help-seeking patients with n = 201 non-help-seeking individuals with chronic tinnitus, and n = 317 age- and gender-matched healthy controls. Results indicated that (1) non-help-seeking individuals with chronic tinnitus did not differ from healthy control subjects (except for the former reporting higher frequency and severity levels of daily hassles and somatic complaints [specifically headaches and muscle tension]) and (2) help-seeking patients with chronic tinnitus differed across a variety of psychological parameters from both groups. For example, help-seeking patients showed elevated scores of anxiety and depression (including problems with sleep and concentration), stress-reactivity, and somatic complaints suggesting psychological predispositions as key motivators for help-seeking behaviour.

Another study that featured a similar between-group design with n = 50, 50, 75 respectively [153] reported similar psychological distress levels in help-seeking patients compared to non-help-seeking individuals and healthy controls. By contrast, however, non-help-seeking individuals were also characterized by higher psychological vulnerability than healthy controls – highlighting the need for psychological assessment and support at the point of symptom onset.

Hearing aid uptake and use.

Although HAs are a first-line treatment options for patients with HL and chronic tinnitus, little is known about audiological or psychological variables that predict their uptake or use-time respectively.

Two reviews of the available literature identified 39 empirical studies published between 1980 and 2009 [154] and 42 studies between 2011 and 2022 [155]. Vestergaard Knudsen et al. [154] examined four groups of variables (e.g. audiological [e.g. hearing sensitivity], psychological [e.g. self-reported activity limitation, source of motivation, expectation, attitude], demographic [e.g. age, gender], and external variables [e.g. cost]) across four outcome domains: (1) help-seeking, (2) obtaining a hearing aid, (3) using the hearing aid, and (4) becoming satisfied with it.

Somewhat surprisingly, age and gender were found to be irrelevant. The most promising predictor across all outcome domains was psychological in nature: '*Self-reported auditory difficulty'* predicted all four outcome domains – which differed from objective hearing sensitivity, which showed less consistent effects on outcomes. This finding demonstrates an interesting overlap with chronic tinnitus symptomatology, which is also influenced – if not characterized – by psychological, rather than audiological influences (and their behavioural or neurophysiological correlates). Using the available data to distil promising future research directions, Vestergaard Knudsen et al. [154] highlight the crucial role of psychological factors in hearing aid use and postulate '*the interaction between the professional and the client throughout an individual's hearing journey, self-efficacy, counselling style, and the role of professionals as gatekeepers*' [154(p144)] as most promising.

In their follow-up review, Knoetze et al. [155] distinguished between hearing help-seeking and hearing aid uptake and also found that age and sex did not influence either variable. As first step, hearing help-seeking was predicted by the perceived potential benefit of amplification; whereas hearing aid uptake was predicted by positive attitudes towards hearing aids, an understanding of their function, severity of HL and – in keeping with the previous review - greater self-reported hearing disability.

Psychological therapy.

Currently, no studies examine predictors of psychological treatment uptake in patients with chronic tinnitus.

Summary

Overall, it appears crucial to emphasize that neither vulnerability, stress, nor coping factors alone can conclusively explain tinnitus symptom onset or TRD respectively. Whereas medical factors may predispose individuals to developing HL or acute tinnitus, a mechanistic approach to understanding TRD appears somewhat unhelpful. Rather, the psychological *context* of individuals' lives and the *meaning* that they assign to the tinnitus symptom in context of their pasts and present may provide a framework for understanding individuals' reactions to the tinnitus sound and help developing helpful psychosomatic treatment pathways.

How can I tell that the past isn't a fiction designed to account for the discrepancy between my immediate physical sensations and my state of mind?

Douglas Adams, The Restaurant at the End of the Universe

Chapter 2 [Vulnerability]

Paper 1: Biomedical Correlates of Tinnitus Vulnerability and Psychological Distress Reactions

Placed at the junction of blood biomarkers and psychological experience, **Study 1** [156] uses blood index screening data to examine a medium-sized sample of patients with chronic tinnitus. The study examines biomedical correlates of vulnerability for tinnitus symptom onset or psychological distress reactions respectively. Results suggest a metabolic risk factor profile for patients with chronic tinnitus, and find tentative evidence for some potential biomarkers of perceived (*not* 'tinnitus-related-') distress in this population[3].

'***Abstract:*** *Little is known about molecular correlates of chronic tinnitus. We examined interrelationships between vascular–metabolic risk factors, perceived stress, and other routine blood values in patients with chronic tinnitus. Two-hundred patients (51% female) were screened for 49 blood parameters pertaining to vascular–metabolic risk, immune function, and redox processes. They further completed perceived stress- and tinnitus-related distress questionnaires. Following descriptive analyses, gender-specific sets of age- and tinnitus-severity-adjusted regression models investigated associations between perceived stress and blood parameters. Patients reported mildly elevated levels of perceived stress. Elevated levels of total cholesterol (65% and 61% of female and male patients, respectively), non-HDL-c (43/50%), LDL-c (56/59%), and lipoprotein_a (28/14%) were accompanied by high rates of overweight (99/100%) and smoking (28/31%). A low-level inflammatory state was accompanied by reduced reactive oxygen species (ROS)-neutralizing capacity (reduced co-enzyme Q10 and SOD1 levels). Most vascular risk factors were not correlated with perceived stress, except for fibrinogen (ß = -0.34) as well as C-reactive protein (ß = -0.31, p < 0.05) in men, and MCV (ß = -0.26, p < 0.05) in women. Interrelations between blood parameters and stress levels need to be investigated within psychobehavioural frameworks across varying distress levels. Alongside psychological interventions, a low-level inflammatory state may be a route for pharmacological therapeutics.*' [156(p1)]

[3] A follow-up study (not presented in the thesis) used the same data and did not identify specific biomarkers of tinnitus-related distress [157].

nutrients

MDPI

Article

Vascular–Metabolic Risk Factors and Psychological Stress in Patients with Chronic Tinnitus

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Abstract: Little is known about molecular correlates of chronic tinnitus. We examined interrelationships between vascular–metabolic risk factors, perceived stress, and other routine blood values in patients with chronic tinnitus. Two-hundred patients (51% female) were screened for 49 blood parameters pertaining to vascular–metabolic risk, immune function, and redox processes. They further completed perceived stress- and tinnitus-related distress questionnaires. Following descriptive analyses, gender-specific sets of age- and tinnitus-severity-adjusted regression models investigated associations between perceived stress and blood parameters. Patients reported mildly elevated levels of perceived stress. Elevated levels of total cholesterol (65% and 61% of female and male patients, respectively), non-HDL-c (43/50%), LDL-c (56/59%), and lipoprotein_a (28/14%) were accompanied by high rates of overweight (99/100%) and smoking (28/31%). A low-level inflammatory state was accompanied by reduced reactive oxygen species (ROS)-neutralizing capacity (reduced co-enzyme Q10 and SOD1 levels). Most vascular risk factors were not correlated with perceived stress, except for fibrinogen ($ß = -0.34$) as well as C-reactive protein ($ß = -0.31$, $p < 0.05$) in men, and MCV ($ß = -0.26$, $p < 0.05$) in women. Interrelations between blood parameters and stress levels need to be investigated within psychobehavioural frameworks across varying distress levels. Alongside psychological interventions, a low-level inflammatory state may be a route for pharmacological therapeutics.

Keywords: chronic tinnitus; blood parameters; biomarkers; perceived stress; vascular–metabolic risk

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1. Introduction

Chronic tinnitus—a symptom of interrelated biopsychological contributions—denotes the conscious awareness of a tonal or composite noise without identifiable corresponding external acoustic source. Prevalence estimates vary widely and range from 5 to 43% [1,2]. Whilst the majority of people habituate to the symptom [3], a proportion of patients experience psychological distress, which appears to facilitate symptom chronification [4]—possibly through interactions of pre-existing psychological vulnerability and cognitive–affective reaction patterns following symptom onset [5–7].

Biomarker research for chronic tinnitus is still in its infancy [8–12], yet a role of vascular risk factors and inflammatory processes has been suggested [13,14]. Other studies investigated cytokine changes [15], mean platelet volumes (MPV), and neutrophil-to-lymphocyte ratios (NLR) with inconclusive results. Some studies reported increased MPV [16,17] or NLRs [17,18] in tinnitus patients, whereas other studies did not find any such differences [19] or reported lower MPV levels in tinnitus patients compared to controls [20]. A few studies further reported an association between zinc status and tinnitus severity [21,22].

'Stress' has been defined as "the quality of experience [...] which, through either overarousal or underarousal, results in psychological or physiological distress" [23]. Tinnitus-correlated psychological distress has been described using a variety of terms, including tinnitus handicap [24], tinnitus severity [25], tinnitus-related distress [26], tinnitus disability [27], tinnitus annoyance [28], tinnitus bother [29], or tinnitus distress [30]. Additionally, "perceived stress", i.e., the degree to which people appraise situations as stressful [31] considerably overlaps with tinnitus-related distress [5,15,32,33].

Emotional distress and tinnitus symptomatology are intricately connected: For instance, perceived stress can trigger sudden hearing loss and facilitate tinnitus onset or chronification [34–36]—likely against a backdrop of psychological vulnerability [37]. Moreover, some low-quality evidence suggests an etiological role of perceived stress in the development of some chronic pain conditions [38]—which may share pathophysiological variance with chronic tinnitus presentations [32,39,40]. Concomitant to the tinnitus-symptom, psychological distress may prevent habituation to the tinnitus sound—and thereby facilitate symptom chronification and maintain affective arousal [41]. Lastly, the tinnitus sound itself can act as a stressor—therein closing a vicious cycle between perceived stress and tinnitus exacerbation [35,42].

Regarding biological underpinnings of perceived stress, Juster et al. [40] proposed 26 putative biomarkers that included immune, vascular-metabolic and oxidative parameters that were also denoted as possible transdiagnostic markers across various psychological conditions [43–45]. In this vain, biomarker candidates that were identified in patients with chronic tinnitus, and that relate to cardiovascular, inflammatory, or immune-related processes [12], may or may not overlap with biomarkers of perceived stress.

In this work, we thus explored interrelationships between perceived stress, vascular-metabolic risk factors, and routine blood parameters in patients with chronic tinnitus. First, we describe the obtained blood parameters relative to their reference ranges in our patient sample. Second, we investigate associations between 'outstanding' biomarkers and patients' perceived stress levels—considering potential gender differences [46,47].

2. Materials and Methods

2.1. Participants

The present study reports questionnaire and blood parameter data from $n = 200$ patients with chronic tinnitus (51% female; $M_{age} = 54.68$; $SD = 8.44$) who (a) self-referred to the Tinnitus Center at Charité Universitätsmedizin Berlin between April 2016 and August 2017; (b) suffered from chronic tinnitus (lasting for >3 months); (c) were 18 years of age or older; and (d) completed, amongst other measures, the German Tinnitus- and Perceived Stress Questionnaire. Exclusion criteria included an inability to consent due to severe psychiatric or physical limitations, as well as a participation in any other research study. Upon arrival at the Tinnitus Center, participants provided blood samples (obtained via 1×2 mL, 1×6 mL EDTA, 2×4.5 mL lithium heparin, 2×4.5 mL serum, and 1×2.7 mL citrate tubes), underwent audiological testing (the results of which are reported elsewhere), and completed the psychological questionnaires. Ethical approval was obtained from Charité Universitätsmedizin Berlin (No: EA1/115/15). All research was performed in accordance with the Declaration of Helsinki and informed consent was obtained from all participants.

2.2. Measures

2.2.1. Blood Index Values

The obtained blood samples were screened for a number of indices. The following (I) cellular immune response markers were obtained: leukocytes, lymphocytes (total), lymphocytes (%), monocytes (total), monocytes (%), neutrophils (total), neutrophils (%), immature granulocytes (total), immature granulocytes (%), eosinophils (total), eosinophils (%), basophils (total), and basophils (%). (II) Inflammatory response markers included cytokines (TNF-α, IL-6) and acute-phase Proteins (CRP, fibrinogen, ferritin, thrombo-

cytes, MPV). (III) Hematological markers included hemoglobin, hematocrit, erythrocytes, MCV, RDW_CV, MCH, and MCHC. Measured (IV) (co-)enzymes comprised superoxide_dismutase_1, superoxide_dismutase_2, lipid_peroxidase, and ubiquinone (Q10). (V) Vascular-metabolic risk markers included total cholesterol, triglycerides, HDL-c, non-HDL-c, LDL-c, and lipoprotein_a. (VI) Liver function markers included albumin, GOT, GPT, and gamma_GT. (VII) Kidney function markers included GFR and creatinine. (VIII) Purine metabolism was indexed by uric acid. Lastly, (IX) vitamins, minerals, and trace elements included calcium, magnesium, zinc, selenium, and vitamin D3.

2.2.2. Perceived Stress

Perceived stress was measured using the Perceived Stress Questionnaire (PSQ; [48,49]). 'Tension' explores tense disquietude, exhaustion, and lack of relaxation. 'Worries' assesses anxious concern for the future, and feelings of desperation and frustration. 'Joy' assesses positive feelings of challenge, joy, energy, and security, and 'Demands' assesses perceived environmental demands, such as lack of time, pressure, and overload. The scale consists of 20 items that are rated on a 4-point scale (1 = almost never; 2 = sometimes; 3 = often; 4 = almost always). All indices are linearly transformed to range from 0 to 100 and summed up to a total score for which joy is recoded.

2.2.3. Tinnitus-Related Distress

The German version of the tinnitus questionnaire [50,51] assesses tinnitus-related psychological distress. It consists of 52 statements that are answered on a 3-point scale (0 = not true; 1 = partly true; 2 = true) across five subscales (cognitive and emotional burden, persistence of sound, hearing difficulties, sleep difficulties, and somatic complaints). Based on clinical and research considerations, we include only the total score in our analysis [52,53]. The total score includes 40 items, with two items being included twice, thus yielding a score from zero to 84. Biesinger et al. [54] suggested a cut-off of 46 points to distinguish high vs. low symptom burden, i.e., "decompensated" vs. "compensated" tinnitus. The scale's test–retest reliability is good (total score: $r = 0.94$; [55]).

2.3. Statistical Analyses

Statistical analyses included descriptive and univariate regression analyses. All analyses were computed using IBM SPSS Statistics (v. 24). The significance level was set to $\alpha = 0.05$.

2.4. Data Preparation

Following visual inspection of the data, "extreme outliers" (defined as featuring z-factor values of >3.29) were excluded for each blood parameter.

2.5. Descriptive Analyses

For the blood parameter data, patient values were categorized as 'normal', 'increased', or 'decreased' using gender-specific norm-reference values that were provided by two processing laboratories (Labor Berlin—Charité Vivantes GmbH, biovis Diagnostik MVZ GmbH). Next, frequency counts of women and men with 'increased' or 'decreased' values were computed for each blood parameter.

2.6. Univariate Regression Analyses

To examine the impact of perceived- but not tinnitus-related distress on the measured blood parameters, we investigated gender-separate univariate regression models, with PSQ scores as independent variables, blood parameters as dependent variables, and age as well as tinnitus-related distress as covariates. Due to the scarcity of blood-parameter research, expected small effect sizes, and the conservativeness of the Bonferroni correction [56,57], we conducted separate regression analyses—thereby tolerating increased type-I error rates. Thus, our findings necessitate replication.

3. Results

Table 1 features an overview of the sociodemographic information.

Table 1. Sociodemographic data and patient characteristics (n = 169).

	n	%
Nationality		
German	158	79.0
Other	11	5.5
Education		
Completed junior apprenticeship	44	22.0
Completed senior apprenticeship	28	14.0
University degree	90	45.0
Employment 'yes'	119	59.5
Relationship status		
Single	31	15.5
Married	114	57.0
Divorced	16	8.0
Widowed	7	3.5
Duration of tinnitus		
<0.5 year	21	10.5
0.5–1 year	25	12.5
1–2 years	12	6.0
2–5 years	31	15.5
>5 years	66	33.0
Past psychotherapy 'yes'	86	43.0

3.1. Descriptive Indices

Table 2 features descriptive results for the obtained psychological indices; Table 3 for vascular-metabolic risk factors, and Table 4 for vascular-metabolic blood parameters.

Table 2. Means and standard deviations for the psychological indices.

	Total (n = 200)		**Women (n = 102)**		**Men (n = 98)**	
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***
PSQ total	50.27	13.19	51.44	12.16	49.07	14.16
Worries	13.62	9.32	13.79	10.04	13.44	8.56
Tension	19.14	16.50	19.99	18.03	18.26	14.79
Joy *	16.80	15.67	15.89	13.31	17.74	17.83
Demands	17.08	14.55	17.46	15.33	16.70	13.76
TQ total	43.80	19.01	45.29	18.27	42.26	19.72

* Reversely coded (i.e., the higher the better). PSQ = Perceived Stress Questionnaire; TQ = Tinnitus Questionnaire (German version).

Table 3. Means and standard deviations of vascular–metabolic risk factors and frequency rates of blood parameters with increased or decreased incidence rates of ≥25%. Relevant indices are highlighted for emphasis.

		Total		**Women**		**Men**	
	Unit	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***
§ Weight	kg	78.86	15.71	78.59	16.04	79.12	15.50
§ BMI	kg/m^2	26.32	4.44	25.94	4.70	26.70	4.17
		Frequency	% (total)	Frequency	% (women)	Frequency	% (men)
† Current smoking	'yes'	59	45.4	33	50.8	26	40.0
†§ Regular drinking	'yes'	29	22.3	14	21.5	15	23.1

§ These risk factors were only available for a subset of n = 128 patients (65% of total sample; n = 65 women; n = 63 men).† Operationalized as drinking regularly "at least weekly". BMI = Body Mass Index (underweight: <18.5; normal: 18.5–25; overweight: 25–30; obese: >30).

No gender differences emerged. Lifetime histories and last-year incidents of vascular events were negligible (lifetime: coronary heart disease (n = 5); stroke (n = 3); cardiac insufficiency (n = 8); last-year: coronary heart disease (n = 2); stroke (n = 2); cardiac insufficiency (n = 5)).

Table 5 features means, standard deviations and reference values for non-vascular-metabolic blood parameters.

High proportions of both female and male patients showed decreased levels of superoxide–dismutase 1, lipid-corrected ubiquinone (Q10), and GFR, as well as increased levels of total cholesterol, non-HDL-c, and LDL-c. High proportions of female patients showed increased levels of lipoprotein_a, whilst high proportions of male patients showed increased levels of monocytes and decreased levels of zinc.

Table 4. Frequency rates of participants with increased or decreased vascular-metabolic blood parameters. Indices with 'outstanding' rates of ≥ 25% are highlighted for emphasis.

	Unit	Mean	*SD*	Reference Values		Frequency Decreased						Frequency Increased					
				Men	Women	Total	(% Total)	Women	(% Women)	Men	(% Men)	Total	(% Total)	Women	(% Women)	Men	(% Men)
Total cholesterol	mg/dL	212.31	38.24	<200	<200	-	-	-	-	-	-	126	**(63.0)**	66	**(64.7)**	60	**(61.2)**
Triglycerides	mg/dL	124.25	62.24	≤200	≤200	-	-	-	-	-	-	23	(11.5)	7	(6.9)	16	(16.3)
HDL-c	mg/dL	63.23	18.34	≥35	≥45	6	(3)	3	(2.9)	3	(3.1)	-	-	-	-	-	-
Non-HDL-c	mg/dL	149.34	39.75	<150	<150	-	-	-	-	-	-	93	**(46.5)**	44	**(43.1)**	49	**(50.0)**
LDL-c	mg/dL	137.10	34.56	<130	<130	-	-	-	-	-	-	115	**(57.5)**	57	**(55.9)**	58	**(59.2)**
Lipoprotein_a	nmol/L	45.83	65.34	<72.0	<72.0	-	-	-	-	-	-	42	(21.0)	28	**(27.5)**	14	(14.3)

HDL-c = high-density lipoprotein; LDL-c = low-density lipoprotein; non-HDL-c = non-high-density lipoprotein.

Table 5. Means, standard deviations, reference values, and frequency rates of participants with increased or decreased non-vascular-metabolic blood parameters. Indices with 'outstanding' rates of ≥25% are highlighted for emphasis.

	Unit	Mean	*SD*	Reference Values		Frequency Decreased						Frequency Increased					
				Men	Women	Total	% Total	Women	% Women	Men	% Men	Total	% Total	Women	% Women	Men	% Men
Leukocytes	nL	6.58	1.58	3.9–10.5	3.9–10.5	6	(3)	3	(2.9)	3	(3.1)	2	(1.0)	-	-	2	(2.0)
Lymphocytes	absolute/nL	1.96	0.56	1.10–4.50	1.10–4.50	8	(4)	5	(4.9)	3	(3.1)	2	(1.0)	-	-	-	-
Lymphocytes	%	30.43	7.76	20.0–44.0	20.0–44.0	17	(8.5)	9	(8.8)	8	(8.2)	12	(6.0)	9	(8.8)	3	(3.1)
Monocytes	absolute/nL	0.52	0.16	0.10–0.90	0.10–0.90	-	-	-	-	-	-	6	(3.0)	1	(1.0)	5	(5.1)
Monocytes	%	7.94	1.92	2.0–9.5	2.0–9.5	-	-	-	-	-	-	35	(17.5)	11	(10.8)	24	**(24.5)**
Neutrophils	absolute/nL	3.87	1.20	1.50–7.70	1.50–7.70	1	(0.5)	1	(1.0)	-	-	-	-	-	-	-	-
Neutrophils	%	58.35	8.74	42.0–77.0	42.0–77.0	9	(4.5)	6	(5.9)	3	(3.1)	5	(2.5)	4	(3.9)	1	(1.0)
NLR	cells/µL	2.10	0.86	1–3 *	1–3 *	-	-	-	-	-	-	-	-	-	-	-	-
Immature_granulocytes	absolute/nL	0.02	0.02	<0.050	<0.050	-	-	-	-	-	-	11	(5.5)	1	(1.0)	10	(10.2)
Immature_granulocytes	%	0.36	0.20	0.0–1.0	0.0–1.0	-	-	-	-	-	-	4	(2.0)	-	-	4	(4.1)
Eosinophils	absolute/nL	0.14	0.10	0.02–0.50	0.02–0.50	3	(1.5)	1	(1.0)	2	(2.0)	1	(0.5)	-	-	1	(1.0)
Eosinophils	%	2.07	1.32	0.5–5.5	0.5–5.5	11	(5.5)	8	(7.8)	3	(3.1)	6	(3.0)	3	(2.9)	3	(3.1)
Basophils	absolute/nL	0.05	0.02	0.00–0.20	0.00–0.20	-	-	-	-	-	-	-	-	-	-	-	-
Basophils	%	0.74	0.32	0.0–1.8	0.0–1.8	-	-	-	-	-	-	-	-	-	-	-	-
TNF-α	pg/mL	0.32	0.05	<8.1	<8.1	-	-	-	-	-	-	-	-	-	-	-	-
IL6	ng/L	1.83	1.12	≤7.0	≤7.0	-	-	-	-	-	-	3	(1.5)	1	(1.0)	2	(2.0)
CRP	mg/L	1.61	1.72	<5.0	<5.0	-	-	-	-	-	-	10	(5.0)	7	(6.9)	3	(3.1)
Fibrinogen	g/L	2.72	0.57	1.60–4.00	1.60–4.00	4	(2)	4	(3.9)	-	-	3	(1.5)	2	(2.0)	1	(1.0)
Ferritin	qg/L	128.29	93.09	30.0–400.0	13.0–150.0	4	(2.0)	2	(2.0)	2	(2.0)	19	(9.5)	14	(13.7)	5	(5.1)
Thrombocytes	nL	244.33	54.29	150–370	150–370	1	(0.5)	-	-	1	(1.0)	5	(2.5)	4	(3.9)	1	(1.0)
MPV	fl	10.68	1.00	7.0–12.0	7.0–12.0	-	-	-	-	-	-	19	(9.5)	7	(6.9)	12	(12.2)
Hemoglobin	g/dL	14.40	1.24	13.5–17.0	12.0–15.6	5	(2.5)	2	(2.0)	3	(3.1)	5	(2.5)	-	-	5	(5.1)
Hematocrit	l/L	0.43	0.04	0.395–0.505	0.355–0.455	6	(3.0)	3	(2.9)	3	(3.1)	6	(3.0)	3	(2.9)	3	(3.1)
Erythrocytes	pl	4.82	0.43	4.3–5.8	3.9–5.2	1	(0.5)	-	-	1	(1.0)	5	(2.5)	-	-	5	(5.1)
MCV	fl	88.33	3.60	80.0–99.0	80.0–99.0	2	(1.0)	1	(1.0)	1	(1.0)	-	-	-	-	-	-

Table 5. *Cont.*

	Unit	Mean	*SD*	Reference Values		Frequency Decreased						Frequency Increased					
				Men	Women	Total	% Total	Women	% Women	Men	% Men	Total	% Total	Women	% Women	Men	% Men
RDW_CV	%	12.79	0.58	11.5–15.0	11.5–15.0	-	-	-	-	-	-	-	-	-	-	-	-
MCH	pg	29.89	1.27	27.0–33.5	27.0–33.5	3	(1.5)	2	(2.0)	1	(1.0)	-	-	-	-	-	-
MCHC	g/dL	33.83	0.94	31.5–36.0	31.5–36.0	5	(2.5)	4	(3.9)	1	(1.0)	3	(1.5)	1	(1.0)	2	(2.0)
Superoxide–Dismutase 1	ng/mL	63.89	4.53	77–531	77–531	190	**(95.0)**	100	**(98.0)**	90	**(91.8)**	-	-	-	-	-	-
Superoxide–Dismutase 2	ng/mL	58.93	15.52	>40	>40	16	(8.0)	16	(15.7)	-	-	-	-	-	-	-	-
Lipid_Peroxidase	µmol/L	64.10	79.66	<200	<200	-	-	-	-	-	-	11	(5.5)	10	(9.8)	1	(1.0)
Q10 (lipid-corrected)	µmol/mmol	0.23	0.07	>0.2	>0.2	77	**(38.5)**	44	**(43.1)**	33	**(33.7)**	-	-	-	-	-	-
Albumin	g/L	46.36	2.50	35.0–52.0	35.0–52.0	-	-	-	-	-	-	3	(1.5)	-	-	3	(3.1)
GOT	U/L	24.84	6.46	<50	<35	-	-	-	-	-	-	4	(2.0)	2	(2.0)	2	(2.0)
GPT	U/L	27.92	12.22	<41	<31	-	-	-	-	-	-	38	(19.0)	15	(14.7)	23	(23.5)
Gamma_GT	U/L	24.64	13.29	8–61	5–36	-	-	-	-	-	-	12	(6.0)	9	(8.8)	3	(3.1)
GFR	mL/min	84.43	8.46	>90	>90	101	**(50.5)**	51	**(50.0)**	50	**(51.0)**	-	-	-	-	-	-
Uric acid	mg/dL	4.93	1.23	3.6–8.2	2.3–6.1	1	(0.5)	-	-	1	(1.0)	5	(2.5)	3	(2.9)	2	(2.0)
Creatinine	mg/dL	0.85	0.15	0.70–1.20	0.50–0.90	1	(0.5)	1	(1.0)	-	-	1	(0.5)	1	(1.0)	-	-
Calcium	mmol/L	2.34	0.09	2.15–2.50	2.15–2.50	5	(2.5)	3	(2.9)	2	(2.0)	-	-	-	-	-	-
Magnesium	mmol/L	0.85	0.05	0.66–1.07	0.66–1.07	-	-	-	-	-	-	-	-	-	-	-	-
Zinc	qmol/L	12.63	1.77	12.0–26.0	9.0–22.0	31	(15.5)	1	(1.0)	30	**(30.6)**	-	-	-	-	-	-
Selenium	qmol/L	1.00	0.21	0.60–1.50	0.60–1.50	4	(2.0)	2	(2.0)	2	(2.0)	4	(2.0)	3	(2.9)	1	(1.0)
Vitamin D3	nmol/L	65.30	21.02	50.0–150.0	50.0–150.0	46	(23.0)	24	(23.5)	22	(22.4)	-	-	-	-	-	-

CRP = C-reactive_protein; GFR = glomerular filtration rate; GOT = glutamate–oxalacetate–transaminase; GPT = glutamate–pyruvate–transaminase; IL6 = interleukin-6; MCH = mean corpuscular/cellular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular/cell volume; MPV = mean platelet volume; NLR = neutrophil/lymphocyte ratio; RDW_CV = red blood cell distribution width; TNF-α = tumor necrosis factor alpha; * reference value obtained from www.mdcalc.com/neutrophil-lymphocyte-ratio-nlr-calculator#pearls-pitfalls (accessed on 2 April 2022).

3.2. Associations between Perceived Stress and Blood Parameters

Age- and tinnitus-related distress-adjusted univariate regression analyses revealed associations between perceived stress and oxidative stress markers predominantly in female—and inflammatory and immunological markers predominantly in male patients with chronic tinnitus.

Specifically, the observed findings included MCV (positive association (+) with perceived stress, i.e., PSQ-total) in women, and CRP (negative association (−) with PSQ-total), fibrinogen (−), selenium (+), GPT (−), and basophils (+) in men.

Investigating subdimensions of perceived stress, the red cell number and volume-increasing stress response values with a reduction in MCHC were confirmed for both women and men. PSQ-worries predicted ferritin (+), MCV (+), MCHC (−), hematocrit (+), magnesium (+), zinc (+), superoxide–dismutase 2 (+), and lipoprotein_a (+) in women; and fibrinogen (−), MCV (+), MCHC (−), basophils (+), leukocytes (−), and neutrophils (−) in men. PSQ-tension predicted ferritin (+), MCV (+), hematocrit (+), hemoglobin (+), RDW-CV (−), zinc (+), and superoxide–dismutase 2 (+) in women; and fibrinogen (−), uric acid (−), MCHC (−), lipid-corrected ubiquinone (Q10) (−), and basophils (+) in men. PSQ-joy predicted ferritin (+), MCV (+), hematocrit (+), hemoglobin (+), RDW-CV (−), and zinc (+) in women; and MCV (+), MCHC (−), and IL-6 (+) in men. Finally, PSQ-demands predicted ferritin (+), MCV (+), MCHC (−), hematocrit (+), hemoglobin (+), superoxide–dismutase 2 (+), selenium (+), magnesium (+), and zinc (+) in women; and ferritin (−), uric acid (−), lipid-corrected ubiquinone (Q10) (−), and basophils (+) in men.

See Table 6 for an overview. Supplementary Figure S1 provides a visual conspectus.

Table 6. Age- and tinnitus-related distress-adjusted univariate regression analyses with perceived stress indices being regressed on blood parameter values for the total sample, female patients, and male patients with chronic tinnitus. Only significant associations are reported (* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$).

Total Sample		**PSQ_Total**		**Worries**		**Tension**		**Joy**		**Demands**	
		β	***t* (3.194)**	***β***	***t* (3.194)**	***β***	***t* (3.194)**	***β***	***t* (3.194)**	***β***	***t* (3.194)**
Vascular risk markers	Lipoprotein_a			0.14	1.99 *						
Inflammatory markers	CRP	−0.19	−2.12 *			−0.15	−2.10 *				
	Fibrinogen					−0.16	−2.36 *				
	Ferritin	−0.19	−2.11 *								
	MCV			0.29	4.27 ***	0.25	3.58 ***	0.25	3.40 **	0.27	3.96 ***
	MCHC			−0.23	−3.27 **	−0.20	2.84 **	−0.20	−2.59 *	−0.21	−2.96 **
Oxidative stress markers	Ubiquinone(Q10)_lipid-corrected			−0.15	−2.08 *	−0.22	−3.14 **			−0.22	−3.09 **
	Selenium			0.17	2.29 *						
	Magnesium			0.15	2.10 *						
	Zinc			0.27	3.78 ***	0.25	3.52 **	0.22	2.85 **	0.24	3.40 **
Cellular immune reponse	Basophils (abs)									0.17	2.35 *
	Basophils (%)			0.16	2.25 *					0.18	2.52 *
Female Patients		**PSQ_total**		**Worries**		**Tension**		**Joy**		**Demands**	
		β	***t* (3.98)**	***β***	***t* (3.98)**	***β***	***t* (3.98)**	***β***	***t* (3.98)**	***β***	***t* (3.98)**
Vascular risk markers	Lipoprotein_a			0.21	1.98 *						
Inflammatory markers	Ferritin			0.25	2.50 *	0.27	2.86 **	0.21	2.18 *	0.22	2.28 *
	MCV	0.26	2.06 *	0.36	3.64 ***	0.29	3.01 **	0.21	2.05 *	0.34	3.57 **
	MCHC			−0.24	−2.30 *					−0.21	−2.12 *
	Hematocrit			0.22	2.19 *	0.28	2.91 **	0.29	2.95 **	0.30	3.20 **
	Hemoglobin					0.24	2.42 *	0.24	2.43 *	0.24	2.44 *
	RDW_CV					−0.21	−2.13 *	−0.20	−1.99 *		
Oxidative stress markers	Selenium									0.21	2.12 *
	Magnesium			0.22	2.23 *					0.20	2.07 *
	Zinc			0.34	3.35 **	0.32	3.23 **	0.22	2.17 *	0.33	3.39 **
	SOD-2			0.22	2.16 *	0.21	2.19 *			0.20	2.07 *

Table 6. *Cont.*

Male Patients		PSQ_Total		Worries		Tension		Joy		Demands	
		β	*t* (3.94)	*β*	*t* (3.94)	*β*	*t* (3.94)	*β*	*t* (3.94)	*β*	*t* (3.94)
Inflammatory markers	CRP	−0.31	−2.35 *								
	Fibrinogen	−0.34	−2.63 *	−0.28	−2.84 **	−0.26	−2.60 *				
	Ferritin									−0.26	−2.54 *
	MCV			0.23	−2.32 *			0.29	2.69 **		
	MCHC			−0.24	2.34 *	−0.23	−2.32 *	−0.24	−2.16 *		
	IL-6							0.31	2.87 **		
	Uric acid					−0.24	−2.33 *			−0.28	2.74 **
Oxidative stress markers	Ubiquinone(Q10)_lipid-corrected					−0.24	−2.43 *			−0.24	−2.71 **
	Selenium	0.30	2.23 *								
Immunological markers	Basophils (abs)			0.22	2.13 *	0.20	1.98 *				
	Basophils (%)	0.38	2.91 **	0.35	3.53 **	0.27	2.77 **			0.27	2.68 **
	Leukocytes			−0.21	−2.03 *						
	Neutrophils (abs)			−0.24	−2.32 *						
	Neutrophils (%)			−0.22	−2.17 *						
Liver function	GPT	−0.28	−2.11 *								

CRP = C-reactive protein; MCV = mean corpuscular/cell volume; MCHC = mean corpuscular hemoglobin concentration; PSQ = Perceived Stress Questionnaire; RDW_CV = red blood cell distribution width; SOD-2 = Superoxide Dismutase 2; GPT = glutamate–pyruvate–transaminase; IL-6 = interleukin-6.

4. Discussion

The present study sought to investigate (1) vascular-metabolic risk factors and blood parameters in patients with chronic tinnitus and (b) their associations with perceived stress.

4.1. Vascular–Metabolic Risk Factors

Substantial proportions of patients showed elevated levels of metabolic–vascular risk factors, including total cholesterol (women/men) (64.7/61.2%), non-HDL-c (43.1/50.0%), and LDL-c (55.9/59.2%), frequently within a context of overweight (BMI $\geq$ 26 for 44.6%/47.6%). Plasma levels of lipoprotein (a) were increased in female patients only (27.5%). Out of keeping with previous findings in patients with chronic tinnitus, IL-6, IL-10, and TNF-α-levels were not elevated in our sample—nor did patients yield elevated rates of mean platelet volumes or neutrophil-to-lymphocyte ratios.

Considering both direct medical and indirect psychobehavioural pathways, these metabolic markers may reflect either (a) primary pathophysiological factors contributing to chronic tinnitus (i.e., through vascular or inflammatory processes that may affect otological processes [58–61]) or (b) secondary factors that might be associated with patients' attempts to regulate distressing psychological states, such as 'unhealthy' dietary intake or sedentary behaviors [62–66].

Overall, our findings point to an unfavorable vascular-metabolic situation in these chronic tinnitus patients that may require special monitoring. Future studies will have to investigate whether pharmacological treatment of vascular risk, inflammation [67] or enzymatic dysregulation [68,69] might be helpful for some patients. Any such approaches, however, ought to consider wider emotional and psychobehavioural influences [70].

4.2. Oxidative Stress

Previous studies suggested possible interrelationships of oxidative stress- and mental-health-related processes, as well as a higher degree of oxidative stress and reduced antioxidative capacity in patients with chronic tinnitus [21]. Moreover, in patients with chronic tinnitus and hearing loss, oxidative stress has been suggested to potentially contribute to tinnitus onset through facilitating hair cell death or cochlear damage [71,72].

In the present study, redox parameters were frequently depleted in both female and male tinnitus patients (superoxide–dismutase 1 [98.0/91.8%] and ubiquinone [Q10] [43.1/33.7%]). Plasma levels of zinc were decreased in men only (30.6%). As a possible explanation for a loss of antioxidant factors, patients' kidney function (GFR) was decreased

in 50% of women and 51% of men. A higher relative proportion of monocytes was observed in 24.5% of men and in 10.8% of the women.

Superoxide-dismutase is a key antioxidant enzyme, which defends cells against oxidative stress. Ubiquinone (Q10) functions as an antioxidant co-enzyme by preventing lipid peroxidation in mitochondria or cell membranes [73,74]. Heightened oxidative stress and impaired defense processes might facilitate inflammatory responses or mitochondrial dysfunction, ultimately influencing neurotransmission and clinical symptom presentations [75,76].

Oxidative stress has been associated with a variety of psychological conditions, including depression [77–79], post-traumatic difficulties [80], and psychosis-spectrum conditions [81]. For the latter, the 'oxidative stress hypothesis' suggests that oxidative damage to lipids, proteins, or DNA might be associated with self-perpetuating changes in enzymatic and non-enzymatic antioxidant systems that may mediate "behavioral and molecular anomalies . . . associated with schizophrenia" [82]. Some evidence further suggests that superoxide–dismutase may be a trait- rather than a state marker for psychotic-spectrum experiences, as both acutely relapsed and stable outpatients were found to yield decreased levels of this enzyme [75]. Lower iron levels (e.g., zinc)—as found in men in the present sample—have further been shown to facilitate oxidative stress and potentially associated inflammatory processes [83], mood-related difficulties [84], or noise-triggered stress responses [85]. Seen from this perspective, previous studies that reported an association between zinc and tinnitus severity [21,22] may be interpreted within an oxidative stress framework that associates oxidative stress markers with audiologically triggered or general psychological distress in the experiences of chronic tinnitus or psychosis-spectrum conditions. Whilst previous research has attempted to delineate tinnitus from acoustic hallucinations by contrasting the former as 'unorganized' [86–88], other researchers have argued for a joint conceptualization [89].

Overall, the observed reductions in oxidative stress markers may reflect psychobiological states that underlie transdiagnostically relevant subjective experiences of perceived stress. Speculatively, oxidative stress might confer a trait vulnerability to psychoaudiological misperception or mood-mediated inflammatory epiphenomena of psychological distress in patients with chronic tinnitus or other psychological conditions.

4.3. Perceived Stress

Age- and tinnitus-related distress-adjusted linear regression analyses investigated the extent to which perceived stress influenced blood parameters in female and male patients with chronic tinnitus. As shown in Table 6 (Figure S1), we observed only marginal associations with the blood parameter conspicuities described before. Rather, associations with perceived stress were found for blood parameters within their respective reference ranges. Whilst somewhat unexpected, this finding is to be interpreted in the context of only mild overall elevation of perceived stress in the current sample.

Overall, women but not men showed positive associations between perceived stress and oxidative stress and anemic markers, whilst men but not women showed signs of worry-associated immunosuppressive processes, as reflected in inverse influences of perceived stress on fibrinogen and ferritin levels alongside positive associations with basophils [90]. Whilst preliminary, these data are in agreement with previous observations, according to which perceived stress may influence hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and red blood cell distribution width (RDW_CV; [91]) values. Moreover, these results are in keeping with previous research suggesting that chronic stress exposure might be associated with oxidative damage in women [92], particularly if associated with maladaptive lifestyle behaviors [93]. Positive associations between perceived stress and hematological markers were previously observed in healthy individuals [91,94,95], and have also been linked to acoustic trauma [96]—suggesting possibilities of direct or indirect (i.e., stress-mediated) effects of aversive noise exposure on hematological markers. Contrary to expectations, we observed negative

associations between perceived stress levels and inflammatory markers in men but not women. Whilst the majority of published studies report positive associations between perceived stress and inflammatory markers [97,98], some small studies reported inverse relations in the context of heightened vascular risk [99]. The reasons for these gender differences remain mostly unknown [100], and future studies are needed to replicate and extend on these findings.

The present study has important limitations. First, the blood parameters were only measured once, and the study design disallowed for the investigation of time-related fluctuations, comparisons with healthy or non-tinnitus control groups, or effects of psychological or pharmacological interventions. Second, both the investigated index symptom ('chronic tinnitus') and the observed metabolic effects may be caused or confounded by a large number of unmeasured influences. Third, whilst we computed separate linear regression models, biomarkers are likely woven into complex interaction networks that need to be identified and investigated jointly in high-powered studies [101]. Therefore, the presented data must be interpreted as exploratory—offering preliminary pointers for possible candidate biomarkers of perceived stress in chronic tinnitus. Moreover, future studies ought to more carefully control sample characteristics, thereby allowing for in-detail differentiations of the effects of perceived stress on biomarkers across various levels of emotional distress and related constructs such as anxiety or depression. Notwithstanding, the current study features a relatively large clinical sample, and provides first indications of vascular–metabolic risk alongside immunosuppressive effects in patients with chronic tinnitus.

5. Conclusions

The results of the present study highlight possible interactions between vascular-metabolic risk factors and perceived stress, which may have a reinforcing role in facilitating or maintaining chronic tinnitus symptomatology. Respective pathways, however, are unclear. To prevent or treat perceived stress-related phenomena, including, but not limited to chronic tinnitus, treatment planning ought to apply a multidisciplinary view with psychological and medical professionals intervening at the intersection of vascular–metabolic risk factors, oxidative-stress-related influences, and psychological affective-behavioural (lifestyle-related) influences, whose functions need to be individually conceptualized [44,102–104].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu14112256/s1: Figure S1: Perceived stress and blood parameters.

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Data Availability Statement: As per Charité Universitaetsmedizin Berlin's ethics committee, unfortunately we cannot make the data public without restrictions because we did not obtain patients' consent to do so at the time. Nevertheless, interested researchers can contact the directorate of the Tinnitus Center Charité Universitaetsmedizin Berlin with data access requests (birgit.mazurek@charite.de) or the Charité' s Open Data and Research Data Management Officer Dr. Evgeny Bobrov (evgeny.bobrov@charite.de).

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Paper 2: Psychological Vulnerability-Stress Interactions in Patients with Chronic Tinnitus

Study 2 [119] examines psychological vulnerability-stress interactions in patients with chronic tinnitus. It demonstrates that TRD presents as a function of predisposing – seemingly antagonistic – personality traits (notably excitability and aggression inhibition) and current perceived stress experiences.

'***Background****: Despite vulnerability-stress models underlying a variety of distress-related emotional syndromes, few studies have investigated interactions between personality factors and subjectively experienced stressors in accounting for tinnitus-related distress.* ***Aim****: The present study compared personality characteristics between patients with chronic tinnitus and the general population. Within the patient sample, it was further examined whether personality dimensions predicted tinnitus-related distress and, if so, whether differential aspects or levels of perceived stress mediated these effects.* ***Method****: Applying a cross-sectional design, 100 patients with chronic tinnitus completed the Freiburger Persönlichkeitsinventar (FPI-R) measuring personality, the Perceived Stress Questionnaire (PSQ-20) measuring perceived stress and the German version of the Tinnitus Questionnaire (TQ) measuring tinnitus-related distress. FPIR scores were compared with normed values obtained from a representative German reference population. Mediation analyses were computed specifying FPIR scores as independent, PSQ20 scores as mediating and the TQ-total score as dependent variables.* ***Results****: Patients with chronic tinnitus significantly differed from the general population across a variety of personality indices. Tinnitus-related distress was mediated by differential interactions between personality factors and perceived stress dimensions.* ***Conclusion****: In conceptualizing tinnitus-related distress, idiosyncratic assessments of vulnerability-stress interactions are crucial for devising effective psychological treatment strategies. Patients' somatic complaints and worries appear to be partly informed by opposing tendencies reflecting emotional excitability vs. aggressive inhibition – suggesting emotion-focused treatment strategies as a promising new direction for alleviating distress.*' [119(p1)]

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Personality Traits, Perceived Stress, and Tinnitus-Related Distress in Patients With Chronic Tinnitus: Support for a Vulnerability-Stress Model

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Background: Despite vulnerability-stress models underlying a variety of distress-related emotional syndromes, few studies have investigated interactions between personality factors and subjectively experienced stressors in accounting for tinnitus-related distress.

Aim: The present study compared personality characteristics between patients with chronic tinnitus and the general population. Within the patient sample, it was further examined whether personality dimensions predicted tinnitus-related distress and, if so, whether differential aspects or levels of perceived stress mediated these effects.

Method: Applying a cross-sectional design, 100 patients with chronic tinnitus completed the Freiburger Persönlichkeitsinventar (*FPI-R*) measuring personality, the Perceived Stress Questionnaire (*PSQ-20*) measuring perceived stress and the German version of the Tinnitus Questionnaire (*TQ)* measuring tinnitus-related distress. FPI-R scores were compared with normed values obtained from a representative German reference population. Mediation analyses were computed specifying FPI-R scores as independent, PSQ20 scores as mediating and the TQ-total score as dependent variables.

Results: Patients with chronic tinnitus significantly differed from the general population across a variety of personality indices. Tinnitus-related distress was mediated by differential interactions between personality factors and perceived stress dimensions.

Conclusion: In conceptualizing tinnitus-related distress, idiosyncratic assessments of vulnerability-stress interactions are crucial for devising effective psychological treatment strategies. Patients' somatic complaints and worries appear to be partly informed by opposing tendencies reflecting emotional excitability vs. aggressive inhibition – suggesting emotion-focused treatment strategies as a promising new direction for alleviating distress.

Keywords: tinnitus, personality, vulnerability-stress, Tinnitus Questionnaire (TQ), perceived stress, FPI

INTRODUCTION

Tinnitus is a symptom denoting the perception of acoustic sensations without an external sound stimulus. The prevalence in the general population ranges between 4 and 32%, and the levels of reported contemporaneous psychological distress vary considerably (Durai and Searchfield, 2016). Whilst some patients report depression and anxiety associated with the tinnitus percept (Schaaf et al., 2003; Durai and Searchfield, 2016), others report little or no tinnitus-related distress. Tinnitus can be acute or chronic with the latter being defined as a symptom duration of > 3 months (Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde Kopf- und Hals-Chirurgie, 2015). Depending on perceived tinnitus-related distress, tinnitus can also be divided into compensated and decompensated presentations with the latter involving high levels of tinnitus-related distress and associated symptoms of low mood and/or anxiety (Biesinger et al., 1998).

Whilst its causes are not always clearly identifiable and closely interlinked, chronic tinnitus has been associated with numerous risk factors (Haider et al., 2018; Trevis et al., 2018; Boecking et al., 2019) that have partly been interpreted within a vulnerability-stress framework. For example, emotional exhaustion and low emotional well-being were found to predict the risk of developing tinnitus (Hébert et al., 2012) with the former also being shown to predict higher sensitivity to sound following an acute stress task (Hasson et al., 2013). Moreover, several studies have shown that existing emotional distress predicted higher tinnitus-related distress (Bartels et al., 2009; Schaaf et al., 2014; Wallhäusser-Franke et al., 2015; Durai and Searchfield, 2016; Strumila et al., 2017; Sahlsten et al., 2018). On the other hand, high psychological resilience (i.e., an individual's ability to adapt to adverse life conditions) was associated with higher emotional well-being that was – in turn – associated with lower tinnitus-related distress (Wallhäusser-Franke et al., 2014). In line with conceptualizations of other functional syndromes such as chronic pain (Flor, 1991; Linton, 2000; Wittchen and Hoyer, 2011), tinnitus-related distress might be conceptualized as a function of an interaction of pre-existing psychological vulnerability and life stressors that may include – but are not limited to – the tinnitus symptom.

Personality, i.e., the sum of an individual's unique and stable aspects [i.e., personality traits] that describe, explain and predict one's behavior (Asanger and Wenninger, 1999), is a well-established vulnerability factor for developing anxiety and depression following stressful experiences (e.g., Boyce et al., 1991; Kotov et al., 2010). Personality traits are psychological constructs that describe individual differences in perception, experience, emotion, cognition, and behavior on selected parameters. Personality factors could either render an individual vulnerable to developing tinnitus (e.g., Mucci et al., 2014), or facilitate the development and experience of psychological distress that, upon the perception of a tinnitus sound, extends toward the tinnitus percept (Peerenboom et al., 2015). Investigating personality factors bears high importance for understanding all psychological components of tinnitus-related distress and its maintenance, as personality may affect both exposure and reactivity to stressful events as well as differential choices of coping efforts and their differential effectiveness (Bolger and Zuckerman, 1995). Moreover, success rates of treatment approaches such as schema (Jacob and Arntz, 2013) or mentalization-based therapy (Vogt and Norman, 2018) increasingly refute the notion that personality-associated persistent emotional difficulties are stable. These treatments offer promising tools to address personality factors as modifiable treatment targets. Regarding tinnitus, some studies have investigated whether certain personality traits predict the presence or degree of tinnitus-related distress. For example, Weber et al. (2008) applied the Freiburg Personality Inventory (Freiburger Persönlichkeitsinventar, FPI-R, Fahrenberg et al., 2010) to a sample of 121 patients with chronic tinnitus and demonstrated significant differences in between patient groups with low and high tinnitus-related distress in the personality traits life satisfaction, excitability, aggressiveness, strain, somatic complaints, health concerns, and emotionality. Durai and Searchfield (2016) showed that tinnitus-related distress was associated with high neuroticism, low extraversion, high stress reaction, higher alienation, lower social closeness, lower well-being, lower self-control, lower psychological acceptance and presence of a type D personality, i.e., a tendency toward negative affectivity and social inhibition, and externalized locus of control. Moreover, several studies reported positive relations between tinnitus-related distress and a subset of "Big-Five" personality traits, namely low agreeableness, low extraversion and high neuroticism (Langguth et al., 2007; McCormack et al., 2014; Mucci et al., 2014; Dehkordi et al., 2015). Welch and Dawes (2008) stated alongside Durai et al. (2017) that compared to non-tinnitus control groups, tinnitus patients were more socially withdrawn, reactive to stress, and alienated as well as less self-controlled. Compared to an adult reference population, Chung et al. (2017) reported that tinnitus patients showed higher levels of harm avoidance and lower scores for novelty seeking, reward dependence, persistence, cooperativeness and self-transcendence. Overall, studies demonstrated mixed relations between tinnitus-related distress and a variety of personality factors. However, due to heterogeneous operationalizations of the investigated personality constructs, no consistent picture has of yet emerged.

The meaning of "stress" varies widely in the scientific field. It can describe external stimuli, the adaptive reaction to them or resulting physical or mental strain. Longitudinal studies that compare differential stress dimensions with regard to tinnitus or tinnitus-related distress do not yet exist (Boecking et al., 2019). However, several studies have investigated the interaction between personality traits and stressors as influencing psychological distress and somatic symptoms. Almeida (2005) used a diary method approach and reported that psychological resilience and sociodemographic factors predicted the likelihood of exposure, appraisal and reactivity to daily stressors. Personality traits can thus influence daily well-being through their interaction with stressors.

Several other studies further suggest that subjects with high neuroticism are more likely to develop depressive symptoms upon exposure to daily hassles (Hutchinson and Williams, 2007; Vinkers et al., 2014; Hentrich et al., 2016) – to which help-seeking patients with tinnitus have also shown to be susceptible (Scott and Lindberg, 2000). Yang et al. (2013) reported that perfectionism – a trait known to be heightened in individuals with chronic tinnitus (Andersson et al., 2005) – predicted depression in interaction with achievement-related, but not interpersonal hassles. A few more studies showed that interactions between perfectionism, daily hassles or major life events had an influence on the occurrence and maintenance of depressive symptoms (Flett et al., 1997; Yang et al., 2013).

Overall personality traits interact with daily stressors in predicting psychological distress. Applying a psychological vulnerability-stress framework, the current study investigates how personality characteristics (as measured by the FPI-R) interact with perceived stress in explaining tinnitus-related distress in patients with chronic tinnitus.

Hypotheses

We examined the following hypotheses:

(1) There are systematic differences in personality factors between patients with chronic tinnitus and the general population;
(2) There are systematic differences in personality factors between patients with decompensated and compensated chronic tinnitus; and
(3) Within patients with chronic tinnitus, the degree of tinnitus-related distress is a function of differential interactions between personality-factors and differing dimensions of perceived subjective stress.

MATERIALS AND METHODS

Procedure

The current study included N = 100 patients with chronic tinnitus who had been referred to the Tinnitus Center at Charité – Universitätsmedizin-Berlin between 2011 and 2012 and who completed [1] the German version of the Tinnitus Questionnaire (TQ) measuring tinnitus-related distress, [2] the Freiburg Personality Inventory (FPI-R) measuring personality factors, and [3] the Perceived Stress Questionnaire – German modified version measuring perceived stress. The reference group for the FPI-R norms consists of 3740 non-institutionalized adult subjects who are representative of the German population (Fahrenberg et al., 2010). The study was carried out in accordance with the recommendations of the German S3 Guideline 017/064: Chronic Tinnitus (Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde Kopf- und Hals-Chirurgie, 2015). Data was collected as part of the clinic's routine diagnostic procedures approved by the Ethics Committee of Charité Universitätsmedizin Berlin (Nr. EA 1/115/15). All participants gave written consent for the use of anonymized data for research purposes in accordance with the Declaration of Helsinki.

Materials

Tinnitus Questionnaire – German Version (TQ; Goebel and Hiller, 1998)

The German version of the Tinnitus Questionnaire is a self-report questionnaire that measures the degree of tinnitus-related distress. The questionnaire consists of 52 items ("disagree" = 0, "partly agree" = 1, "agree" = 2), 40 items of which are included into the total score and two items being entered twice thus yielding a range between 0 and 84 points. The total score can be divided to reflect compensated (slight and moderate tinnitus-related distress, as defined by scores ranging from 0 to 46) and decompensated levels of tinnitus-related distress (severe and catastrophic, as defined by scores ranging from 47 to 84; Biesinger et al., 1998; Goebel and Hiller, 1998). The scale's internal consistency is high ($\alpha = 0.95$; Zeman et al., 2012).

Freiburg Personality Inventory (FPI-R, Freiburger Persönlichkeitsinventar; Fahrenberg et al., 2010)

The Freiburg Personality Inventory consists of 138 items ("not true" = 0, "true" = 1) across 12 personality dimensions that comprise 10 to 14 items each. The inventory has been validated across various languages and populations and the subscales' internal consistencies are sufficient ($\alpha = 0.73$–0.83; Fahrenberg et al., 2010). In the following, the dimensions will be explained in some detail to allow for a psychologically meaningful description of the patient sample. Descriptions have been translated and adapted from the FPI-R handbook (Fahrenberg et al., 2010, pp. 84–90).

Life satisfaction describes feelings of satisfaction, contentment with life, self-acceptance, and an optimistic vision of one's own future. People with lower scores show discontent about past and present life conditions. They lack self-efficacy, tend to ruminate and are often fed up by their circumstances. They express gloomy and unhappy moods, depressiveness and a negative approach to life. People with higher scores are content about their life choices and conditions. They have high self-valuation and show optimism and a positive attitude toward life.

Social orientation describes social solidarity, i.e., one's tendency to be generous, friendly, helping, and warm. Persons with low scores highlight individual responsibility regarding life conditions. They act selfish and with unsympathetic attitudes toward others. Persons with high scores feel a high social responsibility. They express helpfulness, react to worries of others, and are motivated to help, comfort and care. They also tend to feel guilty which motivates them to engage in helping others.

Achievement orientation describes a person's ambition; wish to assert themselves, competition behavior, activism, and determination. Persons with low scores show low competitive behavior and very little ambition. Either because of principles against the competitive vision of life, or because professional and social achievements are not important life goals. People with high scores are achievement orientated and motivated. They are ambitious and solve problems fast and efficient. They also enjoy

being in competition, in their profession and social life. Usually they show higher commitment to their profession than to leisure time activities.

Inhibitedness describes hesitant and shy behavior, which is characterized by withdrawal, inhibition, lack of self-confidence, and little development or verbalization capacities. Persons with low scores are easy-going, spontaneous and self-confident in social groups. Persons with high scores feel inhibited in social situations: they are afraid to enter rooms filled with other people, prefer to stay in the background, have difficulties to speak in front of others. They are easily embarrassed, often anxious and blush often. Interactions with strangers are difficult and hard for them. They have difficulties joining conversations or making friends.

Excitability describes impulsive behavior and lack of self-control – with slightly aggressive manifestations. Persons with a lower score are characterized by serenity. They are difficult to provoke or bother, stay calm and patient even in difficult and hectic situations with multiple disturbances. People with higher scores are easily irritated and worked up. They have difficulties to control their anger, show aggressive behavior in improvident statements. They react sensitive and rushed, even in unimportant situations.

Aggressiveness describes verbal or physical aggressive behavior. It describes mainly spontaneous reactive and dominating behaviors. Persons with lower scores show little aggression. They are either reserved, solitary, inhibited in expressing themselves or socially passive and can control their reactions. They do not use physical violence to enforce their needs or rights. Persons with higher scores show willingness to violent behavior. They can experience joy in rude jokes, showing up faults of others or hurting people. They defend themselves with fury and lack of control, perhaps even with physical violence, if they feel insulted or in their rights violated.

Strain describes a personal perception of subjective overload. This induces tension, stress, nervousness, and exhaustion. Persons with lower scores feel less stressed and overworked. They feel equal to their requirements and are able to fulfill their tasks. Persons with higher scores feel highly stressed: they have a lot of tasks, experience high requirements and time pressure.

Somatic complaints describe the subjective disturbance of one's actual state of health. Persons with low scores rarely complain of physical symptoms. Persons with higher scores complain about sleeping disorders, headaches, meteoropathy, arrhythmia, hot flashes, cold extremities, an irritable stomach, a chest tightness, tics, and/or shivering.

Health concerns describe worries about one's present and future state of health irrespective of the actual state of health. Persons with low scores show little worries about their own health. They are unconcerned, robust, and not over-protective. Persons with high scores describe a health orientated, worried behavior. They try to reduce risk of health-related harm, contagion, infection and accidents. They show hypochondriac tendencies, food and lifestyle control and often ask for medical or therapeutic advice.

Frankness describes open, unreserved and unconventional behaviors, which are characterized by straightforwardness. Persons with lower scores try to make good impressions with active impression management. Different motives can explain these behaviors: lack of self-criticism or self-idealization, reticence or conformity. People with higher scores are able to admit everyday mistakes or weaknesses: being late, procrastination, gloating, occasional lies, nasty thoughts, etc. They admit these deviations from the social norm without shame and do not see these norms as important or deviations as flagrant.

Extraversion describes one of the basic dimensions of most personality theories: it captures the difference between sociable, impulsive, active and socially present, dynamic and vivid persons, and reserved, uncommunicative, controlled, introvert ones. People with lower scores are withdrawn in social situations and prefer to be alone. They are calm and serious, uncommunicative, not enterprising and more likely self-controlled than impulsive. People with higher score are sociable and impulsive. They like to go out, varieties, entertainment, make friends fast, enjoy company of others and can be easy-going. They are active, communicative and eloquent in contact with others. They can be prankful, enterprising, energetic and ready to take command.

Emotionality describes the continuum of emotional stability to emotional lability and neuroticism. People with lower scores are satisfied with themselves and their life. They are serene, relaxed, and calm. They are little anxious or sensitive. They show mostly no health concerns, psychosomatic symptoms or inner conflicts. People with high scores show high numbers of problems and inner conflicts. They are excitable and irritable or feel tired, asthenic or indifferent. Their mood switches a lot, but they feel mainly depressed and anxious. They ruminate a lot and feel misunderstood by their peers and relatives. They are stressed, concerned about their health, nervous and psychosomatically accentuated.

Perceived Stress Questionnaire – German Modified Version (PSQ20; Fliege et al., 2005)

The Perceived Stress Questionnaire is a self-report questionnaire measuring perceived stress. The German modified version consists of 20 items with a four-point Likert-type scale ("almost never" = 1, "sometimes" = 2, "often" = 3, "usually" = 4; Fliege et al., 2005). Higher total scores indicate more severe perceived stress. Items are rated across four subscales: worries (worries, anxious concern for the future, and feelings of desperation and frustration), tension (disquietude, exhaustion and the lack of relaxation), joy (positive feelings of challenge, joy, energy, and security), and demands (perceived environmental demands, such as lack of time, pressure, and overload.). The resulting PSQ20 total und subscale scores are linearly transformed to scores ranging from 0 to 1. For the computation of the total score, the scale joy is inversed. The scale "demands" focuses on the subjective perception of external stressors, while the other three scales focus on internal stress reactions (Fliege et al., 2005). Originally designed in English, this instrument has been translated into French, Italian, German and Spanish, and validated in various populations (Kocalevent et al., 2007). The scale's internal consistency is high ($\alpha = 0.90$; Fliege et al., 2005).

Participants

A total of N = 100 patients with chronic tinnitus (53% female) completed the TQ, FPI-R and PSQ20. On average, patients were 50 years old (SD = 12.38; range = 19–76). Seventy-three patients reported compensated tinnitus whilst 27 reported decompensated tinnitus. To interpret the reported FPI-R scores, scores were compared both with the reference population mean values published in the FPI-R – 8^{th} edition (N = 3740) (Fahrenberg et al., 2010) and between patients with compensated vs. decompensated tinnitus.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows, version 24. Statistical significance was set at $\alpha = 0.05$. For the comparisons of means, effect sizes (Cohen's d) were also calculated. Effect sizes of Cohen's d are defined as d (0.01) = very small, d (0.2) = small, d (0.5) = medium, d (0.8) = large, d (1.2) = very large, and d (2.0) = huge (Sawilowsky, 2009). *First*, we used descriptive statistics to explore sample descriptors. *Second,* we used the SPSS dummy matrix variable approach and independent samples t-tests to compare our sample means with the summarized data from the FPI-R population norms. *Third*, we used independent samples t-tests to compare decompensated and compensated patients. *Finally*, to explore interaction effects between personality traits (vulnerability) and perceived stress (stress) on tinnitus-related distress, mediation analyses were computed, specifying FPI-R dimensions as independent variables, PSQ20 dimensions as mediating variables and the TQ total score as dependent variable. Here, the PROCESS macro (Hayes, 2018) was used to compute a series of path coefficients: the effect of the independent variable X on the dependent variable Y (total effect, c); the effect of X on the mediator M (path a); the effect of M on Y (path b); the indirect effect (ab); and the total effect adjusted for ab (direct effect, c'). Whenever the effect of X on Y decreases to zero once M is included in the model, "complete mediation" is said to have occurred (James and Brett, 1984). In this case, there is strong evidence that the investigated mediator dominantly accounts for almost all variance in the outcome variable. "Partial mediation" is said to have occurred, if the effect of X on Y decreases significantly, but not necessarily to zero (Judd and Kenny, 1981). In the results section, indirect effects will be reported graphically – for an overview of estimates, see **Appendix A**.

RESULTS

Descriptive Statistics

Table 1 shows sociodemographic factors and means for the TQ (German version), FPI-R, and PSQ20.

TABLE 1 | Sample description.

	N	*M*	*SD*	Min	Max
Gender					
Male	47				
Female	53				
Age	100	50.00	12.38	19	76
TQ_Total score	100	33.71	16.80	0	73
FPI-R					
Life satisfaction	100	7.01	3.28	0	12
Social orientation	100	7.52	2.40	1	12
Achievement orientation	100	7.15	2.68	0	12
Inhibitedness	100	5.57	3.14	0	12
Excitability	100	6.81	3.10	0	12
Aggressiveness	100	3.42	2.42	0	11
Strain	100	7.51	3.80	0	12
Somatic complaints	100	4.31	2.38	0	10
Health concerns	100	5.50	2.79	0	12
Frankness	100	5.81	2.86	1	12
Extraversion	100	6.47	3.54	0	14
Emotionality	100	7.36	3.61	0	14
PSQ20					
Total	99	0.44	0.22	0.01	0.92
Worries	99	0.39	0.25	0.00	1.00
Tension	99	0.52	0.26	0.00	1.00
Joy*	99	0.53	0.26	0.00	1.00
Demands	99	0.50	0.28	0.00	1.00

*M, mean; Min, minimum; Max, maximum; SD, standard deviation; TQ, Tinnitus Questionnaire (German version); PSQ20, Perceived Stress Questionnaire. *Higher values indicate more joy; for the total score, the coding is reversed.*

Comparison of Means

First, we compared FPI-R mean values of tinnitus patients to those of the general population. For the tinnitus patients, results showed significantly elevated values in [+] social orientation (p = 0.000, d = 0.426), excitability (p = 0.000, d = 0.528), strain (p = 0.000, d = −0.588), somatic complaints (p = 0.000, d = 0.282), emotionality (p = 0.000, d = 0.430), and significantly lower values in [−] aggressiveness (p = 0.000, d = −0.359) and health concerns (p = 0.000, d = 0.426) (see **Figure 1**). Differences in social orientation, aggressiveness, somatic complaints, health concerns and emotionality yielded small effect sizes; differences in excitability and strain medium effect sizes. We then explored Pearson correlations between the personality dimensions that distinguished tinnitus patients from the general population in our sample. Here, coefficients suggested an affectively centered cluster comprising strong correlations between emotionality and excitability, strain and somatic complaints (see **Table 2**).

Third, we compared FPI-R values between decompensated and compensated tinnitus patients. Results showed significantly higher values in [+] excitability, strain, somatic complaints, and emotionality alongside significantly lower values in [−] life satisfaction (**Table 3**). Medium effect sizes emerged for life satisfaction, excitability and strain; large effect sizes for emotionality and somatic complaints.

Mediation Analyses

Exploring possible interactions of vulnerability (personality dimensions) and stress (perceived stress) factors in predicting tinnitus-related distress, we computed sets of mediation analyses specifying those personality factors as independent variables that

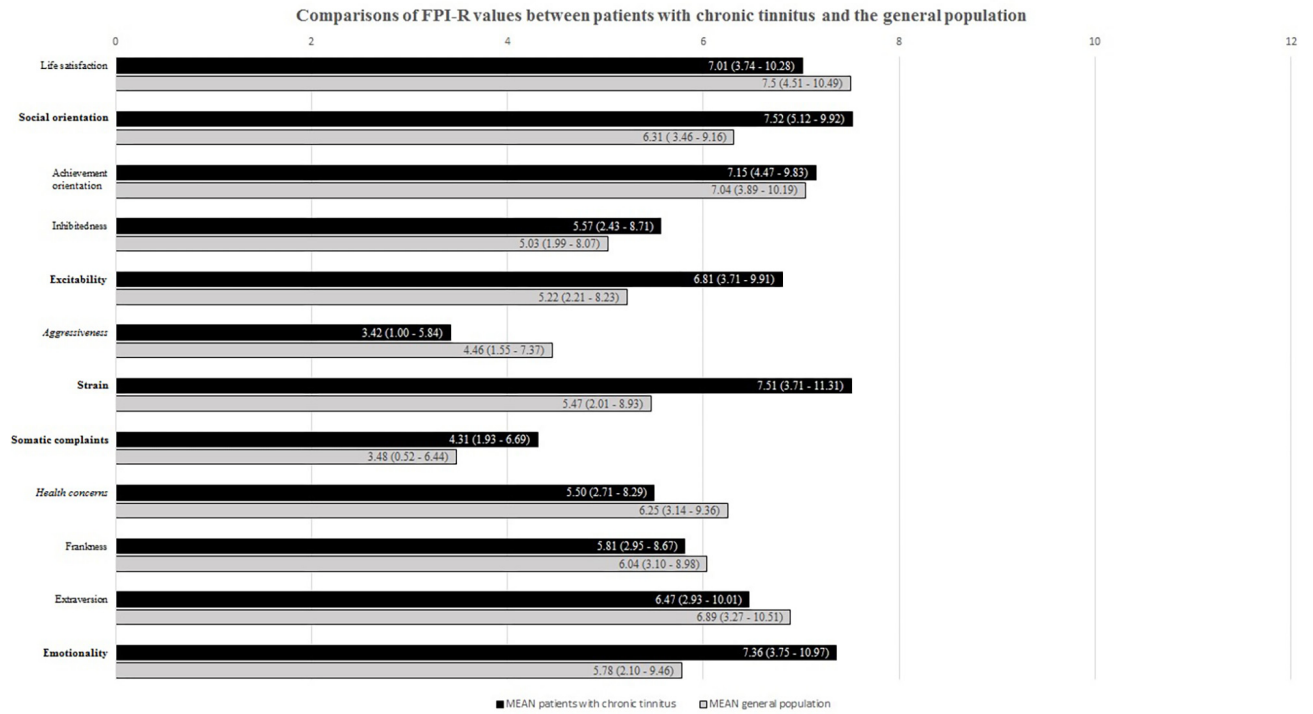

FIGURE 1 | FPI-R values for patients with chronic tinnitus and the general population. Compared to the general population, bold labels indicate significantly higher; italicized labels significantly lower scores for patients with chronic tinnitus.

TABLE 2 | Intercorrelations of factors that distinguish patients with chronic tinnitus from the general population.

	Aggressiveness	Strain	Somatic complaints	Emotionality
Aggressiveness				*0.275***
Strain			0.479**	**0.726****
Somatic complaints				**0.582****
Excitability	*0.256**	**0.495****	0.338**	**0.616****

*Only significant coefficients are reported. *p < 0.05, **p < 0.01 (two-tailed). Italicized values denote small (below ± 0.29), underlined values medium (± 0.30 and ± 0.49), and bold values strong correlations (± 0.50 and ± 1).*

TABLE 3 | Comparisons of FPI-R values between patients with decompensated and compensated chronic tinnitus.

FPI-R scale	*Decompensated* tinnitus patients *n* = 27	*Compensated* tinnitus patients *n* = 73	*p*	*d*
Life satisfaction	**5,67 ± 3,15**	**7,51 ± 3,20**	**0.012**	**−0,577**
Social orientation	7,85 ± 2,41	7,40 ± 2,40	0.408	
Achievement orient.	7,22 ± 2,91	7,12 ± 2,60	0.869	
Inhibitedness	5,41 ± 3,24	5,63 ± 3,13	0.758	
Excitability	**7,89 ± 2,67**	**6,41 ± 3,18**	**0.034**	**0,485**
Aggressiveness	3,56 ± 2,58	3,37 ± 2,37	0.729	
Strain	**9,26 ± 2,40**	**6,86 ± 4,03**	**0.005**	**0,654**
Somatic complaints	**6,11 ± 1,74**	**3,64 ± 2,24**	**0.000**	**1,166**
Health concerns	5,26 ± 2,10	5,59 ± 3,02	0.603	
Frankness	5,56 ± 2,98	5,90 ± 3,02	0.617	
Extraversion	6,67 ± 3,93	6,40 ± 3,41	0.737	
Emotionality	**9,41 ± 2,58**	**6,60 ± 3,66**	**0.000**	**0,825**

Bold values denote significant differences between the groups, p < 0.05.

were found to significantly differ for tinnitus patients compared to the general population (cf. **Figure 1**). As mediators, we specified the total and subscale scores of the PSQ20 questionnaire with the dependent variable being specified as tinnitus-related distress as measured by the TQ total score. **Figure 2** shows the significant effects of the explorative mediation analyses.

Overall, the following indirect effects accounted for the relationship between personality factors and tinnitus-related distress:

(1) For personality traits that were significantly more pronounced in patients with chronic tinnitus compared to the general population:

- Higher excitability interacting with (a) higher perceived tension, (b) higher worries, (c) less joy, and (d) higher demands;
- Higher strain interacting with (a) higher perceived tension and (b) higher worries;
- Higher somatic complaints interacting with (a) higher perceived tension, (b) higher worries, and (c) higher demands; and
- Higher emotionality interacting with (a) higher perceived tension.

(2) For personality traits that were significantly less pronounced in patients with chronic tinnitus compared to the general population:

- Higher aggressiveness interacting with (b) higher worries.

Social orientation and health concerns did not interact with perceived stress in predicting tinnitus-related distress. **Appendix A** reports the detailed results of the mediation analyses (a three-step logistic regression analysis) outlining coefficients "*a*" (effects of the independent variables on the mediators), "*b*" (effect of the mediators on the dependent variable), "*c*" (total effect of the independent variable on the dependent variable), "*c'*" (direct effect; i.e., the total effect adjusted for the indirect effect) and the indirect effect "*ab*" that is tested for significance using a *bootstrapping* approach yielding 95% confidence intervals.

DISCUSSION

The present study investigated interrelations between personality factors as measured by the FPI-R, perceived stress (PSQ20) and tinnitus-related distress (TQ-German version) in a sample of 100 patients with chronic tinnitus.

Comparisons Between Tinnitus Patients and Between Tinnitus Patients and the General Population

Hypothesis 1: There are systematic differences in personality factors between patients with chronic tinnitus and the general population.

Results of this study indicate differences in personality traits between patients with chronic tinnitus and the general population as measured using the FPI-R. Compared to the general population, patients rated themselves as [1] experiencing higher social responsibility and reacting more readily to the worries of others (+ social orientation), [2] being more easily irritated, worked up, sensitive and rushed – with slight aggressive manifestations (+ excitability), [3] having a substantively higher personal perception of subjective overload; including habitual stress, nervousness and exhaustion (+ strain), [4] complaining more about somatic symptoms (+ somatic complaints), [5] being more excitable and irritable *or* tired, asthenic or indifferent and feeling not understood by their peers and relatives (+ emotionality), [6] being more inhibited in expressing themselves and socially passive (− aggressiveness), and, [7] being *less* worried about their personal state of health – possibly underlying fewer health-orientated behaviors (− health concerns).

The results are partly in keeping with previous studies researching relations between tinnitus-related distress and personality factors: in particular, patients' higher emotionality and excitability scores support previous findings reporting higher scores of neuroticism and type D personality characteristics (e.g., Langguth et al., 2007; McCormack et al., 2014; Mucci et al., 2014; Durai and Searchfield, 2016) thereby supporting the importance of these constructs as risk factors for tinnitus-related distress.

Hypothesis 2: There are systematic differences in personality factors between patients with decompensated and compensated chronic tinnitus.

In keeping with results from the comparisons of the overall sample with the general population, patients with decompensated (vs. compensated) tinnitus yielded higher expressions of excitability, strain, somatic complaints and emotionality and lower expressions of life satisfaction. By contrast, we did not find differences in aggressiveness and health concerns between the two subpopulations. These results partly reflect previous findings from Weber et al. (2008) who compared tinnitus patients across severity grades I–IV of the Tinnitus Questionnaire and reported that, compared to grade I patients, grade IV patients had lower life satisfaction and higher excitability, aggressiveness, somatic complaints, and emotionality ratings whilst health concerns were found to differ between grade I and III patients only.

Overall, patients with chronic tinnitus show predispositions toward interpreting and responding to stimuli in a manner characterized by easy irritation, high levels of subjective overload, inner conflict, and higher ruminative tendencies whilst being more inhibited in expressing their emotional needs alongside a guilt-associated tendency to orientate themselves toward others' needs. Interestingly, patients also report a lower degree of health concerns that might interact with higher excitability and higher social orientation in reflecting a coping style potentially aiming to regulate unexpressed emotion such as inhibited aggressivity (e.g., not using hearing protection). Relative to comparisons between tinnitus patients and the general population, the subsample of patients with *decompensated* tinnitus showed a somewhat similar, yet more pronounced profile across the excitability, strain, somatic complaints, and emotionality dimensions. Whilst the distinction between patients with compensated vs. decompensated tinnitus is clinically common (e.g., Stobik et al., 2005; Graul et al., 2008; Heinecke et al., 2008), results of the present study challenge the helpfulness of this dichotomization. Rather, personality traits appear to inform state cognitive-affective reactions to stimuli along a *continuum* of vulnerability-stress interactions with decompensation indicating a more pronounced expression of underlying, yet comparable, processes.

Vulnerability-Stress Interactions

Hypothesis 3: Within patients with chronic tinnitus, the degree of tinnitus-related distress is a function of differential interactions between personality-factors and differing dimensions of perceived subjective stress.

While personality constructs are understood as comparably stable traits of a person, perceived stress – as measured in the present study – can be understood as reflecting negative state stress-related perceptions. The results of the mediation analyses may thus represent vulnerability-stress interactions that contribute to tinnitus-related distress yet do not, however, allow for assuming causality. Results indicated that tinnitus-related distress was predicted by vicious cycles between dispositional patterns of feeling easily irritated, strained, and emotional which interact

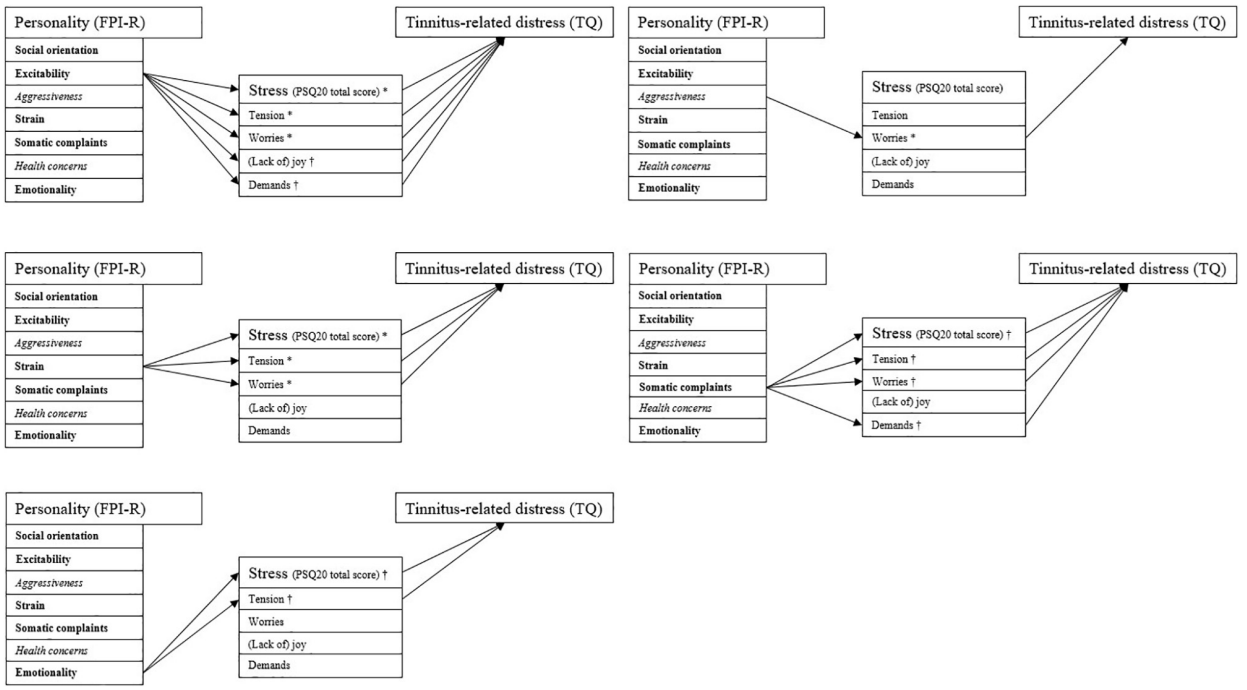

FIGURE 2 | Indirect effects of the mediation analyses. The PSQ20 subscale "joy" was inverted for reasons of consistent presentation (i.e., higher scores indicating higher perceived stress). Arrows indicate significant indirect effects ($p < 0.05$). All path coefficients are positive. Compared to the general population, bold labels indicate significantly higher; italicized labels significantly lower scores for patients with chronic tinnitus. *Complete mediation (total effect reduced to non-significance upon inclusion of *ab*); † partial mediation (total effect not reduced to non-significance upon inclusion of *ab*).

with state experiences of high perceived stress, in particular emotional tension and worries, in response to a variety of stimuli. Thus, tinnitus-related distress appears to be one possible expression of distress within a broader experience of dispositional stimulus-processing and behavioral patterns associated with psychological distress (or the inhibition thereof) and mild risk-taking behaviors.

The relationship between aggressiveness and tinnitus-related distress was found to be mediated by worries against the background of an overall inhibited expression of aggressiveness relative to the general population. Placing this finding in context, patients' high levels of concerns for others, inhibited expression of aggression, and *lower* levels of health anxiety and –related safety behaviors suggest that patients' high levels of worries may be less indicative of illness concerns (of which they express many), but may instead reflect *internal coping attempts to regulate aggressive tendencies*. On the extreme end of this spectrum, vicious cycles between high degrees of (suppressed) aggressiveness, high impulsivity, and high social orientation would be reflected in a clinical presentation of a self-sacrificing patient reporting high levels of tinnitus-related distress and worries that he/she might be attributing to the tinnitus sound, yet which may instead reflect unexpressed aggressive tendencies stemming from a felt need for behaving socially desirable in the face of possibly challenging interpersonal circumstances.

Interestingly, only the relationships between excitability and somatic complaints on tinnitus-related distress were mediated by demands (i.e., the *internal perception of external* stressors). By contrast, most other effects were mediated by patients' experiences of their *internal stress reactions* – notably *emotional tension* and *worries*. We believe that *emotional tension* reflects an affective state that patients with chronic tinnitus attempt to regulate through cognitive avoidance expressing itself in high levels of worry (Borkovec et al., 2004). Clinically, this lends support to the hypothesis that the *inner experience* of distress associated with patients' broader life situations may form a primary target for case conceptualization and intervention in patients with chronic tinnitus. By contrast, patients' frequently reported emphases of somatic symptoms or external stressors should be understood as emotion regulation attempts that are possibly informed by patients' needs for interpersonal support and validation upon struggling with guilt or distress-informed ways of interpreting their internal and external worlds.

Overall, the observed interaction patterns highlight the importance of considering personality traits in interaction with state experiences when trying to explain and treat tinnitus-related distress on a general or individual level. Whilst several studies have demonstrated effects of cognitive-behavioral therapy (CBT) interventions that included "stress management" techniques (Cima et al., 2014), the individual conceptualization of perceived "stress" in the context of dispositional personality traits appears crucial in understanding and meeting the needs of patients with chronic tinnitus. These idiosyncratic conceptualizations ought to consider *individual interactions of early experiences*

and personality traits, and their situational activation and expression across different stimulus-processing contexts that may include, but are not limited to the tinnitus sound thus allowing for individualized case conceptualizations and derived treatment strategies.

Psychological interventions that aim to encourage and facilitate emotional expression and -regulation may successfully reduce "emotional tension" thus providing a protective shield in the face of perceived stressors – even in the face of more stable personality traits indicating high vulnerability. Crucially, psychological interventions should focus on the *symptom function*, *affective states* and *difficulties in emotion regulation* that are likely to underlie observed (and commonly reported) worries about the tinnitus sound – and not necessarily attempt to address the worries' content "at face value" only. If indicated, treatment approaches should further address personality factors that predispose individuals to reacting toward a broad range of stimuli with high levels of perceived distress. There is now good evidence that personality factors continue to change in adulthood (Roberts and Mroczek, 2008) and psychological treatment approaches for personality problems have shown considerable effects (Cristea et al., 2017). Here, treatment frameworks that are based on third-generation behavior therapy models such as Compassion-Focused Therapy (CFT; Gilbert, 2010) or Schema Therapy (Young et al., 2003) provide useful bases for addressing more engrained stimulus-processing patterns and have been shown to meaningfully improve depression and anxiety-related difficulties (Leaviss and Uttley, 2015; Taylor et al., 2017). Although these approaches have not yet been trialed in patients with chronic tinnitus, preliminary evidence suggests their potential conceptual relevance in patients with somatization disorder (e.g., Davoodi et al., 2018); however, respective research strands are in their infancy.

Limitations

The current study has several limitations: in comparing patients' ratings with the general population, it cannot be ruled out, that a proportion of the FPI-R reference population might have also suffered from tinnitus symptomatology. However, the representative sample was normed against criteria including "state of health," "chronic illness," "hospital admissions," "doctor appointments," and "psychological therapy," rendering an above-chance proportion of chronic tinnitus patients unlikely to have been included. Moreover, whilst clinically common, the subdivision of patients into subgroups with compensated vs. decompensated tinnitus yields several disadvantages. These include, for example, the loss of statistical information and potential miscategorizations of patients close to the cut-off point as different rather than similar (Purgato and Barbui, 2013). The mediation analyses, by contrast, conceptualize tinnitus-related distress as a continuous variable. Owing to the cross-sectional design of the study, however, temporal lags between the formation of personality traits and their interaction with currently perceived stress cannot be established. Similarly, mediation analyses neither imply nor allow for assumptions of causality. Intercorrelations between habitual processing styles and state perceived stress variables are likely confounded; however, provide two different-yet-related targets for reducing tinnitus-related distress within psychological treatment frameworks.

CONCLUSION

Individual personality traits and their differential interactions with subjective experiences of internal or external stimulus-processing contexts provide valuable targets for assessments, case-conceptualizations, and treatments of patients with chronic tinnitus. Whilst the literature on personality factors and tinnitus-related distress is mixed, theorization and empirical investigation of vulnerability-stress models offers a more nuanced and ultimately more meaningful way of modeling and predicting tinnitus-related distress within a broader psychological conceptualization framework. Moreover, psychological trait x state models offer helpful ways of identifying and clustering patient-subpopulations that may benefit from respectively matched treatment protocols. Future studies ought to conceptualize tinnitus-related distress and psychological trait and state variables as continuous, interacting factors in order to predict, prevent or treat maladaptive exacerbations of psychological distress pathways.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Charité Universitätsmedizin Berlin EA 1/115/15. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RB: literature review, data analysis, data interpretation, and co-wrote article (Introduction, Materials and Methods, and Results). BB: literature review, devised data analysis strategy, data analysis, data interpretation, wrote substantive section of article (Abstract, Introduction, Materials and Methods, and Discussion), and addressed reviewer comments. PB: idea for study conceptualization/design, first data analysis, and commented on previous draft of the manuscript. RG: responsible for data collection. BM: idea for study conceptualization/design, supervision of publication, and head of department.

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Conflict of Interest: 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 interest.

APPENDIX

TABLE A1 | Path coefficients, confidence intervals and indirect effects for mediation analyses with FPI-R [independent variables], PSQ20 [mediators] and TQ total score indices [dependent variable].

FPI-E	PSQ20	Path *a*	*LLCI*	*ULCI*	Path *b*	*LLCI*	*ULCI*	*ab*	*LLCI*	*ULCI*	Path *c*	*LLCI*	*ULCI*	Path *c'*	*LLCI*	*ULCI*
Excitability	total	0.0381	0.0264	0.0497	36.7785	21.0639	52.4931	1.4001	0.7353	2.1866	2.0471	1.0468	3.0473	0.6470	−0.4408	1.7349
	worries	0.0414	0.0276	0.0551	28.8191	15.3195	42.3186	1.1919	0.6227	1.9099	2.0471	1.0468	3.0473	0.8552	−0.2235	1.9339
	tension	0.0419	0.0274	0.0565	28.7590	16.0916	41.4264	1.2057	0.6152	1.9383	2.0471	1.0468	3.0473	0.8414	−0.2153	1.8982
	joy	−0.0399	−0.0543	−0.0254	−19.8637	−33.2608	−6.4666	0.7916	0.1728	1.5300	2.0471	1.0468	3.0473	1.255	0.1543	2.3566
	demands	0.0359	0.0193	0.0525	16.6896	4.9618	28.4114	0.5997	0.1297	1.1395	2.0471	1.0468	3.0473	1.4474	0.3933	2.5015
Aggressiveness	worries	0.0221	0.0020	0.0422	34.2950	22.3140	46.2761	0.7576	0.0367	1.6186	0.7878	−0.5889	2.1645	0.0302	−1.1960	1.2564
Strain	total	0.0456	0.0388	0.0523	37.3904	15.1495	59.6312	1.7032	0.6465	2.8026	2.0217	1.2364	2.8070	0.3185	−0.9405	1.5774
	worries	0.0435	0.0337	0.0534	24.7134	9.3000	40.1269	1.0760	0.3779	1.8164	2.0217	1.2364	2.8070	0.9457	−0.0614	1.9528
	tension	0.0521	0.0432	−0.0610	26.8539	9.7738	43.9340	1.3981	0.5777	2.3826	2.0217	1.2364	2.8070	0.6230	−0.5421	1.7881
Somatic	total	0.0474	0.0317	0.0631	23.8626	10.0870	37.6382	1.1313	0.4422	1.8991	4.3041	3.1714	5.4367	3.1727	1.9154	4.4301
complaints	worries	0.0537	0.0355	0.0720	18.2776	6.2707	30.2844	0.9821	0.3330	1.7301	4.3041	3.1714	5.4367	3.3220	2.0570	4.5870
	tension	0.0575	0.0386	0.0764	18.3932	6.8327	29.9537	1.0581	0.4651	1.7433	4.3041	3.1714	5.4367	3.2460	1.9745	4.5175
	demands	0.0412	0.0188	0.0636	11.9519	1.9955	21.9082	0.4921	0.0805	1.0327	4.3041	3.1714	5.4367	3.8120	2.6321	4.9919
Emotionality	total	0.0456	0.0380	0.0533	23.0133	2.9236	43.1031	1.0500	0.0164	1.9647	2.5071	1.7300	3.2842	1.4571	0.2657	2.6484
	tension	0.0504	0.0402	0.0606	18.0812	3.1095	33.0529	0.9109	0.1592	1.6423	2.5071	1.7300	3.2842	1.5962	0.5264	2.6661

All analyses were computed using the PROCESS macro (Hayes, 2018); resampling procedures (bootstrapping) comprised 10000 replicates. LLCI = Lower level confidence interval (95%), ULCI = Upper level confidence interval (95%). Path a denotes the effect of the independent variable on the mediator; path b the effect of the mediator on the dependent variable; ab denotes the product term, i.e., indirect effect. Path c denotes the total effect of the independent variable on the dependent variable; path c' the direct effect; i.e., the total effect adjusted for ab.

The dogmas of the quiet past, are inadequate to the stormy present. The occasion is piled high with difficulty, and we must rise with the occasion. As our case is new, so we must think anew and act anew.

Abraham Lincoln, Annual Message to Congress, December 1, 1862

Chapter 3 [Stress]

Paper 3: Transdiagnostic Relevance of Perceived Stress across Different Chronic Symptom Clusters

Because previous research hypothesized phenomenological overlap between chronic pain and chronic tinnitus presentations [158,159], **Study 3** [120] uses a vulnerability-stress-coping framework to demonstrate that psychological variables such as depression or perceived stress are transdiagnostically relevant for explaining both chronic tinnitus and pain-related distress symptomatology.

'***Objective:*** *To investigate the co-occurrence of tinnitus-related distress and pain experiences alongside psychological factors that may underlie their association.* ***Method:*** *Patients with chronic tinnitus (N = 1238) completed a questionnaire battery examining tinnitus-related distress and affective and sensory pain perceptions. A series of simple, parallel and serial multiple mediator models examined indirect effects of psychological comorbidities as well as -process variables including depressivity, perceived stress and coping attitudes. Moderator and moderated mediation analyses examined differential relational patterns in patients with decompensated vs. compensated tinnitus.* ***Results:*** *There were significant associations between tinnitus-related distress and pain perceptions. These were partially mediated by most specified variables. Psychological comorbidities appeared to influence tinnitus-pain associations through their impact on depressivity, perceived stress, and coping attitudes. Some specific differences in affective vs. sensory pain perception pathways emerged. Patients with decompensated tinnitus yielded significantly higher symptom burden across all measured indices. Tinnitus decompensation was associated with heightened associations between [1] tinnitus-related distress and pain perceptions, depressivity and negative coping attitudes; and [2] most psychological comorbidities and sensory, but not affective pain perception. Moderated mediation analyses revealed stronger indirect effects of depressivity and anxiety in mediating affective-, and anxiety in mediating sensory pain perception in patients with decompensated tinnitus.* ***Conclusion:*** *Psychological constructs mediate the co-occurrence of tinnitus- and pain-related symptoms across different levels of tinnitus-related distress. Psychological treatment approaches should conceptualize and address individualised interactions of common cognitive-emotional processes in addressing psychosomatic symptom clusters across syndromatic patients with varying distress levels.*' [120(p1)]

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RESEARCH ARTICLE

Tinnitus-related distress and pain perceptions in patients with chronic tinnitus – Do psychological factors constitute a link?

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Data Availability Statement: As per Charité Universitaetsmedizin Berlin's ethics committee, unfortunately, we cannot make the data public without restrictions because we did not obtain patients' consent to do so at the time. Nevertheless, interested researchers can contact the directorate of the Tinnitus Center Charité Universitaetsmedizin Berlin with data access requests (birgit.mazurek@charite.de). Alternatively, interested researchers may also contact Charité's

Abstract

Objective

To investigate the co-occurrence of tinnitus-related distress and pain experiences alongside psychological factors that may underlie their association.

Method

Patients with chronic tinnitus ($N = 1238$) completed a questionnaire battery examining tinnitus-related distress and affective and sensory pain perceptions. A series of simple, parallel- and serial multiple mediator models examined indirect effects of psychological comorbidities as well as -process variables including depressivity, perceived stress and coping attitudes. Moderator and moderated mediation analyses examined differential relational patterns in patients with decompensated vs. compensated tinnitus.

Results

There were significant associations between tinnitus-related distress and pain perceptions. These were partially mediated by most specified variables. Psychological comorbidities appeared to influence tinnitus-pain associations through their impact on depressivity, perceived stress, and coping attitudes. Some specific differences in affective vs. sensory pain perception pathways emerged. Patients with decompensated tinnitus yielded significantly higher symptom burden across all measured indices. Tinnitus decompensation was associated with heightened associations between [1] tinnitus-related distress and pain perceptions, depressivity and negative coping attitudes; and [2] most psychological comorbidities and sensory, but not affective pain perception. Moderated mediation analyses revealed stronger indirect effects of depressivity and anxiety in mediating affective-, and anxiety in mediating sensory pain perception in patients with decompensated tinnitus.

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Conclusion

Psychological constructs mediate the co-occurrence of tinnitus- and pain-related symptoms across different levels of tinnitus-related distress. Psychological treatment approaches should conceptualize and address individualised interactions of common cognitive-emotional processes in addressing psychosomatic symptom clusters across syndromatic patients with varying distress levels.

Introduction

Both chronic tinnitus and pain are subjective, multifactorially influenced sensations [1, 2]. Beyond potential sensory or neurological contributors [3, 4], cognitive-affective processes are known to play key roles in the subjective experience, maintenance and potential chronification of each syndrome [5, 6, 7]. A subgroup of people with chronic tinnitus–conceptualized as a phantom auditory perception [8]–experience considerable emotional distress [9, 10] and report high levels of depression [11], anxiety [12] and other somatoform symptoms [13, 14] constituting the phenomenon of "decompensated" (vs. "compensated") tinnitus. In a more process-focused domain, those affected report high levels of perceived stress [15, 16, 17, 18, 19] and negative coping-related attitudes such as lowered optimism, self-efficacy beliefs, or heightened pessimism. These coping attitudes may affect tinnitus-related distress through their impact on general emotional distress [20, 21, 22]. Analogously, pain perceptions is frequently accompanied by high levels of emotional [23, 24, 25] or perceived stress [26], and a substantial body of work has highlighted interactions of cognitive and affective factors in mediating experiences of pain sensations [27, 28, 29, 30, 5, 31, 32, 33]. Consequently, tinnitus- or pain related distress are key targets of psychological or multimodal interventions that have been shown to be effective [13, 34, 35, 36]. However, despite the intriguing overlap between tinnitus-related distress and pain perceptions [3], hardly anything is known about their potential co-occurrence–or the role of psychological factors in mediating possible associations. Only one clinical study investigated the co-occurrence of pain perceptions and tinnitus and reported that 54.2% of $N = 77$ patients with pain perceptions also reported suffering from tinnitus [37]. Some other studies reported associations between tinnitus and headaches or migraines [38, 39, 40, 41] or temporomandibular joint pain [42, 43, 44]. However, these studies did not hypothesize or examine psychological factors such as psychological comorbidities, perceived stress, or coping attitudes as possible common denominators. Given the conceptual similarity of both symptom clusters, as well as the established importance of cognitive-emotional distress in contributing to the maintenance of either, the current study investigates tinnitus-related distress and pain perceptions in a sample of $N = 1238$ patients with chronic tinnitus. We hypothesized that both factors correlated and that psychological comorbidities would mediate respective associations. Exploratory analyses further examined whether [1] psychological comorbidities might exert their effects through their impact on individuals' levels of depressivity, perceived stress and coping attitudes and [2] tinnitus decompensation, i.e. high levels of tinnitus-related distress [45], differentially influence relations between symptom-related and mediating factors. Specifically, we investigated the following hypotheses:

1. Tinnitus-related distress is significantly associated with affective and sensory pain perceptions. Each construct correlates positively with psychological comorbidities, depressivity, perceived stress, and pessimism and negatively with self-efficacy and optimism.

2. Psychological comorbidities, depressivity, perceived stress and coping attitudes mediate the relationships between tinnitus-related distress and affective or sensory pain perceptions.
3. [Exploratory]: Psychological comorbidities may exert such effects *through* their impact on depressivity, perceived stress and coping attitudes.
4. Compared to patients with compensated tinnitus, patients with decompensated tinnitus show significantly higher levels of symptom burden across indices of pain perception and putative mediators.
5. [Exploratory]: Compared to patients with compensated tinnitus, patients with decompensated tinnitus may show differences in relationships between [a] tinnitus-related distress and putative mediators, [b] putative mediators and pain perception, and [c] tinnitus-related distress and sensory and affective pain perceptions.
6. [Exploratory]: Indirect effects may differ for patients with decompensated vs. compensated tinnitus.

Method

Participants

The present study includes self-report data from $N = 1238$ patients who [a] self-referred to the Tinnitus Centre at Charité Universitätsmedizin Berlin between January 2011 and October 2015, [b] suffered from chronic tinnitus (lasting for > 3 months), [c] were 18 years of age or older and [d] completed both the Tinnitus Questionnaire and the Pain Perception Scale. Exclusion criteria comprised the presence of acute psychotic illness or addiction, (untreated) deafness and insufficient knowledge of the German language. The total dataset comprised $N = 3851$ patients with chronic tinnitus with equal gender proportions (47.1% female). Two-thousand-six-hundred-thirteen ($n = 2613$; 67.9%) datasets were excluded for containing missing values for the Pain Perception Scale (2585; 67.1%) and/or the Tinnitus Questionnaire. Potential–unrecorded–reasons may have included patient refusal, technical difficulties or fatigue effects (as the Pain Perception Scale featured last in the questionnaire dataset). Note that missing values for the Pain Perception Scale do *not* indicate the absence of pain experiences–which could be explicitly indicated in the scales' ratings. Excluded cases were slightly, but significantly older than those included in the final sample ($M_{exluded} = 51.22$; $SD_{exluded} = 13.49$; $t(3849) = -2.34$, $p = .02$). Table 1 provides an overview of the sample's sociodemographic characteristics. Upon arrival at the Tinnitus Centre, patients completed a routine questionnaire assessment battery on Acer Pocket PC n300 electronic handheld information devices. Participants provided written consent for data to be collected and used for research purposes, and the Charité Universitätsmedizin Berlin's ethics committee approved data collection and analysis (No: EA1/040/08).

Measures

Tinnitus-related distress. The German version of the tinnitus questionnaire [46] assesses the impact of tinnitus across various psychological dimensions. It consists of 52 statements that are answered on a 3-point scale (0 = *not true*, 1 = *partly true*; 2 = *true*) across five subscales (cognitive and emotional burden, persistence of sound, hearing difficulties, sleep difficulties, and somatic complaints). It has been suggested that only the total score should be interpreted [47]–a recommendation that is followed in this paper. The total score uses 40 items with two being included twice, thus yielding a score from zero to 84. Biesinger et al. [48] suggested a

Table 1. Sociodemographic information (*N* = 1238 patients with chronic tinnitus).

Variable	*M*	*SD*
Age	50.17	12.02
	n	%
Gender		
Male	614	49.6
Female	624	50.4
Duration of tinnitus		
<1/2 year	159	12.8
1/2–1 year	252	20.4
1–2 years	188	15.2
2–5 years	216	17.4
>5 years	423	34.2
Degree		
None	37	3
Current: senior	9	0.7
Current: apprentice	8	0.6
Current: university	41	3.3
Apprenticeship	349	28.2
Polytechnic degree	193	15.6
University degree	601	48.5
Nationality		
German	1177	95.1
Other	61	4.9
Relationship status		
Single	382	30.9
Married	645	52.1
Divorced	188	15.2
Widowed	23	1.9
Work status		
Employed	902	72.9
Unemployed	336	27.1

M = mean, *SD* = standard deviation.

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cut-off of 46 points to distinguish high vs. low symptom burden; i.e. denote decompensated vs. compensated tinnitus. The scale's test-retest reliability is good (total score: $r = 0.94$; [49]). In the current sample, the scale's internal consistency was excellent ($\alpha = 0.92$).

Pain characteristics. Frequency and intensity of patients' pain perceptions were measured using two visual-analogue scales anchored at 0 [*never/minimal*] and 10 [*permanently/maximal*].

Pain perception. The Pain Perception Scale *("Schmerzempfindungsskala""-SES;* [50]) measures subjective pain perceptions across an affective and sensory scale. The former comprises 14 items that inquire about subjective pain-related affective distress [general affective pain statement, persistence indication of pain] whilst the latter comprises 10 items that inquire about subjective descriptions of physically experienced pain sensations [rhythm, local intrusion, and temperature]. All items are answered on a 4-point-scale (1 = *does not apply*, 2 = *hardly applies*, 3 = *somewhat applies*, 4 = *completely applies*) with scores ranging from 14–56 [affective pain perception] and 10–40 respectively [sensory pain perception]. Relative to a

clinical reference population of patients with pain perceptions, the affective pain perception scale yields cut-off ranges of < 22 (below average), 22–44 (average), and > 44 (above average). For the sensory pain perception scale, cut-off score-ranges are < 12, 12–25, and > 25. Notably, given the nature of reference sample, below-average values can also indicate considerable pain-related distress compared to the healthy general population [51]. In the present study, both types of pain perception were conceptualized as dimensionally distributed traits; however, category frequencies are reported descriptively. The scale's test-retest reliability is good (r = 0.89–0.96) with internal consistency being moderate to high (α = 0.72–0.92; [50]). In the current sample, internal consistencies were excellent ($\alpha_{affective}$ = 0.96; $\alpha_{seensory}$ = 0.90).

Psychological comorbidities. Psychological comorbidities concomitant to the index symptom "chronic tinnitus" were measured using the ICD-10 Symptom Rating [52,53]. The ISR consists of 29 items that are answered on a 5-point-scale (0 = *does not apply*, 1 = *hardly applies*, 2 = *somewhat applies*, 3 = *considerably applies*, 4 = *completely applies*). The measure includes five subscales that measure the presence or severity of depressive, anxiety-related, obsessive-compulsive, somatoform [including health-anxiety] and eating-related symptoms which link to syndromatic diagnostic categories as defined in the International Classification of Diseases-10 [54]. A supplementary scale further measures additional indices of psychological distress, clinical relevance or specific syndromes. Indexing the extent of overall emotional impairment, a total score is calculated that weighs the supplementary scale twice. All indices are linearly transformed to range from 0 to 1. Cut-off scores are 0.5 (total score), 0.75 (depressive and anxiety-related syndromes), 0.67 (obsessive-compulsive syndrome), and 0.33 (somatoform and eating-related syndromes) [55]. Test-retest reliability is good (r = 0.84–0.84; [52]). In the current sample, internal consistency was excellent (α = 0.93).

Depressivity. Depressivity was measured using the German version of the Center for Epidemiological Studies Depression Scale ("Allgemeine Depressionsskala"-ADS; [56, 57]. The scale comprises 20 items that measure emotional, motivational, cognitive, somatic and motoric symptoms of low mood on a 4-point-Likert scale (0 = *rarely*, 1 = *sometimes*, 2 = *often*, 3 = *almost always*) yielding a range from 0 to 60. A cut-off score of 23 suggests major depressive disorder; however, the present study conceptualized depressivity as a dimensionally distributed trait [58,59]. Test-retest reliability is moderate (r = 0.51–0.67) with internal consistency ranging from 0.85 to 0.92 [57]. In the current sample, internal consistency was sufficient (α = 0.73).

Perceived stress. Subjectively perceived stress was measured using the Perceived Stress Questionnaire-PSQ [60,61]. The scale measures perceived stress across four dimensions three of which constitute facets of one's internal stress reaction (tension, worries, [lack of] joy) and one of which measures perceived external stressors (demands). *Tension* explores tense disquietude, exhaustion and lack of relaxation. *Worries* assesses anxious concern for the future, and feelings of desperation and frustration; *joy* assesses positive feelings of challenge, joy, energy, and security and *demands* assesses perceived environmental demands such as lack of time, pressure, and overload. The scale consists of 30 items that are rated on a 4-point scale (1 = *almost never*, 2 = *sometimes*, 3 = *often*, 4 = *almost always*). All indices are linearly transformed to range from 0 to 1. All scores are subsumed in a total score for which *joy* is recoded. Whilst the present paper analyses perceived stress as a dimensional concept, suggested cut-off scores (defined as one *SD* > healthy population mean) are 0.50 (total score), 0.55 (tension), 0.46 (worries), <0.41 (joy), and 0.57 (demands) [61]. In the current sample, internal consistency was good (α = 0.90).

Coping attitudes. Adaptive and maladaptive coping attitudes were measured using the *Self-Efficacy-Optimism-Pessimism-Scale ("Selbstwirksamkeits-Optimismus-Pessimismus-Skala"-SWOP;* [62]). The scale comprises nine items that are answered on a 4-point scale (1 = *does not apply*, 2 = *hardly applies*, 3 = *somewhat applies*, 4 = *completely applies*) and load on three

independent scales with mean scores ranging from 1 to 4: self-efficacy, optimism and pessimism. In the current sample, internal consistencies were sufficient ($\alpha_{self\text{-}efficacy} = 0.82$; $\alpha_{optimism} = 0.79$; $\alpha_{pessimism} = 0.65$).

Data analyses

We used IBM SPSS Statistics for Windows, Version 24 to conduct the reported statistical analyses. Pearson's correlation coefficient (*r*) examined the relationship between all measures. The visual analogue scales were split into quartiles for descriptive reports of patients scoring in each scale range. Crosstabulations investigated frequencies of patients scoring above vs. below cut-off scores across the pain perception and tinnitus-related distress scales. Comparisons of descriptives between patients with decompensated vs. compensated tinnitus were computed using univariate ANOVA. Effect sizes *d* were calculated separately [63] with estimates being defined as small (0.20–0.49), medium (0.50–0.79) or large (> 0.80; [64]). Moderator and mediator analyses were conducted using the *process* macro by Hayes [65]. Effects of the independent variable *X* on the dependent variable *Y* are denoted as *total effects c*; effects of X on the mediator *M* as paths *a*; and effects of M on Y as *b*. Indirect effects are denoted as *ab*; and the total effects adjusted for *ab* as *direct effects c'*. Whenever the effect of X on Y decreases significantly (but not to zero), upon consideration of *ab*, "partial mediation" occurs [66]. First, simple mediator models specified tinnitus-related distress as independent (X), the total scores of the candidate process variables as mediating (M_i), and affective or sensory pain perception as dependent variables (Y). Follow-up analyses specified parallel multiple mediator models to investigate indirect effects via the PSQ and ISR's subscale scores to account for the subscales' intercorrelations whilst assuming non-causal associations (Fig 1, *Panel a*). Second, serial multiple mediator models explored whether psychological comorbidities exerted indirect effects *through* their impact on depressivity, perceived stress or coping attitudes. Here, tinnitus-related distress was specified as independent, psychological comorbidities (ISR) as first-step mediating, psychological process variables (ADS, PSQ, SWOP) as second-step mediating, and affective or sensory pain perceptions as dependent variables (*Panel b*). Third, to investigate differences in effects associated with tinnitus decompensation, path coefficients *c*, *a* and *b* were compared specifying decompensated vs compensated tinnitus severity as binary moderator *W* (*Panel c*). Finally, moderated mediation analyses tested whether potential indirect effects *ab* differed across categories of *W* (*Panel d*).

Results

Descriptive indices

Table 2 provides means and standard deviations for the total sample as well as descriptors of symptom levels where applicable. Overall, patients reported considerable rates of both pain frequency and intensity. Quartile (Q) splits of the *visual analogue pain frequency* scale revealed *n* = 486 patients (39.3%) as falling into Q1, 198 (16.0%) into Q2, 163 (13.2%) in Q3 and 377 (30.5%) in Q4. For the *visual analogue pain intensity scale*, *n* = 667 patients (53.9%) fell into Q1, 282 (22.8%) into Q2, 192 (15.5%) in Q3 and 83 (6.7%) in Q4). All constructs were significantly interrelated (**Hypothesis 1**). Correlation coefficients are given in the Online Supplemental Material (S1 Table).

Mediation analyses

Overview. The associations between tinnitus-related distress and pain perceptions were mediated by most psychological comorbidities and process variables. Depressivity emerged as

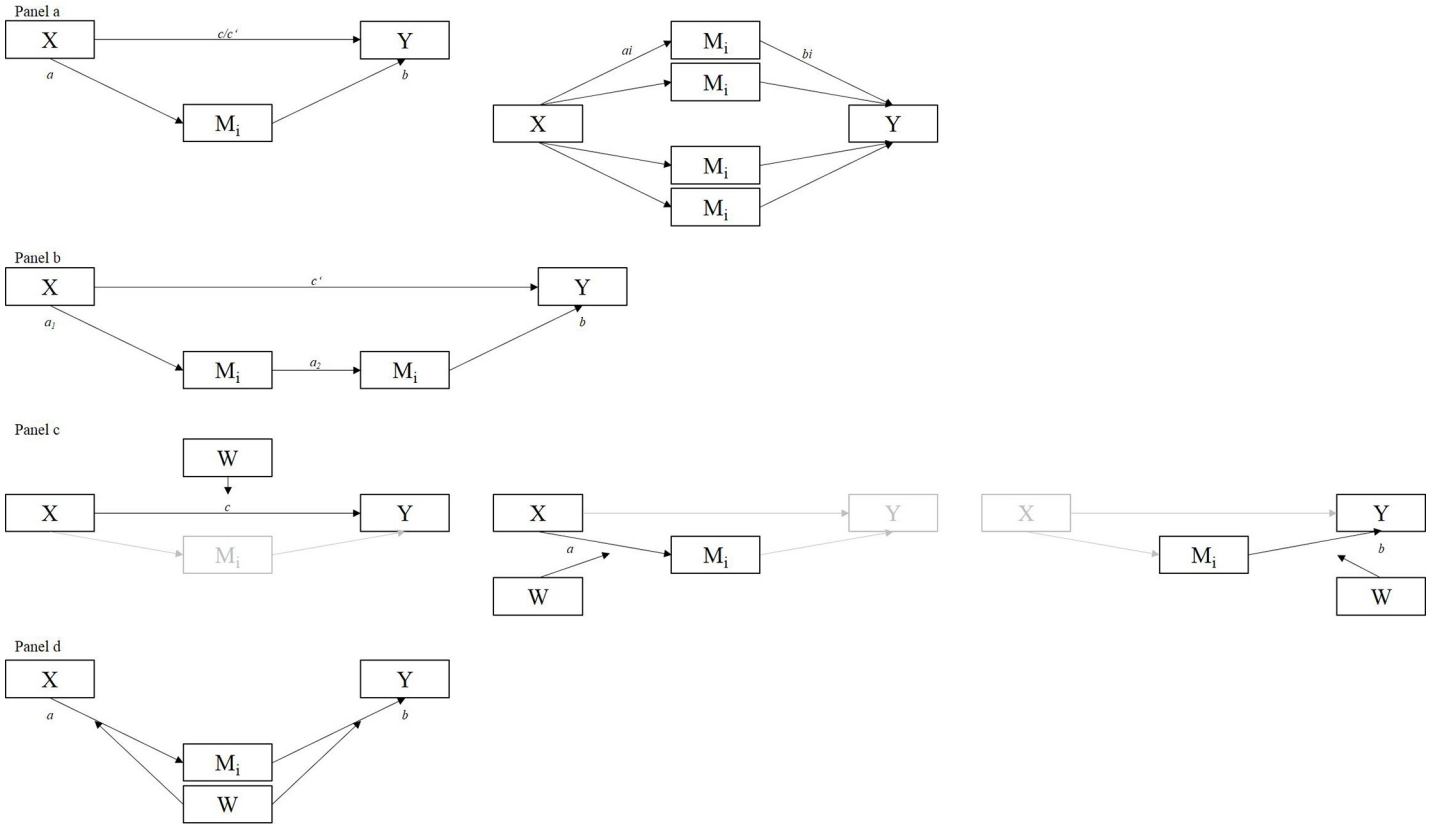

Fig 1. Conceptual diagrams of the specified models. *Panel a*: Simple and parallel multiple mediator models specifying tinnitus-related distress as independent, the putative mediators' total (left) or subscale scores (right) as mediating, and affective or sensory pain perception as dependent variables. *Panel b*: Serial multiple mediator models specifying tinnitus-related distress as independent, psychological 'comorbidities' as first-level mediating variables, psychological process variables (depressivity, perceived stress, and coping attitudes) as second-level mediating variables, and affective or sensory pain perception as dependent variables. *Panel c*: Simple moderator models investigating the effect of tinnitus decompensation vs. compensation (W) on paths c (left), a (middle), or b (right). *Panel d*: Moderated mediation model investigating the effect of tinnitus decompensation vs. compensation on *ab*.

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a key factor in mediating the effects of psychological comorbidities on affective and sensory pain perceptions. Anxiety-based comorbidities appear to influence [a] tinnitus-related distress and affective pain perceptions through heightened perceived stress and reduced coping abilities and [b] tinnitus-related distress and sensory pain perceptions through heightened worry and pessimism. Somatization-based comorbidities appear to additionally influence sensory pain perceptions through heightened emotional tension. The following paragraphs yield a more detailed description of results.

Simple and parallel multiple mediator analyses (independent variable: TQ; dependent variables: SES_A or SES_S; mediating variables: ISR, ADS, PSQ, SWOP).

Hypothesis 2. Simple mediation analyses revealed significant indirect effects of tinnitus-related distress on affective and sensory pain perceptions via the total scores of most measured mediating variables. Optimism mediated the relationship between tinnitus-related distress and affective, but not sensory pain perception (Fig 2, *Panel a*). Parallel multiple mediator analyses of the PSQ subscales revealed significant indirect effects of worry and lack of joy on both types of pain perceptions, with tension exerting an influence on affective pain perception only. Demands did not exert an indirect effect on either pain perception index. Analysis of the ISR subscales revealed that all psychological comorbidities mediated the relationship between tinnitus-related distress and affective pain perception. By contrast, the relationship between

Table 2. Means, standard deviations and symptom level descriptors for the total sample (*N* = 1238 patients with chronic tinnitus).

	M	*SD*	*Symptom level descriptors (M +/- 1 SD)*
Tinnitus-related distress [Tinnitus Questionnaire–German version, TQ]			
Total	39.55	17.07	[n/a]
Pain characteristics [Visual Analogue Scales]			
Frequency	4.56	3.66	[n/a]
Intensity	2.80	2.59	[n/a]
Pain perception [Pain Perception Scale, SES]			
Affective	24.23	10.08	[average*]
Sensory	13.75	5.12	[average*]
Psychological comorbidities [ICD-10 Symptom Rating, ISR]			
Total	0.81	0.59	[mild–moderate**]
Depressive syndrome	1.18	0.92	[mild–moderate**]
Anxiety-related syndrome	0.93	0.91	[elevated–mild**]
Obsessive-compulsive syndrome	0.78	0.87	[elevated–mild**]
Somatoform syndrome	0.62	0.81	[elevated–moderate**]
Eating-related syndrome	0.68	0.81	[mild–moderate**]
Supplementary scale	0.75	0. 57	[n/a]
Depressivity [Center for Epidemiological Studies Depression Scale, ADS]			
Total	18.33	11.85	[n/a]
Perceived stress [Perceived Stress Questionnaire, PSQ]			
Total	0.46	0.18	[normal–mildly elevated**]
Tension	0.59	0.22	[normal–moderately elevated**]
Worries	0.40	0.23	[normal–mildly elevated**]
Joy	0.48	0.22	[normal–mildly depleted**]
Demands	0.50	0.23	[normal–mildly elevated**]
Coping attitudes [Self-Efficacy-Optimism-Pessimism-Scale, SWOP]			
Self-efficacy	2.76	0.58	[n/a]
Optimism	2.72	0.76	[n/a]
Pessimism	2.14	0.72	[n/a]

M = mean, *SD* = standard deviation; n/a = not applicable. Degrees of symptom levels: PSQ: normal, mildly elevated / depleted, moderately elevated, severely elevated; ISR: normal, elevated, mild, moderate, severe.

* relative to a clinical sample of patients with pain perceptions

** relative to the general population

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tinnitus-related distress and sensory pain perception was mediated by anxiety-, somatoform, and eating-related symptoms only (*Panel b*).

Serial multiple mediator analyses (independent variable: TQ; first-level mediating variables: ISR subscale scores; second-level mediating variables: ADS, PSQ, SWOP scores; dependent variables: SES_A or SES_S).

Hypothesis 3. Serial multiple mediator analyses revealed that depressivity partly explained the indirect effects of psychological comorbidities on the relationship between tinnitus-related distress and *affective pain perception*. A more anxiety-based comorbidity cluster (anxiety-, obsessive-compulsive, somatoform and eating-related syndromes) further appeared to exert influence through its impact on perceived stress, self-efficacy and pessimism. Indirect effects that explained the relationship between tinnitus-related distress and *sensory pain perception* were also mediated by depressivity. Here, however, anxiety-based comorbidities affected sensory pain primarily through heightened worry and pessimism. Somatoform and eating-related

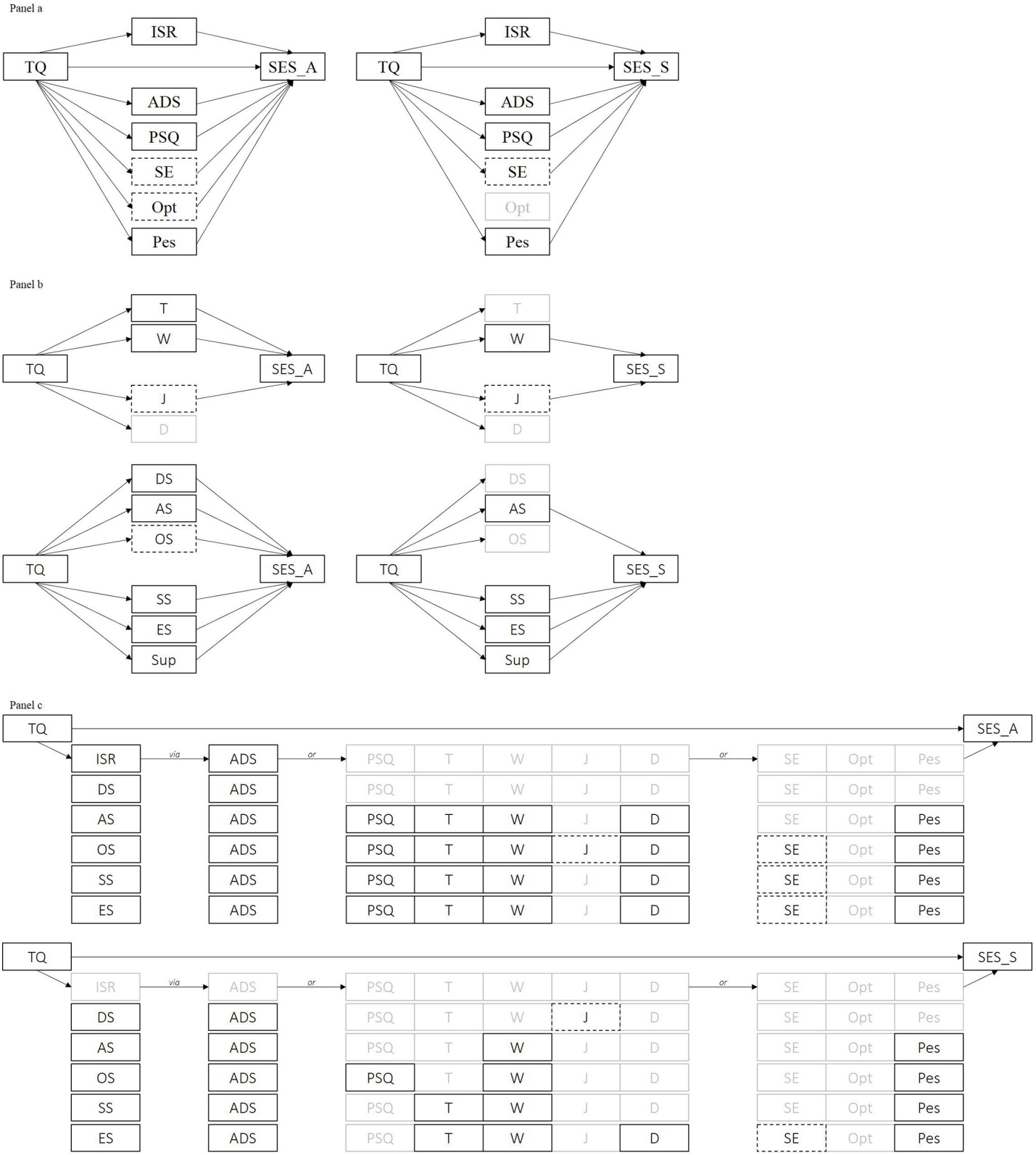

Fig 2. Graphical illustration of significant indirect effects. Black box frames indicate significant positive, dotted box frames significant negative and greyed-out boxes non-significant indirect effects. *Panel a*: Results of the simple mediator models for affective (left) or sensory pain perception (right). *Panel b*: Results of the parallel multiple mediator models for PSQ- (upper row) and ISR subscales (lower row) mediating affective (left) or sensory pain perception (right). *Panel c*: Results of the serial

multiple mediator models that examine the effects of shared psychological process variables across psychological 'comorbidities" on affective (upper row) or sensory pain perception (lower row). *Reading example for upper row*: *the indirect effect of tinnitus-related distress [TQ] on affective pain perception [SES_A] through psychological comorbidities [ISR] is explained by the latters impact on depressivity [ADS], but not perceived stress [PSQ, T, W, reduced J, D] or coping attitudes [reduced SE, Opt, heightened Pes]*. TQ = Tinnitus Questionnaire–German version total score, SES_A = Affective Pain Perception Scale: SES_S = Sensory Pain Perception Scale, ISR = ICD-10 Symptom Rating total score, DS = depressive syndrome, AS = anxiety-related syndrome, OS = obsessive-compulsive syndrome, SS = somatoform syndrome, ES = eating-related syndrome, Sup = supplementary scale, ADS = Center for Epidemiological Studies Depression Scale total score, PSQ = Perceived Stress Questionnaire total score, T = tension, W = worries, J = joy, D = demands, SE = Self-efficacy scale, Opt = Optimism scale; Pes = Pessimism scale. Significance level set at $p < .05$.

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syndromes were further associated with heightened emotional tension (Fig 2, *Panel c*). All path coefficients are provided in the Online Supplemental Material (S2 Table).

Tinnitus decompensation

In the current sample, $n = 810$ patients (65.4%) reported compensated and 428 patients (34.6%) decompensated tinnitus-related distress levels. For *affective pain perceptions*, $n = 640$ (51.7%) reported below-, 533 (43.1%) average and 65 (5.3%) above average levels. For *sensory pain perceptions*, $n = 569$ (46.0%) reported below-, 618 (49.9%) average and 51 (4.1%) above average levels relative to the pain perceptions reference sample. Table 3, *Panel a* provides a categorical tinnitus-x pain-related distress frequency matrix. Means, standard deviations and group comparisons for patients with decompensated vs. compensated tinnitus are reported in Table 3, *Panel b*.

Hypothesis 4. Compared to patients with compensated tinnitus, patients with decompensated tinnitus reported significantly higher symptom burden across all measured indices with pain perceptions, depressivity, perceived stress (tension, worries) as well as psychological comorbidities (depressive syndrome) yielding large, and [reduced] joy, remaining psychological comorbidities and coping attitudes yielding medium-effect-size differences.

Moderation analyses investigating the impact of tinnitus decompensation vs. compensation on relations between tinnitus-related distress, mediating variables, and affective or sensory pain perception.

Hypothesis 5. Moderation analyses for each pathway revealed significant differences for patients with decompensated vs. compensated tinnitus in the extents to which tinnitus-related distress was related to affective and sensory pain perception indices as well as depressivity, emotional tension, self-efficacy and pessimism. Tinnitus decompensation further appeared to exacerbate relationships between [1] anxiety and affective pain perception, and [2] depressive, obsessive-compulsive, somatoform, and eating-related difficulties and sensory pain. Tinnitus decompensation did not significantly impact upon relationships between PSQ and SWOP indices on affective or sensory pain perception respectively. See Fig 3 for a graphical illustration of significant differences in path coefficients for patients with decompensated vs. compensated tinnitus (S3 Table).

Moderated mediation analyses

Hypothesis 6. Last, moderated mediation analyses revealed significantly stronger indirect effects of tinnitus-related distress through [1] anxiety (ISR) on both pain perception indices and [2] depressivity (ADS) on affective, but not sensory pain perception in patients with decompensated vs. compensated tinnitus (Fig 4). All coefficients are provided in the Online Supplemental Material (S4 Table).

Discussion

Variations in depressivity, internal stress reactions, psychological comorbidities and coping attitudes underlay observed relationships between tinnitus-related distress and affective and

Table 3. Panel a: Frequencies across tinnitus- x pain-related distress categories. Panel b: Means, standard deviations, comparisons of means and effect sizes d for the total, compensated and decompensated patient samples.

A						
Tinnitus-related distress	**Affective pain perception**					
	Below average (n)	Average (n)	Above average (n)			
Compensated	529 (82.7%)	273 (51.2%)	8 (12.3%)			
Decompensated	111 (17.3%)	260 (48.8%)	57 (87.7%)			
	Sensory pain perception					
Compensated	453 (79.6%)	347 (56.1%)	10 (19.6%)			
Decompensated	116 (20.4%)	271 (43.9%)	41 (80.4%)			
B						
Subsample	Compensated (n = 810)		Decompensated (n = 428)			
	M	*SD*	*M*	*SD*	Group effect	*d (CI)*
Pain characteristics [Visual Analogue Scales]						
Frequency	3.95	3.55	5.73	3.58	$F(1, 1223) = 68.96^{***}$	0.50 (0.38–*0.62*)
Intensity	2.12	2.16	4.1	2.83	$F(1, 1223) = 186.02^{***}$	*0.79* (*0.76*–**1.00**)
Pain perception [Pain Perception Scale, SES]						
Affective	20.7	7.1	30.91	11.43	$F(1, 1237) = 373.44^{***}$	**1.16** (**1.03**–**1.28**)
Sensory	12.34	3.44	16.42	6.35	$F(1, 1237) = 207.57^{***}$	**0.88** (*0.75*–**1.00**)
Depressivity [Center for Epidemiological Studies Depression Scale, ADS]						
Total	13.82	9.5	26.96	11.08	$F(1, 1158) = 444.92^{***}$	**1.31** (**1.17**–**1.44**)
Perceived stress [Perceived Stress Questionnaire, PSQ]						
Total	0.41	0.16	0.56	0.16	$F(1, 1235) = 246.16^{***}$	**0.94** (**0.81**–**1.06**)
Tension	0.52	0.21	0.72	0.19	$F(1, 1235) = 280.31^{***}$	**0.98** (**0.86**–**1.11**)
Worries	0.33	0.2	0.53	0.21	$F(1, 1235) = 251.50^{***}$	**0.98** (**0.86**–**1.11**)
Joy	0.53	0.21	0.37	0.19	$F(1, 1235) = 168.20^{***}$	*-0.79* (*-0.67-* **-0.91**)
Demands	0.47	0.22	0.54	0.24	$F(1, 1235) = 26.69^{***}$	0.31 (0.19–0.43)
Psychological comorbidities [ICD-10 Symptom Rating, ISR]						
Total	0.63	0.47	1.17	0.64	$F(1, 1183) = 271.73^{***}$	**1.01** (**0.89**–**1.14**)
Depressive syndrome	0.87	0.76	1.78	0.91	$F(1, 1183) = 327.77^{***}$	**1.12** (**1.00**–**1.25**)
Anxiety-related syndrome	0.72	0.74	1.36	1.05	$F(1, 1183) = 144.69^{***}$	*0.75* (*0.62*–**0.87**)
Obsessive-compulsive syndrome	0.63	0.77	1.1	0.96	$F(1, 1183) = 83.30^{***}$	*0.56* (0.44–*0.68*)
Somatoform syndrome	0.44	0.67	0.97	0.93	$F(1, 1183) = 122.19^{***}$	*0.69* (*0.57*–**0.81**)
Eating-related syndrome	0.44	0.67	0.97	0.93	$F(1, 1183) = 122.19^{***}$	*0.69* (*0.57*–**0.81**)
Supplementary scale	0.62	0.74	0.79	0.92	$F(1, 1183) = 11.74^{**}$	0.21 (0.10–0.33)
Coping attitudes [Self-Efficacy-Optimism-Pessimism-Scale, SWOP]						
Self-efficacy	2.89	0.53	2.52	0.6	$F(1, 1237) = 124.72^{***}$	*-0.67* (*-0.55-* -0.79)
Optimism	2.88	0.69	2.41	0.79	$F(1, 1237) = 116.75^{***}$	*-0.65* (*-0.56-* **-0.80**)
Pessimism	1.98	0.66	2.45	0.73	$F(1, 1237) = 134.82^{***}$	*0.69* (*0.59*–**0.84**)

Within affective or sensory pain perception indices, all horizontal and vertical cell comparisons significantly differ from each other (chi^2 $p <. 05_{\text{Bonferroni corrected}}$).
Percentages are referring to respective pain perception categories.

M = mean, SD = standard deviation, d = Cohen's d (small effect d >.20 < .50; *medium effect* > .50 < .80; large effect > .80). CI = 95% Confidence Interval

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sensory pain perceptions in a sample of patients with chronic tinnitus. Thus, conceptualizing and therapeutically addressing individual interactions of these psychological constructs may contemporaneously attenuate both symptom clusters. These findings are in keeping with findings that have repeatedly highlighted the effectiveness of psychological treatments for relieving tinnitus- [13, 67, 68] and pain-related distress [69, 70, 71].

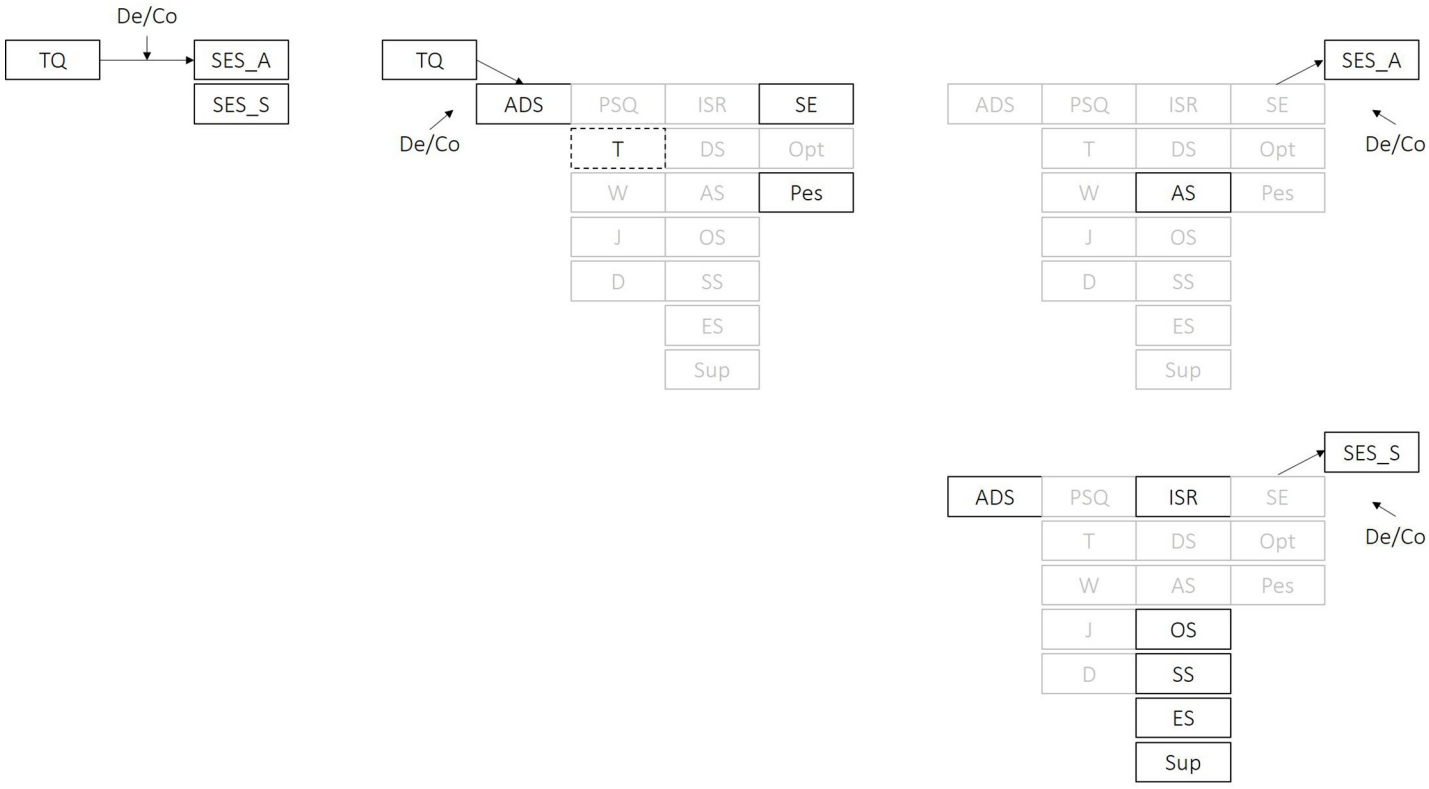

Fig 3. Graphical illustration of simple moderation effects. *De/Co* indicates the specification of tinnitus decompensation vs. compensation as a putative moderator of paths *c* (left), *a* (middle) and *b* (right upper row: affective pain perception; lower row: sensory pain perception). Continuous black box frames indicate that respective effects are stronger in patients with decompensated vs. compensated tinnitus, dotted box frames the opposite. Greyed out boxes indicate non-moderated effects. TQ = Tinnitus Questionnaire–German version total score, SES_A = Affective Pain Perception Scale: SES_S = Sensory Pain Perception Scale, ADS = Center for Epidemiological Studies Depression Scale total score, PSQ = Perceived Stress Questionnaire total score, T = tension, W = worries, J = joy, D = demands, ISR = ICD-10 Symptom Rating total score, DS = depressive syndrome, AS = anxiety-related syndrome, OS = obsessive-compulsive syndrome, SS = somatoform syndrome, ES = eating-related syndrome, Sup = supplementary scale, SE = Self-efficacy scale, Opt = Optimism scale; Pes = Pessimism scale. Significance levels were set at $p < .05$.

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Optimism, tension [PSQ], depressivity [ADS], and obsessive-compulsive symptoms [ISR] mediated the link between tinnitus-related distress and affective, but not sensory pain perception. Viewed from an emotion regulation perspective, the observed negative indirect effect of obsessions (with higher obsessive symptoms reducing affective pain perception) might point to a possible function of these symptoms in regulating underlying affective states [72,73,74,75]. Similarly, emotional tension has been described in individuals with difficulties in identifying or regulating emotions [76]–which have also been observed in individuals with psychosomatic symptoms or emotionally avoidant coping styles [77,78,79,80]. The positive impact of optimism on tinnitus-related distress or pain perception has been demonstrated before [81, 20, 82], and increasing optimism thus constitutes a target for psychological interventions [83, 84]. Pessimism, conversely, has been associated with heightened inducibility of pain perceptions in healthy individuals [85], and therefore also warrants psychological targeting within broader therapeutic strategies aimed to reduce depressivity [86]. Overall, coping attitudes may constitute important vulnerability or maintaining factors for the co-occurrence of tinnitus-related distress and pain perceptions.

Investigating whether psychological comorbidities accounted for the co-occurrence of tinnitus-related distress and pain perceptions *through* affecting depressivity, perceived stress or coping attitudes, depressivity emerged as a key factor that determined the impact of all

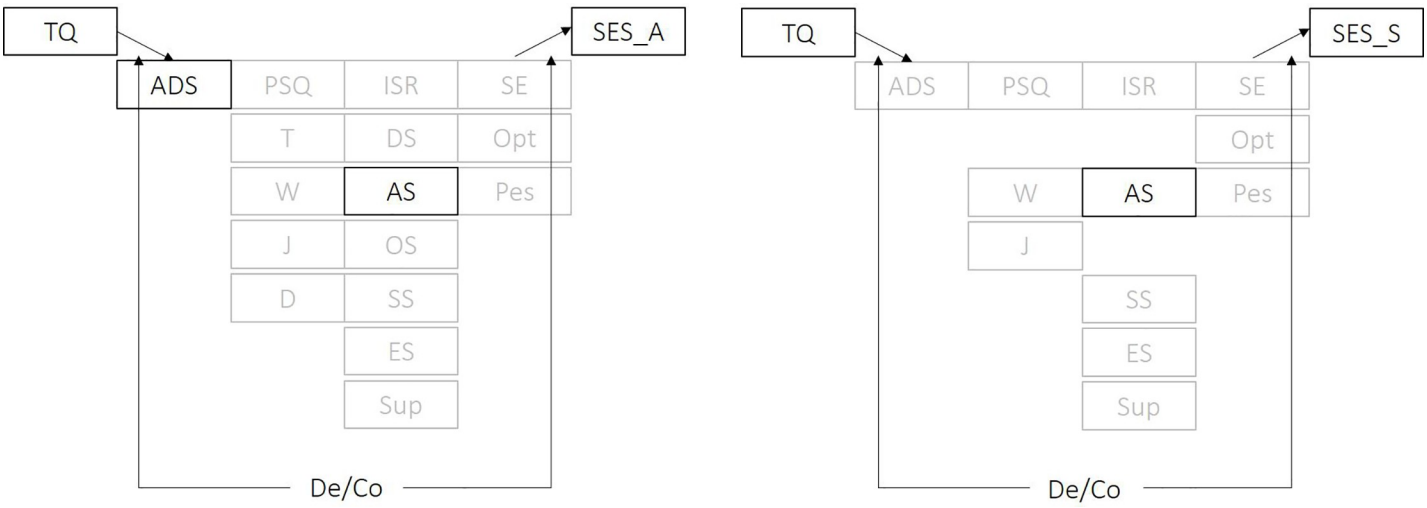

Fig 4. Graphical illustration of moderated mediation models for affective (left) and sensory pain perception (right). *De/Co* indicates the specification of tinnitus decompensation vs. compensation as a putative moderator of the indirect effects of tinnitus-related distress on affective or sensory pain perceptions through the specified process variables. Continuous black box frames indicate that respective indirect effects are stronger in patients with decompensated vs. compensated tinnitus. Greyed out boxes indicate non-moderated indirect effects. TQ = Tinnitus Questionnaire–German version total score, SES_A = Affective Pain Perception Scale: SES_S = Sensory Pain Perception Scale, ADS = Center for Epidemiological Studies Depression Scale total score, PSQ = Perceived Stress Questionnaire total score, T = tension, W = worries, J = joy, ISR = ICD-10 Symptom Rating total score, DS = depressive syndrome, AS = anxiety-related syndrome, OS = obsessive-compulsive syndrome, SS = somatoform syndrome, ES = eating-related syndrome, Sup = supplementary scale, SE = Self-efficacy scale, Opt = Optimism scale; Pes = Pessimism scale. Significance level set at $p < .05$.

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psychological comorbidities. Comorbidities that may contain aspects of affective avoidance such as anxiety, obsessive-compulsive, somatoform and eating-related syndromes [87,88] were found to affect the link between tinnitus-related distress and *affective pain perception* by exacerbating perceived stress and pessimism alongside lowering self-efficacy beliefs. For *sensory pain perception*, a broadly similar pattern was observed; here, however, worry and pessimism influenced sensory pain perceptions more strongly. This finding is in keeping with studies highlighting the role of these factors in influencing anxiety in the context of sensory misperceptions [89, 90, 91, 92]. Emotional tension—which was primarily associated with affective pain perceptions—may similarly be addressed by applied emotion regulation interventions [93, 94, 95].

Tinnitus decompensation was associated with [1] considerably higher symptom burden across all measured psychological indices, [2] stronger relationships between tinnitus-related distress and [a] both types of pain perception (paths *c*) as well as [b] depressivity and reduced coping attitudes (paths *a*), [3] stronger relationships between anxiety and *affective*, and depressivity, obsessive-compulsive, somatoform, as well as eating-related symptoms and *sensory* pain perception (paths *b*). Tinnitus decompensation was further associated with [4] significantly stronger indirect effects of depressivity and anxiety in mediating affective pain perceptions; and anxiety in mediating sensory pain perceptions.

Tinnitus decompensation has previously been associated with heightened psychological distress across different domains of experience [96, 97, 45, 98]. These, as well as the current findings may reflect conceptual similarities between tinnitus-related distress and related psychological constructs–such as pain perceptions, depressivity, pessimism, and reduced self-efficacy beliefs. The exacerbation of relations between the specified mediators and sensory, but not affective pain perceptions with tinnitus decompensation may potentially point to a somatoform shift in emotional experience with higher emotional distress being associated with a stronger sensory focus on psychophysiological experience. If this were the case, future studies

should investigate reversed u-shaped relationships between sensory perceptions and patients' emotional experiences. Interestingly, the relationship between tinnitus-related distress and emotional tension *decreased* alongside increasing severity of these factors. It may also be speculated that increasing tinnitus-related distress might lead to a chronification process that involves perceived stress becoming an independent risk factor [99, 100, 101]. Alternatively, perceived emotional tension might shift towards tinnitus-related distress in an effort to regulate emotional destabilization.

In keeping with previous studies that highlight the roles of depression and anxiety in patients with chronic tinnitus [102, 103] or pain [104, 105, 106], tinnitus decompensation appeared to exacerbate the impact of anxiety on affective, and depressivity and anxiety-centred symptoms on sensory pain perceptions. In addition to the psychological impact of these symptom clusters, physiological arousal may also influence fear of pain thereby forming a possible link between anxiety and pain perceptions [107]. Similarly, the impact of depressivity on altered sensory perceptions has also been highlighted [108]. The moderated mediation analyses' findings thus highlight that depressivity and anxiety take center stage in underlying the co-occurrence of tinnitus-related distress and pain perceptions.

Strength and limitations

The current study has several limitations. Most importantly, the cross-sectional nature of the data as well as the absence of a control group limit its causal interpretability and generalizability. Cross-sectional mediation analyses do not imply causation; however, they are suited to generate causal hypotheses that ought to be tested in future prospective or experimental studies. Partial mediation of the observed associations further suggests the existence of important third variables that need to be theoretically deduced, measured and interactionally examined in future studies. Whilst the study conceptualized patients' tinnitus and pain perceptions within a broader biopsychosocial framework [28, 109] it did not stratify patients' pain ratings according to the presence or absence of specific medical conditions [110] thereby limiting the identification of differentially caused sensory pain stimuli. Similarly, information about pain or antidepressant medication was not available. The visual analogue scales that we used to quantify pain frequency and intensity have been subject of scientific controversy [111, 112]; however were chosen for reasons of clinical feasibility. Last, given the exploratory nature of the study, we used lenient tests for possible indirect effects. We preferred committing Type I over Type II errors at this stage of empirical investigation into identifying common psychological pathways between tinnitus-related distress and pain perceptions. Consequently, however, the findings need to be cautiously interpreted and replicated in future studies.

Notwithstanding, the present study is the first to investigate the co-occurrence of chronic tinnitus and pain perceptions in a large clinical sample of patients with chronic tinnitus. It provides important first insights into the roles of psychological factors that explain shared variance between the two symptom clusters thus highlighting their importance in conceptualizing and treating these syndromes. Whilst depressivity emerged as a key factor, associated constructs such as perceived stress (in particular worry and emotional tension) and subjectively impaired coping attitudes constitute promising intervention targets. Locating the pathways through which psychological processes may generate distress gives way to conceptualizing and testing transdiagnostic psychological treatment approaches that improve the well-being of patients with chronic tinnitus with or without concurrent pain symptoms. Whilst some studies conceptualize psychological distress within a diagnostic framework that assumes the presence of "comorbidities" as distinct clinical entities that exist in addition to an "index disease" such as chronic tinnitus or -pain [113,114], the present study challenges the helpfulness of this view.

It seems somewhat ill-suited to conceptualize and treat separate conditions suited given the co-occurring and functionally similar psychosocial conditions that patients with chronic tinnitus commonly face [115, 116, 59].

Conclusions

Results of the present study point to a key role of *psychological processes* as common denominators that may account for co-occurrences of chronic tinnitus, pain perceptions and psychological "comorbidities". Transdiagnostic interventions that focus on shared cognitive-emotional factors are thereby likely to reduce the distress associated with co-occurring syndromatic conditions [117, 118]. Indeed, such treatment approaches have been gaining momentum in offering useful tools to conceptualize and treat co-occurring symptom clusters [119, 115, 120, 121]. Any such intervention may prevent symptom chronification or alleviate distress by developing individualised case conceptualizations and thereon based idiosyncratic treatment plans that may feature a range of interventions aimed at modifying individual interactions of memories, situational stimulus interpretations, habitual or current emotional states and behaviours. Future research needs to continue to investigate interactions of psychological process variables pertinent to tinnitus-related distress and co-occurring affective or sensory phenomena.

Supporting information

S1 Table. Correlation matrix for the obtained measures.
(DOCX)

S2 Table. Path coefficients for significant indirect effects.
(DOCX)

S3 Table. Simple moderation effects for paths *c*, *a* and *b*.
(DOCX)

S4 Table. Moderated mediation effects for affective and sensory pain perception.
(DOCX)

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There are three things needed to eliminate human misery. Unfortunately, nobody knows what they are.

David Levy, Humor in Psychotherapy

Chapter 4 [Coping]

Paper 4: Psychological Effects of a 'Psychological' Treatment Approach

Study 4 [121] advocates for the psychological treatment of transdiagnostically relevant factors across different 'somatic' symptom expressions. It consolidates the previous study's findings by demonstrating that an emotion-focused psychological treatment approach can ameliorate both chronic TRD and -pain experiences.

'***Background:*** *Psychological factors link the co-occurrence of tinnitus-related distress and pain perceptions in patients with chronic tinnitus.* ***Objective:*** *This study examines, if treatment-related changes in these factors ameliorate both tinnitus-related distress and pain perceptions in a sample of patients with chronic tinnitus.* ***Methods:*** *N = 1238 patients with chronic tinnitus provided pre- and post-treatment ratings of tinnitus-related distress and affective or sensory pain perceptions alongside measures of depressive symptoms and perceived stress. Treatment comprised an intensive tinnitus-specific multimodal treatment program. Using serial indirect-effects analyses, we examined association patterns between baseline values and change rates of those variables that were found to respond to treatment.* ***Results:*** *Small effect sizes emerged for changes in tinnitus-related distress, affective (but not sensory) pain perceptions, depressive symptoms, emotional tension and worry. At pre- or posttreatment respectively, baseline values and change rates intercorrelated. Across timepoints, (1) baseline tinnitus-related distress and affective pain perceptions were positively associated with improvements in tinnitus-related distress, affective pain perceptions and depressive symptoms. (2) Baseline depressive symptoms or emotional tension mediated positive associations between baseline tinnitus-related distress and improvement in affective pain perceptions. (3) Change in depressive symptoms mediated the effect of baseline tinnitus-related distress on change in affective pain perceptions – partly through associated change in emotional tension or worry. Mood-independent aspects of emotional tension were negatively associated with improvement in affective pain perceptions.* ***Conclusions:*** *Depressive symptoms, emotional tension and worry emerge as key predictors of treatment response and transdiagnostic treatment targets for alleviating tinnitus-related distress and functionally associated affective pain perceptions.*' [121(p1)]

PLOS ONE

RESEARCH ARTICLE

Two birds with one stone–Addressing depressive symptoms, emotional tension and worry improves tinnitus-related distress and affective pain perceptions in patients with chronic tinnitus

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Abstract

Background

Psychological factors link the co-occurrence of tinnitus-related distress and pain perceptions in patients with chronic tinnitus.

Objective

This study examines, if treatment-related changes in these factors ameliorate both tinnitus-related distress and pain perceptions in a sample of patients with chronic tinnitus.

Methods

N = 1238 patients with chronic tinnitus provided pre- and post-treatment ratings of tinnitus-related distress and affective or sensory pain perceptions alongside measures of depressive symptoms and perceived stress. Treatment comprised an intensive tinnitus-specific multimodal treatment program. Using serial indirect-effects analyses, we examined association patterns between baseline values and change rates of those variables that were found to respond to treatment.

Results

Small effect sizes emerged for changes in tinnitus-related distress, affective (but not sensory) pain perceptions, depressive symptoms, emotional tension and worry. At pre- or post-treatment respectively, baseline values and change rates intercorrelated. Across time-points, (1) *baseline* tinnitus-related distress and affective pain perceptions were positively associated with *improvements* in tinnitus-related distress, affective pain perceptions and depressive symptoms. (2) *Baseline* depressive symptoms or emotional tension mediated positive associations between *baseline* tinnitus-related distress and *improvement* in affective pain perceptions. (3) *Change* in depressive symptoms mediated the effect of baseline

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tinnitus-related distress on *change* in affective pain perceptions–partly through associated change in emotional tension or worry. Mood-independent aspects of emotional tension were negatively associated with improvement in affective pain perceptions.

Conclusions

Depressive symptoms, emotional tension and worry emerge as key predictors of treatment response and transdiagnostic treatment targets for alleviating tinnitus-related distress and functionally associated affective pain perceptions.

Introduction

Both chronic tinnitus and pain are index symptoms of multifactorially influenced syndromes that combine sensory, neurological and psychological components [1–6].

The majority of people who experience tinnitus report no discomfort following symptom onset [7]; however a proportion of people report increased levels of perceived stress [8–10] or low mood [11–13].

Similarly, pain experiences have long been shown to be considerably influenced by cognitive and affective factors [14–17] including perceived stress [18–20], worry [21, 22], and depressive symptoms [23, 24].

Linking these two constructs, Boecking et al. [25] analysed cross-sectional data from a large sample of 1238 patients with chronic tinnitus and reported that [a] a substantive number of patients described notable levels of pain experiences and [b] this co-occurrence was partly explained by common underlying psychological factors including depressive symptoms, emotional tension, worry, and coping attitudes.

Psychological interventions have been shown to be effective in alleviating both tinnitus-related distress [26–29] and pain experiences [30–32]. Similarly, multimodal treatment approaches have shown promising effects for each symptom cluster [33–37].

Among the tinnitus-focused multimodal therapy concepts, our group offered an intensive tinnitus-specific multimodal treatment program between 2011 and 2015. This treatment approach had been previously shown to successfully reduce tinnitus-related distress [38]. However, no study has since investigated [a] if this treatment is effective in a large clinical sample, [b] if beneficial effects on tinnitus-related distress might extend towards pain experiences due to the psychological overlap between the two symptom clusters, and [c] whether any such joint improvements may be attributable to baseline values of or changes in common underlying psychological factors.

The study sample, data collection procedures and measures were previously described in Boecking et al. [25], which reports cross-sectional data from the same sample at baseline. The previous study established psychological factors as common denominators of tinnitus-related distress and pain perceptions. Building on these findings, the present study focuses on treatment-related changes in tinnitus-related distress, pain perceptions and common underlying psychological factors following an intensive tinnitus-specific multimodal treatment program. The study investigates the following research questions: [1] does the brief, intensive tinnitus-specific multimodal treatment program ameliorate tinnitus-related distress, pain experiences, and common underlying psychological factors; [2] is the relationship between *baseline* tinnitus-related distress and *change* in pain perception associated with *baseline* values or [3] *change rates* of psychological factors; and [4] is the relationship between *change* in tinnitus-related

distress and pain perception associated with *change* patterns in psychological factors? Based on the previously demonstrated effectiveness of the multimodal treatment program on alleviating tinnitus-related distress [38], the cross-sectional association of tinnitus-related distress and pain perceptions in patients with chronic tinnitus [25], and the reported mediation of this association through shared psychological factors including depressive symptoms and perceived stress [25], we hypothesize positive associations between baseline and change values of tinnitus-related distress and pain perceptions that we expect to be mediated by baseline and/or change values of the previously identified underlying psychological process variables.

Materials and methods

Participants

Data were drawn from a large dataset obtained during routine clinical practice of $N = 3851$ patients with chronic tinnitus who [a] self-referred to the Tinnitus Center at Charité Universitaetsmedizin Berlin between January 2011 and October 2015, [b] suffered from chronic tinnitus (lasting for > 3 months), and [c] were 18 years of age or older. Patients with acute psychotic illness or addiction and insufficient knowledge of the German language were not included in the sample. Given the present paper's focus on treatment-responses of psychological factors and associated changes in tinnitus-related distress and pain perceptions, patients who did not complete the Tinnitus Questionnaire and the Pain Perception Scale at baseline were excluded ($n = 2613$). The final sample included $N = 1238$ patients (50.4% female), $n = 1098$ and 1039 of whom provided post treatment data for the Tinnitus Questionnaire and Pain Perception Scale respectively ($M_{included} = 50.17$; $SD_{included} = 12.02$). Excluded cases ($n = 2613$) were slightly, but significantly older than those included in the analysis sample ($M_{exluded} = 51.22$; $SD_{exluded} = 13.49$; $t(3849) = -2.34$, $p = .02$; see also [25].

Procedure

Upon arrival at the Tinnitus Center for the start of the treatment program, patients completed a routine questionnaire assessment battery on Acer Pocket PC n300 electronic handheld information devices (cf. [25]). The same measures were completed post treatment. Charité Universitaetsmedizin Berlin's Ethics Committee granted ethical approval (No: EA1/040/08).

Treatment

Prior to starting treatment, ear-nose-throat and psychosomatic specialists conducted individual otological, audiological and psychosomatic diagnostics alongside physical examinations. Treatment then comprised an intensive tinnitus-specific multimodal treatment program that included psychoeducation-, cognitive-behaviour therapy-oriented-, relaxation-, audiological- and physiotherapeutic treatment components. Upon beginning treatment, patients were familiarized with progressive muscle relaxation (PMR) by Edmund Jacobson [39] and practiced this relaxation strategy daily throughout therapy. Additionally, patients participated in daily group physiotherapy exercises and were offered two single sessions of physiotherapy each. The psychological aspects of the treatment program included [1] psychoeducation about basic hearing physiology, and the anatomy and function of the auditory system as well as models of stress and stress management, [2] daily auditory training, which comprised audiological defocusing exercises, [3] daily cognitive-behavioral group therapy focusing on dysfunctional cognitions concerning tinnitus, anxieties, sleep disturbances and stress; and [4] two individual psychological consultations that focused on individual difficulties reported by the patients. An

interdisciplinary team of trained clinical psychologists or physiotherapists delivered all interventions. Medical professionals were available to address medical issues where applicable.

Measures

Tinnitus-related distress. The German version of the tinnitus questionnaire [TQ; 40] was administered to assess the psychosocial impact of tinnitus symptomatology. It consists of 52 statements that are answered on a 3-point scale (0 = *not true*, 1 = *partly true*, 2 = *true*). The total score uses 40 items—two of them twice—thus yielding a score between zero and 84. The scale's test-retest reliability is good (total score: $r = 0.94$; [41]), and the TQ has been found to be sensitive to change [42]. In the current sample, the scale's internal consistency was excellent ($\alpha = 0.92$).

Pain perception. The Pain Perception Scale *("Schmerzempfindungsskala"-SES;* [43]) measures subjective pain perceptions across an affective and sensory subscale. The former uses 14 items to obtain indications of subjective pain-related affective distress [e.g. "I experience my pain as intolerable"]. The latter uses 10 items to obtain indications of subjective experiences of physically experienced pain sensations [e.g. "I experience my pain as throbbing"]. All items are answered on a 4-point-scale (1 = *does not apply*, 2 = *hardly applies*, 3 = *somewhat applies*, 4 = *completely applies*) with scores ranging from 14–56 [affective pain perception] and 10–40 respectively [sensory pain perception]. The scale's test-retest reliability is good ($r = 0.89$–0.96) with internal consistency being moderate to high ($\alpha = 0.72$–0.92; [43]). In the current sample, internal consistencies were excellent ($\alpha_{affective} = 0.96$; $\alpha_{sensory} = 0.90$).

Psychological comorbidities. Psychological "comorbidities" (i.e. psychological epiphenomena reciprocally associated with chronic tinnitus as the index symptom in focus) were measured using the ICD-10 Symptom Rating [ISR; 44, 45]. The ISR consists of 29 items that are answered on a 5-point-scale (0 = *does not apply*, 1 = *hardly applies*, 2 = *somewhat applies*, 3 = *considerably applies*, 4 = *completely applies*). The measure includes five subscales that measure the presence of depressive, anxiety-related, obsessive, somatoform [including health-anxiety] and eating-related symptoms that are linked to syndromatic diagnostic categories as defined by the International Classification of Diseases-10 [46]. An additional supplementary scale measures various aspects of psychological distress or clinical relevance. Indexing the extent of overall emotional impairment, a total score is calculated that weighs the supplementary scale twice. All indices range from zero to 4. Test-retest reliability is good ($r = 0.84$–0.84; [44]) and the scale has been shown to be sensitive to change [44, 47]. In the current sample, internal consistency was excellent ($\alpha = 0.93$).

Depressive symptoms. Depressive symptoms were measured using the German version of the Center for Epidemiological Studies Depression Scale ("Allgemeine Depressionsskala"-ADS; [48, 49]). The scale features 20 items that measure emotional, motivational, cognitive, somatic and motoric symptoms of low mood on a 4-point-Likert scale (0 = *rarely*, 1 = *sometimes*, 2 = *often*, 3 = *almost always*) yielding a range from zero to 60. Test-retest reliability is moderate ($r = 0.51$–0.67) with internal consistency ranging from 0.85 to 0.92 [49]. In the current sample, internal consistency was acceptable ($\alpha = 0.73$).

Perceived stress. Perceived stress was measured using the German version of the Perceived Stress Questionnaire [PSQ; 50, 51]. The scale contains four dimensions three of which focus on internal stress reactions (tension, worry, [lack of] joy) and one on perceived external stressors (demands). *Tension* explores tense disquietude, exhaustion and lack of relaxation. *Worry* assesses anxious concern for the future, and feelings of desperation and frustration; *joy* assesses positive feelings of challenge, joy, energy, and security and *demands* assesses perceived environmental demands such as lack of time, pressure, and overload. The scale consists of 30

items that are rated on a 4-point scale (1 = *almost never*, 2 = *sometimes*, 3 = *often*, 4 = *almost always*). All indices are linearly transformed to range from 0 to 1 and are subsumed in a total score for which *joy* is recoded. The PSQ has been found to be sensitive to change [50]. In the current sample, internal consistency was excellent ($\alpha = 0.90$).

Coping attitudes. The *Self-Efficacy-Optimism-Pessimism-Scale ("Selbstwirksamkeits-Optimismus-Pessimismus-Skala"-SWOP;* [52]) measures adaptive and maladaptive coping attitudes. The scale comprises nine items that are answered on a 4-point scale (1 = *does not apply*, 2 = *hardly applies*, 3 = *somewhat applies*, 4 = *completely applies*) and that load on three independent scales each ranging between one and 4: self-efficacy, optimism and pessimism. In the current sample, internal consistencies were good, acceptable and questionable respectively ($\alpha_{self\text{-}efficacy} = 0.82$; $\alpha_{optimism} = 0.79$; $\alpha_{pessimism} = 0.65$).

Whilst some of the measured questionnaires feature published cut-off scores, we conceptualize all psychological traits as dimensionally distributed along an individual differences continuum [53–56].

Data analyses

All analyses were conducted using IBM SPSS Statistics for Windows, Version 24. Correlation coefficients between baseline and change values were calculated using Spearman's ρ. Pre- and post-treatment scores were compared using paired-samples *t*-tests. Effect sizes *g* were calculated separately [57]. Estimates were defined as small ($0.10<g<0.20$), medium ($0.21<g<0.30$), large ($0.31<g<0.40$) or very large ($g>0.40$; [58]).

The present paper focuses on interactions of treatment-responsive variables in potentially influencing tinnitus-related distress and functionally associated pain perceptions. Consequently, we included only those variables in the indirect-effects analyses that showed treatment-related change with at least small effect sizes. Because sensory pain perception (SES), anxiety-related, obsessive, somatoform and eating-related symptoms (ISR), joy, demands (PSQ), and coping attitudes (SWOP) did not meet this criterion, these variables were dropped from further analyses. Indirect-effects models were computed using Hayes et al.'s *process* macro [59, 60]. These models aimed to examine interactions between baseline values and change rates of tinnitus-related distress, affective pain experiences, and the identified psychological factors. We do explicitly not postulate causality between the independent, mediating and dependent variables [61]. Models were specified within a *main effect* x *paired treatment-responsive factors* for [a] *baseline values* and [b] *change rates*—matrix. Each model featured baseline- or change in tinnitus-related distress or affective pain perception as independent or dependent variables respectively (see Figs 1–3):

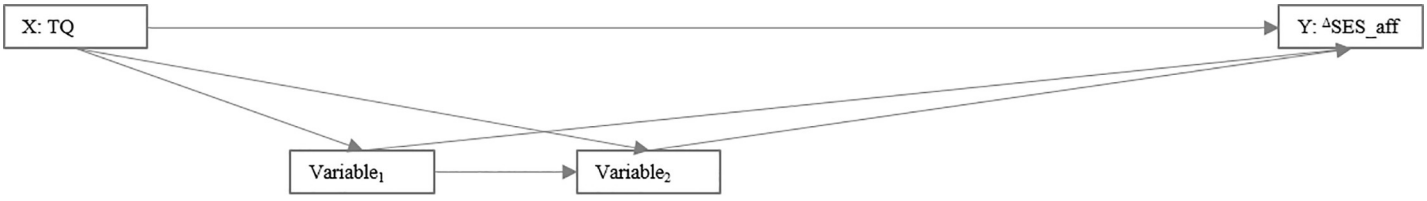

Fig 1. Indirect-effects models. TQ = tinnitus-related distress [Tinnitus Questionnaire (German version)—total score]; SES_aff = affective pain perception [Pain Perception Scale–subscale score]; X = independent variable; Y = dependent variable; Variables 1 and 2: alternate pairs of treatment-responsive process variables (depressivity [Center for Epidemiological Studies Depression Scale–total score or ICD-10 Symptom Rating–subscale score], emotional tension and worry [Perceived Stress Questionnaire–subscale scores]); t_0 = pre treatment; t_1 = post treatment; $^{\Delta}$ = change score (t_1 minus t_0). Fig 1 illustrates the model specification that investigates if the relationship between *baseline* tinnitus-related distress and *change* in affective pain perception is associated with *baseline* values of psychological process variables.

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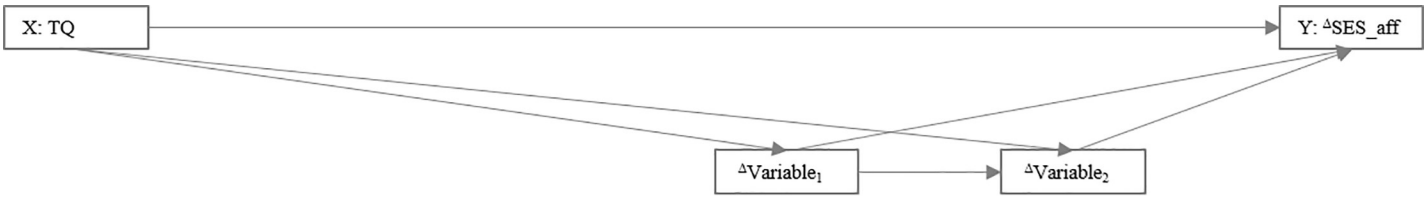

Fig 2. Model specification that investigates if the relationship between baseline tinnitus-related distress and change in affective pain perception is associated with *change* patterns in psychological process variables.

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Results

Descriptive indices

Table 1 provides means and standard deviations for the sample at pre- and post-treatment alongside effect size indicators of change. Small effect sizes *g* emerged for changes in tinnitus-related distress, affective pain perceptions, depressive symptoms, emotional tension and worry.

Indirect-effects analyses

Most baseline values and change rates intercorrelated except for change in emotional tension, which appeared to ensue irrespective of most measured variables' baseline values (Table 2).

Figs 4–6 outline significant effects for the indirect-effects models that were specified within a *main effect* [TQ–$^{\Delta}$SES_aff, $^{\Delta}$TQ–$^{\Delta}$SES_aff] x *paired treatment-responsive factors* [ADS–ISR-D, ADS–PSQ-T, ADS–PSQ-W, ISR-D–PSQ-T, ISR-D–PSQ-W, PSQ-T–PSQ-W] for [a] *baseline values* and [b] *change rates*—matrix. Path coefficients are given in the S1 Table.

The positive relationship between baseline tinnitus-related distress and improvement in affective pain perception was mediated by pathways involving positive associations between baseline tinnitus-related distress and [a] baseline depressivity (ISR_D) or emotional tension each of which were positively associated with improvement in affective pain perception. Moreover, controlling for baseline tinnitus-related distress and depressivity, baseline worry was negatively associated with improvement in affective pain perception.

Discussion

We previously reported that psychological factors—notably depressive symptoms, emotional tension and worry—underlay an association of tinnitus-related distress and affective as well as

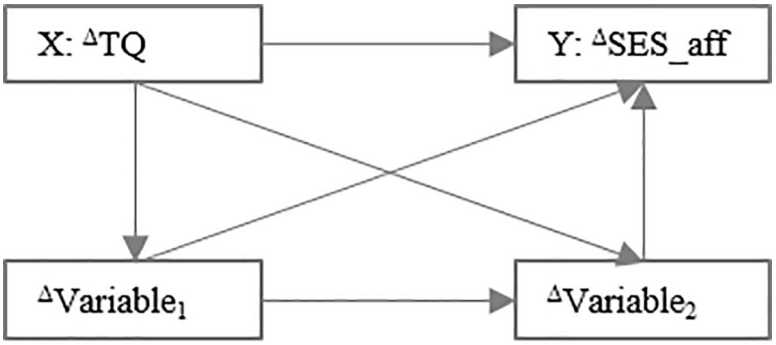

Fig 3. Model specification that investigates if the relationship between *change* in tinnitus-related distress and affective pain perception is associated with *change* patterns in psychological process variables.

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Table 1. Means, standard deviations and effect sizes of change for the sample at pre and post treatment (N = 1238 patients with chronic tinnitus).

	Pre		Post		Group effect	Effect size
	M	*SD*	*M*	*SD*		*g CI*
TQ						
Total	*39.66*	*16.98*	*32.63*	*17.24*	*F(1, 1097) = 576.05****	*0.37–0.45*
SES						
Affective	*24.18*	*10.00*	*22.69*	*9.67*	*F(1, 1038) = 45.65****	*0.11–0.20*
Sensory	13.71	4.98	13.59	5.07	F(1, 1038) = 0.89	-0.02–0.07
ISR						
Total	.81	.56	.76	.59	F(1, 971) = 19.40***	0.05–0.13
Depressive syndrome	*1.18*	*.91*	*1.03*	*.92*	*F(1, 971) = 58.14****	*0.12–0.21*
Anxiety-related syndrome	.94	.90	.89	.91	F(1, 971) = 6.71*	0.01–0.10
Obsessive-compulsive syndrome	.79	.86	.80	.84	F(1, 971) = 0.55	-0.07–0.04
Somatoform syndrome	.61	.79	.59	.78	F(1, 971) = 1.08	-0.02–0.07
Eating-related syndrome	.68	.80	.64	.82	F(1, 971) = 5.55*	0.01–0.09
Supplementary scale	.75	.54	.68	.57	F(1, 971) = 30.93***	0.09–0.17
ADS						
Total	*18.23*	*11.82*	*13.26*	*10.83*	*F(1, 1009) = 349.32****	*0.39–0.49*
PSQ						
Total	.46	.18	.43	.19	F(1, 1097) = 121.40***	0.13–0.19
Tension	*.59*	*.22*	*.53*	*.23*	*F(1, 1097) = 163.68****	*0.23–0.31*
Worry	*.40*	*.22*	*.36*	*.23*	*F(1, 1097) = 69.17****	*0.14–0.21*
Joy	.48	.22	.50	.24	F(1, 1097) = 34.95***	0.05–0.12
Demands	.50	.23	.47	.22	F(1, 1097) = 49.18***	0.09–0.17
SWOP						
Self-efficacy	2.76	.57	2.83	.58	F(1, 1087) = 37.20***	0.08–0.16
Optimism	2.72	.75	2.80	.76	F(1, 1087) = 33.15***	0.06–0.15
Pessimism	2.12	.71	2.15	.73	F(1, 1087) = 1.71	-0.09-[-0.01]

Notes: *M* = mean; *SD* = standard deviation; *CI* = 95% Confidence Interval; *g* = Hedge's *g*; TQ = Tinnitus Questionnaire–German version (tinnitus-related distress); SES = Pain Perception Scale (pain perception), ISR = ICD-10 Symptom Rating (psychological 'comorbidities'), ADS = Center for Epidemiological Studies Depression Scale (depressive symptoms), PSQ = Perceived Stress Questionnaire (perceived stress), SWOP = Self-Efficacy-Optimism-Pessimism-Scale (coping attitudes). Variables that differ on the $p < .001$ level and with an at least small effect size (defined as confidence intervals of *g* lying between 0.10 and 0.20 [58]) are *italicized*.

* = $p < .05$

*** = $p < .001$

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sensory pain perceptions in patients with chronic tinnitus [25]. Building on these findings, the present study investigated if an intensive tinnitus-specific multimodal treatment program [a] alleviated tinnitus-related distress, [b] alongside conceptually and functionally similar pain perceptions; and [c] may have exerted such a joint effect through addressing common underlying psychological factors.

Does the brief, intensive tinnitus-specific multimodal treatment program ameliorate tinnitus-related distress, pain experiences, and common underlying psychological factors?

The multimodal treatment program—which included psychosomatic diagnostics, psychoeducation components, cognitive-behaviour therapy-oriented interventions, relaxation exercises, and physiotherapy—was associated with at least small-effect sized improvements in tinnitus-related distress, affective (but not sensory) pain perceptions, depressive symptoms,

Table 2. Correlation coefficients [ρ] for baseline values and change rates of those variables that responded to treatment.

	t_0					$^{\Delta}$ [$t_1 - t_0$; negative values indicate improvement]					
	SES_aff	**ADS**	**ISR_D**	**PSQ_T**	**PSQ_W**	**$^{\Delta}$TQ_total**	**$^{\Delta}$SES_aff**	**$^{\Delta}$ADS**	**$^{\Delta}$ISR_D**	**$^{\Delta}$PSQ_T**	**$^{\Delta}$PSQ_W**
TQ_total	.53***	.64***	.55***	.52***	.50***	-.25***	-.09**	-.20***			
SES_aff		.50***	.49***	.42***	.41***	-.09**	-.41***	-.21***	-.08*		
ADS			.81***	.69***	.73***	-.08**	-.08**	-.48***	-.12***		
ISR-D				.67***	.71***	-.11***	-.12***	-.35***	-.34***		-.06*
PSQ-T					.67***	-.12***	-.10**	-.32***	-.11***	-.28***	-.09**
PSQ-W						-.10**		-.28***	-.09*		-.26***
$^{\Delta}$TQ_total							.26***	.35***	.32***	.36***	.35***
$^{\Delta}$SES_aff								.30***	.29***	.22***	.26***
$^{\Delta}$ADS									.38***	.29***	.23***
$^{\Delta}$ISR-D										.27***	.23***
$^{\Delta}$PSQ-T											.39***

Notes. Only significant effects are featured.

*** = $p < .001$

** = $p < .01$

* = $p < .05$.

TQ_total = tinnitus-related distress [Tinnitus Questionnaire (German version)—total score]; SES_aff = affective pain perception [Pain Perception Scale–subscale score]; ADS = depressive symptoms ["Allgemeine Depressionsskala"–total score]; ISR-D = depressive symptoms [ICD-10 Symptom Rating–subscale score]; PSQ-T = emotional tension; PSQ-W = worry [Perceived Stress Questionnaire—subscale scores]); t_0 = pre-treatment; t_1 = post-treatment; $^{\Delta}$ = change score (t_1 minus t_0).

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emotional tension and worry. This finding is in keeping with previous research highlighting the rather psychological makeup of affective—relative to sensory—pain perception, which is consequentially more likely to respond to psychologically focused interventions like the one examined in this paper [62–65]. Similarly, a recent study reported that subgroups of patients with varying levels of affective pain experiences reported analogous levels of depressive

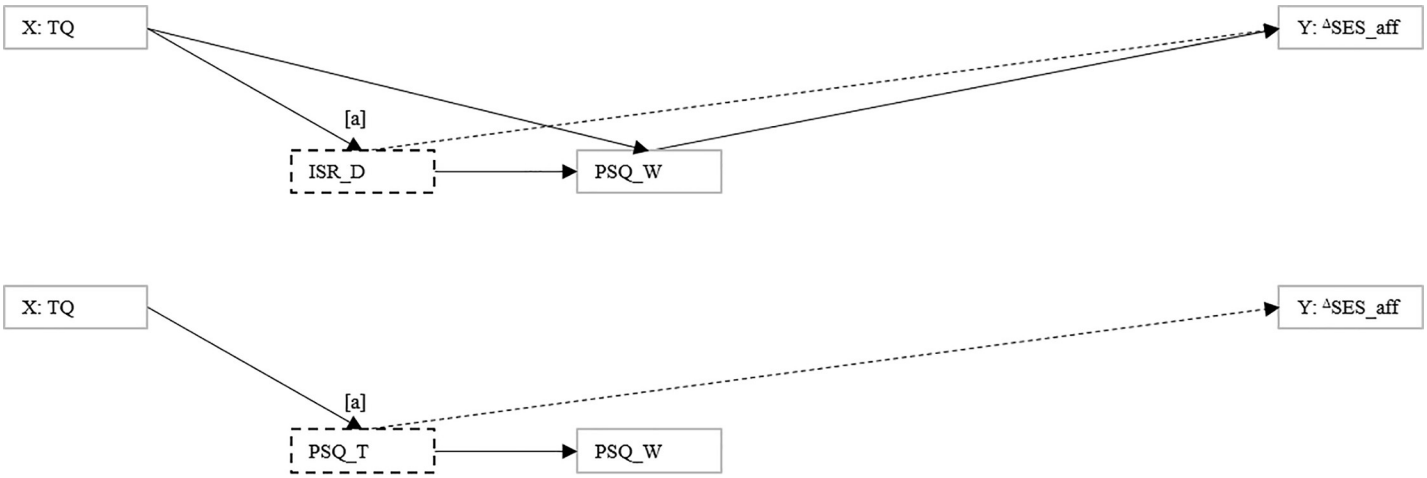

Fig 4. Indirect-effects models. Black continuous arrows indicate significant positive; black dotted arrows significant negative effects. Black continuous box frames indicate significant positive; black dotted box frames significant negative indirect effects through the respective variables. TQ = tinnitus-related distress; SES_aff = affective pain perception; ADS-L and ISR_D = depressivity; PSQ_T = emotional tension; PSQ_W = worry; X = independent variable; Y = dependent variable; t_0 = pre treatment; t_1 = post treatment; $^{\Delta}$ = change score (t_1 minus t_0; negative values denote improvement). For those models that yielded significant indirect effects, all significant effects are illustrated. Fig 4 shows *the relationship between baseline tinnitus-related distress and change in affective pain perception as influenced by baseline values of psychological process variables*.

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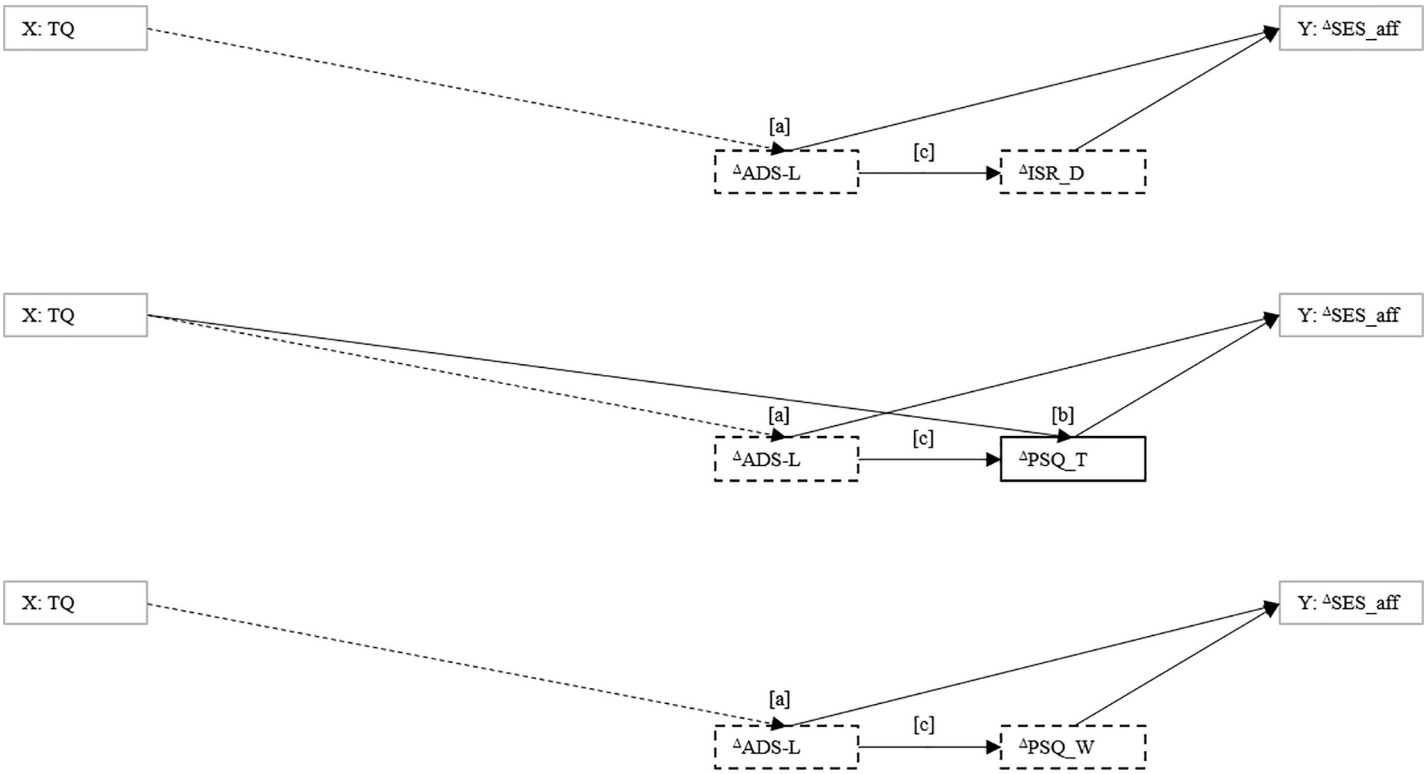

Fig 5. The relationship between baseline tinnitus-related distress and change in affective pain perception as mediated by change patterns in psychological process variables. The positive relationship between baseline tinnitus-related distress and improvement in affective pain perception was mediated by pathways involving [a] a positive association between baseline tinnitus-related distress and improvement in depressivity (ADS-L) or [b] a negative association between baseline tinnitus-related distress and improvement in emotional tension that were both positively associated with change in affective pain perception. Significant three-way interactions further revealed pathways involving positive associations between baseline tinnitus-related distress and [c] improvements in depressivity (ADS-L), *additional* changes in depressivity (ISR_D), emotional tension or worry, and change in affective pain perception.

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difficulties. For sensory pain experiences, by contrast, respective mappings appeared more heterogeneous [66]. No changes in coping attitudes were observed. Whilst optimism [67, 68] or lowered self-efficacy beliefs [25] have been shown to contribute to tinnitus-related distress or chronic illness more generally [69, 70], the treatment program did not have beneficial effects on these constructs–possibly owed to its short duration. Whilst addressing these constructs within a broader psychotherapeutic context may yield additional effects [71–73] the scales' low internal consistencies further suggests that alternative measures may be more suitable when wishing to test related hypotheses.

Both baseline values and change rates were positively intercorrelated suggesting a conceptual overlap between the measured constructs–or possibly a general factor of psychopathology that may reflect common aspects of tinnitus-related distress, depressive symptoms, worry, affective pain experiences and emotional tension on an individual differences continuum [74–76]. The treatment program may facilitate well-being and improve tinnitus-related distress by targeting [a] shared variance of the measured constructs, or [b] specific variance of each measured factor—an explanation that seems somewhat less likely given that the psychological interventions were more transdiagnostic in nature.

At baseline, most patients showed only mild-to-moderate symptom severity levels, thus restricting the potential of therapeutic improvement and raising the possibility of Type-II errors for some of the measured indices. Notwithstanding, symptom severity was positively

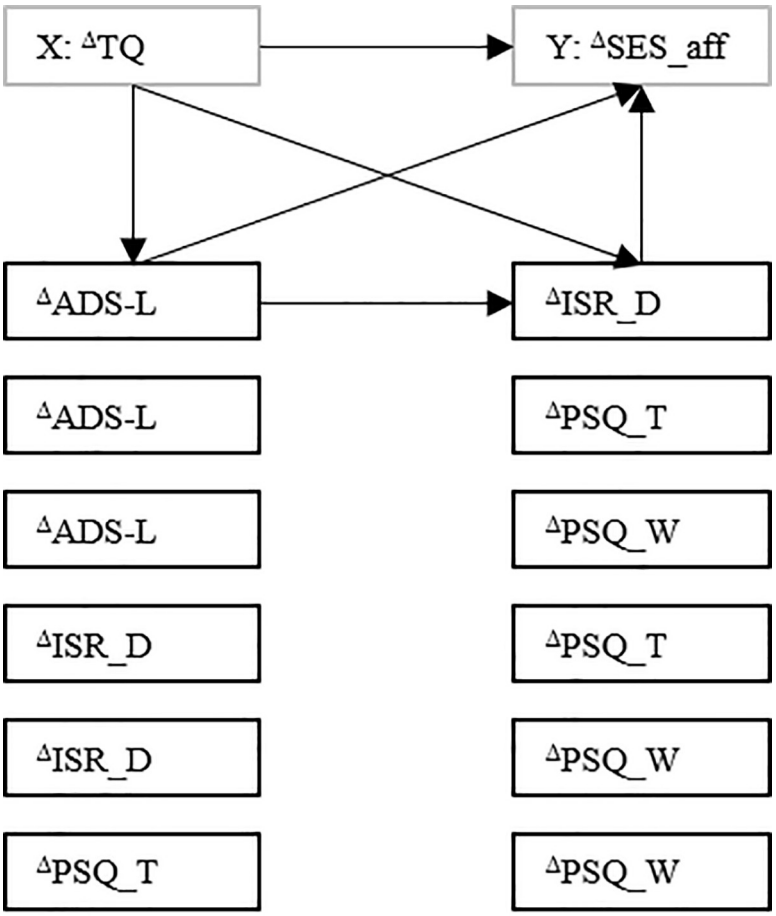

Fig 6. The relationship between change in tinnitus-related distress and affective pain perception as influenced by change patterns in psychological process variables. The positive relationship between changes in tinnitus-related distress and affective pain perception was positively associated with (relationships between) contemporaneous changes in all process variables.

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associated with improvement in the measured key indices. Multimodal treatment as examined in the present paper thus appears to benefit patients along the presenting range of symptom severity. Interestingly, treatment-related improvements in emotional tension and—to a lesser extent—worry appeared to occur somewhat irrespective of the measured constructs' baseline values. These factors thus emerge as potential common "third variables" whose therapeutic targeting may bear beneficial effects on emotional distress as reflected in the measured variables. Supporting this view, emotional exhaustion–a component of emotional tension as measured in the present study–has been previously found to be a common risk factor for burnout and posttraumatic stress disorder following triggering circumstances [77], hyperacusis in women following triggering circumstances [78] and chronic pain [79, 80]. Similarly, worry has been identified as a transdiagnostic construct common to depressive symptoms, anxiety [81, 82] and pain [3] possibly serving a psychological function to reduce negative affect associated with underlying interpretational thought-memory-interactions [83].

Is the relationship between baseline tinnitus-related distress and change in pain perception associated with baseline values of psychological factors?

The association between baseline tinnitus-related distress and change in affective pain perception was mediated by baseline levels of depressive symptoms or emotional tension. This finding is in keeping with previous reports whereby depressive symptoms accounted for considerable shared variance in both tinnitus-related distress, pain experiences and psychological epiphenomena–sometimes somewhat misleadingly labelled comorbidities (i.e. suggesting separate or separable illness entities; [25]). When controlling for baseline tinnitus-related distress and depressive symptoms, worry was negatively associated with improvements in affective pain perception. Worry has long been conceptualized as part of a cognitive-attentional syndrome that maintains emotional distress [84, 85]–possibly by functioning to avoid the emotional processing of underlying distressing experiences [86, 87]. Studies from older adult populations have further identified worry as a predictor of treatment outcome [88, 89]. Worry therefore presents as an important treatment target–alongside depressive symptoms–whose modification is likely to benefit patients across different somatization phenomena. Psychologically anchored treatment approaches may thus benefit from formulating and addressing interactions of negative affect, emotional avoidance / worry and depressive symptoms across the spectra of treatment programs for patients with chronic tinnitus [e.g. 90].

Is the relationship between baseline tinnitus-related distress and change in pain perception associated with change rates of psychological factors?

Baseline tinnitus-related distress was positively associated with improvement in affective pain experiences alongside *more* improvement in depressive symptoms—as measured by two different questionnaires. Whilst the treatment program may have addressed parts of the common or specific variance of each factor (see above), the used measures of depressive symptoms further appear to reflect different aspects of low mood [91] that bear conjoint importance for tinnitus-related distress. Indeed, whilst the ICD-10 Symptom Rating preliminary uses mood-related items (e.g. "During the last week, my mood was low and depressed"), the ADS further incorporates items inquiring about somatic (e.g. "During the last week, I hardly had any appetite") and intra-interpersonal expressions of depressive symptoms (e.g. "During the last week, other people were unfriendly to me"). Patients' experiences of depressed mood seem to incorporate symptoms across all of these dimensions with some patients possibly endorsing more somatic-, and others more cognitive-emotional conceptualizations. In addition, patients' pain symptomatology–although partly influenced by depressive symptoms as influencing factor–may conversely confound depressive symptoms ratings by influencing patients' response patterns on the applied questionnaires (for discussions of this difficulty in other areas, see e.g. [92–94]).

Baseline tinnitus-related distress was further associated with improvement in affective pain experiences alongside *less* improvement in emotional tension. Thus, the specific variance of emotional tension (as a dimension of "perceived stress") emerges as important when conceptualizing and addressing tinnitus-related distress and pain symptomatology. Importantly, any such "perceived stress" conceptualization ought to occur within psychological frameworks that consider psychological vulnerability-stress interactions [95], personality dimensions [96], and individual constructions of meaning; *not* seemingly "external" factors such as "workload" [97, 98].

Is the relationship between change in tinnitus-related distress and pain perception associated with change patterns in psychological factors?

Finally, the relationship between change in tinnitus-related distress and affective pain perception was associated with change patterns in all psychological factors. The observed interdependencies of change again challenge the notion and helpfulness of a "disease entity" approach wherein "tinnitus" and "comorbidities" are conceptualized as interdependently connected, yet separate illness entities. Rather, dimensional, empirically defined conceptualizations of mental health difficulties [55, 99–101] are more suitable in understanding the interplay of factors that may underlie both symptom maintenance and change as observed in the present study.

Transdiagnostic approaches (that accommodate specific factors that are characteristic of certain medical conditions, but focus on transdiagnostic psychological mechanisms) have the potential to alleviate distress across a range of functionally associated, somatoform symptom clusters; particularly if overlap exists in cognitive-emotional or behavioural distress expressions or responses [102]. Importantly, psychological interventions that aim to address emotional tension or worry ought to facilitate a process of "meaning-making" [103–106]. Herein, biographical perspectives are considered alongside current life stressors and cognitive-emotional as well as behavioural coping attempts in order to understand the functions of and "chip away" at the maintaining factors of persistent negative affect.

Limitations of the present study include the absence of a control group as well as its two-timepoint design: the observed changes are confounded by the passage of time, spontaneous recovery, non-specific effects or other unknown factors. Thus, the specific efficacy of the examined treatment program remains to be demonstrated. Similarly, the estimated indirect effects do not imply "true mediation" and cannot be interpreted in a causal manner—as change in the independent variable should temporally precede change in the mediator which should precede change in the outcome variable [61]—a postulate that can only be examined within prospective studies featuring multi-timepoint measurements. Overall, observed effect sizes were small. Given the overall mild–to–moderate baseline symptom severity—and associated variance limitations—results need to be interpreted with caution. Notwithstanding, the present study is the first to demonstrate a joint tinnitus and pain-related benefit in a psychologically anchored, multimodal treatment program. Refocusing treatment efforts on transdiagnostic cognitive-emotional factors may thus benefit a variety of 'co-morbid' patient populations.

Conclusions

The present study highlights the roles of depressive symptoms, emotional tension and worry as both predictors of treatment outcome and transdiagnostic treatment targets in a patient population with chronic tinnitus, tinnitus-related distress and co-occurring affective pain experiences. Idiosyncratic interactions of these factors should be [a] empirically conceptualized using dimensional frameworks of psychopathology [55, 100, 101] rather than categorical psychiatric illness-models and [b] clinically addressed within meaning-making, transdiagnostic psychological treatment frameworks that allow for the formulation and treatment of cognitive-emotional and behavioural expressions of individual vulnerability-stress interactions [107–109].

Supporting information

S1 Table. Path coefficients for significant indirect effects.
(DOCX)

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Visualization: Benjamin Boecking.

Writing – original draft: Benjamin Boecking.

Writing – review & editing: Benjamin Boecking.

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Paper 5: Psychological Effects of a 'Somatic' Treatment Approach [Hearing Amplification]

Having focused on the psychological operationalization and treatment of TRD, **Study 5** [160] broadens the psychological perspective by examining psychological effects of hearing amplification within a randomized controlled cross-over design[4]. It demonstrates that a 'somatic' intervention – i.e. a specifically fitted hearing aid – also bears psychological benefit.

'***Background****: The psychological effects of hearing aids and auditory training are underinvestigated. Objective: To assess the short- and long-term effects of an industry-developed auditory training on tinnitus-related distress, perceived stress, and psychological epiphenomena in patients with chronic tinnitus and mild-to-moderate hearing loss.* ***Method****: One-hundred-seventy-seven gender-stratified patients were randomized to an immediate [IIG] or delayed [DIG] intervention group. Following binaural hearing aid fitting, participants completed a CD-enhanced 14-days self-study program. Applying a randomized-controlled cross-over design, psychological measures were obtained at four times: pre-treatment/wait [IIG: t_1; DIG: wait], post-treatment/pre-treatment [IIG: t_2; DIG: t_1], follow-up/post-treatment [IIG: t_3; DIG: t_2], and follow-up [DIG: t_3]. Between- and within-group analyses investigated treatment-related effects and their stability at a 70-day follow-up.* ***Results****: Overall, distress symptom severity was mild. Unlike the DIG, the IIG showed significant improvements in tinnitus-related distress. Some psychological epiphenomena, notably anxiety, slightly improved in both groups. Within-group analyses demonstrated the stability of the tinnitus-distress related effects, alongside uncontrolled improvements of perceived stress and mood-related symptoms at follow-up.* ***Conclusions****: The investigated hearing therapy lastingly improves tinnitus-related distress in mildly distressed patients with chronic tinnitus and mild-to-moderate hearing loss. Beneficial psychological knock-on effects deserve further investigation.*' [160(p1)]

[4] A follow-up study (not presented in the thesis) used the same data to also examine audiological effects of hearing amplification [161].

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Hearing Therapy Improves Tinnitus-Related Distress in Mildly Distressed Patients with Chronic Tinnitus and Mild-to-Moderate Hearing Loss: A Randomized-Controlled Cross-Over Design

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Abstract: Background: The psychological effects of hearing aids and auditory training are underinvestigated. Objective: To assess the short- and long-term effects of an industry-developed auditory training on tinnitus-related distress, perceived stress, and psychological epiphenomena in patients with chronic tinnitus and mild-to-moderate hearing loss. Method: One-hundred-seventy-seven gender-stratified patients were randomized to an immediate [IIG] or delayed [DIG] intervention group. Following binaural hearing aid fitting, participants completed a CD-enhanced 14-days self-study program. Applying a randomized-controlled cross-over design, psychological measures were obtained at four times: pre-treatment/wait [IIG: t_1; DIG: wait], post-treatment/pre-treatment [IIG: t_2; DIG: t_1], follow-up/post-treatment [IIG: t_3; DIG: t_2], and *follow-up* [DIG: t_3]. Between- and within-group analyses investigated treatment-related effects and their stability at a 70-day follow-up. Results: Overall, distress symptom severity was mild. Unlike the DIG, the IIG showed significant improvements in tinnitus-related distress. Some psychological epiphenomena, notably anxiety, slightly improved in both groups. Within-group analyses demonstrated the stability of the tinnitus-distress-related effects, alongside uncontrolled improvements of perceived stress and mood-related symptoms at follow-up. Conclusions: The investigated hearing therapy lastingly improves tinnitus-related distress in mildly distressed patients with chronic tinnitus and mild-to-moderate hearing loss. Beneficial psychological knock-on effects deserve further investigation.

Keywords: auditory training; hearing aids; mild-to-moderate hearing loss; tinnitus-related distress; psychological epiphenomena

1. Introduction

Chronic tinnitus denotes the longstanding (>3 months) perception of sound without external acoustic stimulation [1]. Tinnitus is a common phenomenon with an estimated prevalence of 10–15% in the adult population [2]; however, prevalence rates differ widely between studies [3]. Whilst a majority of people adjust to the percept and report little emotional distress [4], some people experience considerable psychological distress in its wake [5,6]. Such tinnitus-related distress is commonly measured using self-report questionnaires, amongst which the Tinnitus Questionnaire (TQ), Tinnitus Handicap Inventory (THI), and Tinnitus Functional Index (TFI) are the most common. These measures' total scores

suitably capture both tinnitus-related distress and intervention-related change [7]; however, some content differences remain with the TQ and THI, emphasizing psychological over more audiological or functional impairments, respectively (TFI).

Whilst chronic tinnitus likely develops at the interface of various psychobiological influences [1], hearing loss has been identified as one of its main risk factors [2,8]. It has been found to correlate with tinnitus loudness [9], tinnitus-related distress [10], and—somewhat unsurprisingly—poorer speech-comprehension-in-noise [11–13]—which is further commonly impaired in tinnitus patients [14]. In order to compensate for hearing loss-related difficulties, hearing aids can offer an important interventional strategy [15]. Hearing aids have been found to improve individuals' hearing ability, as measured by self-report [16] or audiological data (e.g., speech-reception threshold in noise [17]). Further, hearing aids appear to ameliorate some forms of chronic tinnitus [18–21]—potentially through reducing tinnitus awareness via an enhanced perception of external auditory input [22] or, for some patients, through psychological processes such as enhanced experiences of self-efficacy, control, or social inclusion.

Psychologically, chronic tinnitus, hearing loss, and difficulties with speech-comprehension-in-noise hold the potential to negatively affect individuals' well-being—notably by causing or exacerbating anxiety, low mood, or perceived stress [14,23–28]. Therefore, hearing aids can be regarded as one important tool for the alleviation of hearing difficulties and—secondarily—tinnitus-related or broader psychological distress [15,29]. However, although there are several studies [30–32] that examine the effect of hearing aids and auditory training on hearing-related outcomes (such as speech-comprehension-in-noise or sound localization), potential effects of such an intervention on tinnitus-related distress and psychological parameters remain underinvestigated.

The present study aims to fill this gap and applies a randomized, controlled, three-timepoint cross-over design to investigate the effects of an industry-developed hearing therapy (which combines binaural hearing aid fitting with a specifically developed auditory training) on tinnitus-related distress, perceived stress, and psychological epiphenomena in patients with chronic tinnitus and mild-to-moderate hearing loss. We hypothesized:

1. Compared to a waiting, delayed-intervention group (DIG), an immediate intervention group (IIG) shows higher reductions in tinnitus-related distress and psychological distress following Terzo© (Sonneberg, Germany) hearing therapy;
2. Given the primarily audiological–cognitive focus of the intervention, treatment-related change may be most strongly reflected in TFI (vs. TQ or THI) scores;
3. Any observed effects will be stable at a 70-day follow-up.

2. Materials and Methods

2.1. Participants

Between 2018 and 2020, 177 participants (54.2% female; M_{age} = 59.61, SD = 7.46) were recruited from Charité Universitätsmedizin, Berlin. Adults (aged $\geq$ 18 years) with a tinnitus duration of more than 3 months and mild-to-moderate hearing loss were included in the study (averaged pure tone audiometry [PTA] thresholds (in decibel [dB]: M_{right} = 37.94, SD = 8.54; M_{left} = 35.97, SD = 8.43; classification: <20 = normal; 20–40 = mild; 41–60 = moderate; >60 = severe [33]). Past psychotherapeutic treatment, present psychiatric treatment, and current hearing aid use were recorded. Patients with past or present diagnoses of Ménière's disease, acoustic neuroma or other tumours (e.g., brain tumour), identifiable organic causes of tinnitus (e.g., epilepsy), severe psychological conditions requiring treatment in their own right, severe hearing impairment, indication for a cochlea implant, ototoxic medication (e.g., diuretics), drug, alcohol or medication addiction, chemotherapy, or insufficient mastery of the German language were excluded from study participation. In order to detect an improvement of seven (SD = 15) points on the Tinnitus Questionnaire with an assumed alpha of 0.05 and a power of 0.80, n = 58 subjects were required per arm. Assuming an average drop-out rate of 20% (=12 additional subjects), seventy subjects were

necessary. In the present study, the target *n* was eventually set to 75 treatment completers per arm.

See Table 1 for an overview of patient characteristics.

Table 1. Sociodemographic data and patient characteristics (*n* = 177).

		n	%
Education			
	Completed junior apprenticeship	72	40.7
	Completed senior apprenticeship	40	22.6
	University degree	60	33.9
	Other	4	2.3
Employment 'yes'		105	59.3
Relationship status			
	Single	25	14.1
	Married	114	64.4
	Divorced	27	15.3
	Widowed	10	5.6
Duration of tinnitus			
	<0.5 year	5	2.8
	0.5–1 year	9	5.1
	1–2 years	23	13.0
	2–5 years	24	13.6
	>5 years	107	60.5
Tinnitus onset			
	gradual	92	52.0
	sudden	73	41.2
Frequency			
	very high	37	20.9
	high	104	58.8
	middle	32	18.1
	low	3	1.7
Past psychotherapy 'yes'		53	29.9
Use of hearing aid 'yes'		53	31.5

2.2. Procedure

Participants were informed about the scope and aims of the study and signed an informed consent agreement. The Charité Universitätsmedizin's ethics committee approved the study (EA1/114/17). All methods were carried out in accordance with relevant guidelines and regulations. The original protocol was retrospectively registered with the DRKS ("Deutsches Register für Klinische Studien"—German Registry of Clinical Studies; registration number DRKS00015312; retrospectively registered on 17 September 2021), which meets the International Committee for Medical Journal Editors' (ICMJE) clinical trial registration requirements (https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00015312, accessed on 9 August 2021).

For the randomization protocol, two types of identical envelopes were created. The envelopes contained a card with a printed "A" (IIG; 75) or "B" (DIG; 75) stamp, respectively. Following a simple randomization protocol, an enrolling clinician (NA) presented participants with a box from which an envelope was drawn. The enrolling clinician was blind to the drawn intervention. Following this allocation procedure, participants met with a Terzo employee, handed over the envelope, and the respective trial protocol and procedures were explained. Randomization was continued until the target *n* of 75 patients was reached in both treatment arms. The present study reports all available data from all participants that were included in the initial randomization process (*n* = 177).

2.3. Study Protocol

Following recruitment and prior to treatment onset, participants completed an initial data screening, the results of which are reported elsewhere [34]. By applying a randomized-controlled cross-over design, participants were then randomized to an immediate or delayed intervention group. Tinnitus-related distress, perceived stress, and psychological epiphenomena were obtained at four times: pre-treatment/wait [IIG: t_1; DIG: wait], post-treatment/pre-treatment [IIG: t_2; DIG: t_1], follow-up/post-treatment [IIG: t_3; DIG: t_2], and follow-up [DIG: t_3] (Figure 1). Between and within-group analyses investigated treatment-related psychological effects and their stability over a 70-day follow-up period after the end of the intervention phase (Figure 2).

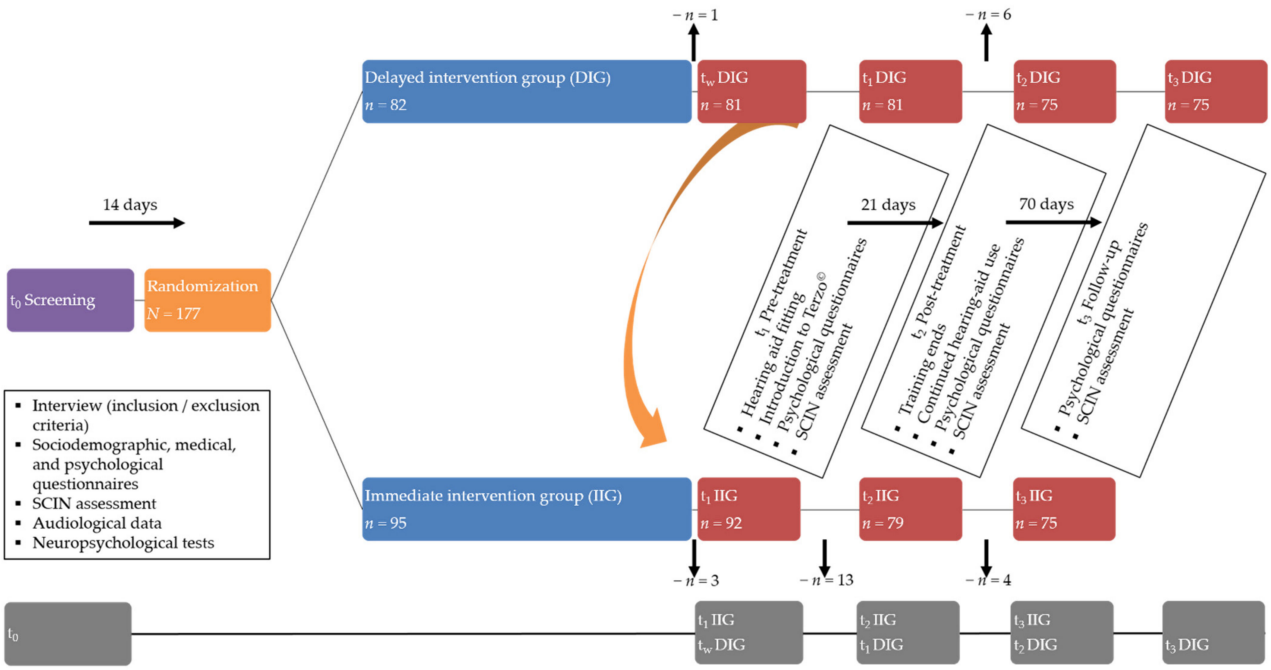

Figure 1. Overview of the randomized-controlled cross-over design, measurement timepoints, and dropouts. IIG = immediate intervention group and DIG = delayed intervention group. SCIN = Speech-comprehension-in-noise; t_1 = Pre-treatment; t_2 = Post-treatment; t_3 = Follow-up; and t_w = Waiting timepoint (DIG only). Dropout rates are indicated for each arm and measurement timepoint.

2.4. Hearing Ability

Prior to study inclusion, participants' hearing ability was tested using pure tone audiometry (PTA). Here, participants indicated the quietest detectable sound (dB) at several points across the frequency range (250 Hertz [Hz], 500 Hz, 1000 Hz, 1500 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 6000 Hz, 8000 Hz, and 10,000 Hz). Right-sided tinnitus perception was reported by 15 participants (8.5%); left-sided by 31 participants (17.5%), and bilateral by 131 participants (74%). Pure (sinus) tone perception was reported by 121 participants (68.4%) and narrow-band noise by 54 participants (30.5%). The average reported tinnitus frequency was 5.98 kilohertz (kHz; *SD* = 2.46) at 55.91 dB (*SD* = 19.24).

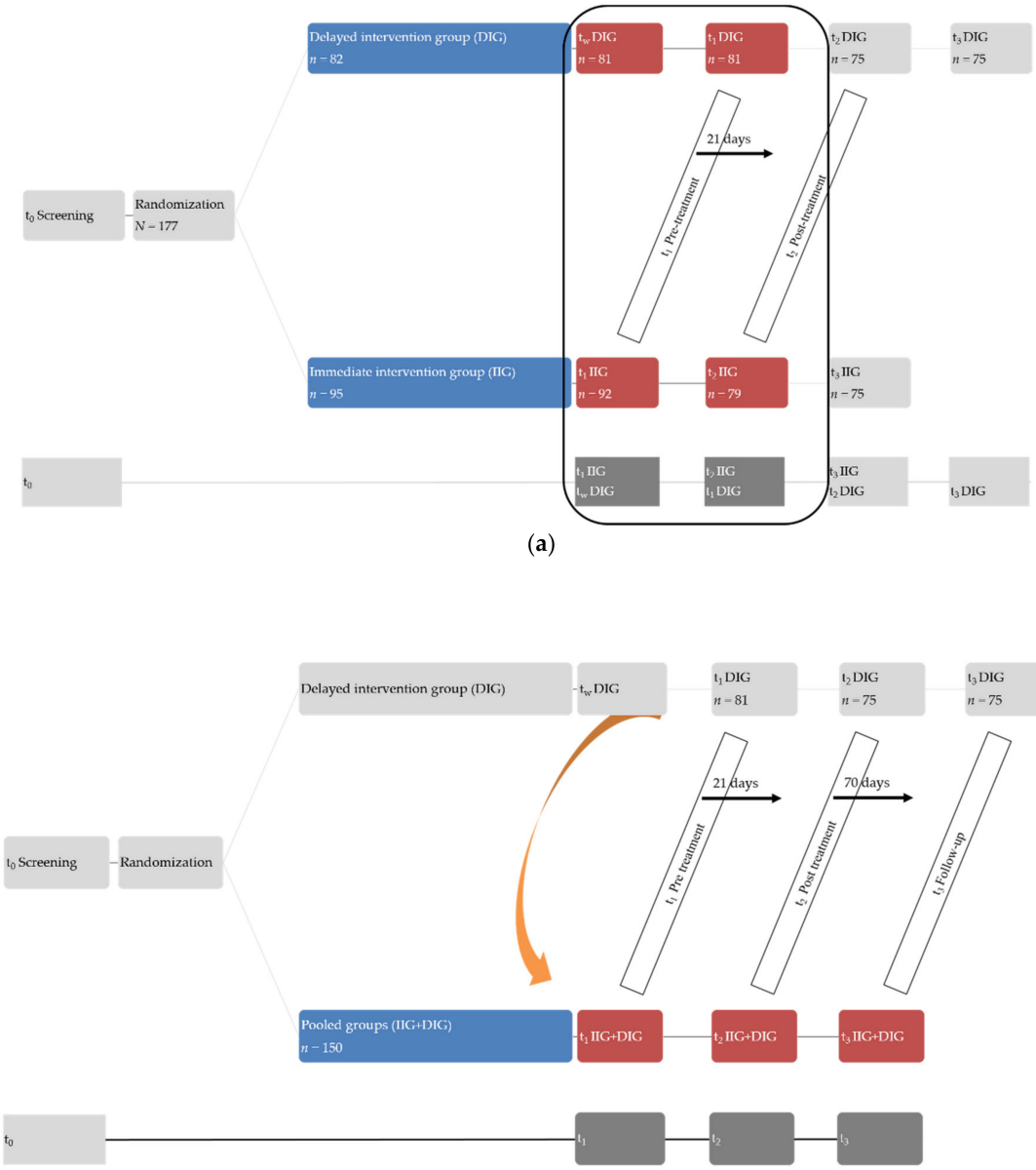

Figure 2. Between-subject analyses (**a**) and within-subject analyses (**b**), investigating treatment-related effects. Note: the IIG and DIG did not differ on any of the investigated outcome measures at pre-treatment (t_1IIG; t_1DIG).

2.5. Terzo© Hearing Therapy

Terzo© hearing therapy [35] was originally developed for patients with hearing loss. It is characterized by a combination of hearing aid fitting, and a Terzo-specific auditory training.

During Terzo© hearing therapy, subjects were initially provided with brief educational counselling about (1) tinnitus, (2) the mechanisms of tinnitus onset and the relationship between tinnitus and hearing loss, as well as (3) principles and methods of treatment with hearing aids. In addition, subjects were prepared for their acoustic impressions when wearing hearing aids in order to improve the acceptance of hearing aid amplification. All participants underwent binaural hearing aid fitting and, subsequently, completed the auditory training. Hearing aid fittings were adjusted to subjects' individual levels of hearing loss. Because the present sample included participants with mild-to-moderate hearing loss

(i.e., of <30 dB), fittings were based on the Desired Sensation Level (DSL), v5 child's formula to maximize speech audibility across a variety of real-world settings [36,37]. Ear moulds were used routinely, and language-specific adaptive parameters were largely deactivated.

Following a one-week adjustment period, participants were instructed to independently practice a standardized training intervention for approximately 1 h/day over a period of 14 days. The training intervention comprised a combination of auditory materials (CD) and daily, workbook-based exercises aimed to improve speech-comprehension-in-noise. The exercises included comprehension tasks pertaining to numbers, texts, similar-sounding words, syllables, and required mnestic as well as concentration elements. Thematic blocks were labelled (1) speech comprehension with and without noise, (2) concentration, (3) acoustic retention, (4) semantic memory, and (5) acoustic crossword puzzles. The training manual featured a variety of sequential exercises that were linked to specific days of the intervention period. Participants could record their progress in daily protocol sheets.

The present paper reports the effects of Terzo© hearing therapy on tinnitus-related distress and psychological wellbeing. Training intensity was quantified using participants' self-reports obtained at the post-treatment timepoint as well as the hearing aids' automated usage recordings. At the end of the intervention (post-treatment), participants returned the training CD. Hearing aids and self-instruction materials were returned at follow-up.

2.6. Measures

2.6.1. Tinnitus-Related Distress

The German version of the Tinnitus Questionnaire (TQ) by Goebel and Hiller [38] assesses tinnitus-related distress. It is widely established in Germany and features 52 items that are answered on a 3-point scale (0 = "disagree," 1 = "partly agree," and 2 = "agree"). Forty items—two of which twice—are condensed into a total score that ranges from 0 to 84. For the current sample, internal consistency was excellent (Cronbach's $\alpha_{total} = 0.94$).

The Tinnitus Handicap Inventory (THI [39]; German version [40]) assesses tinnitus-related impairment in daily life activities. It is a self-evaluation instrument and consists of 25 items that are answered on a 3-point scale (0 = "no," 2 = "occasionally," and 4 = "yes"). The total score ranges from 0 to 100. For the current sample, internal consistency was excellent (Cronbach's $\alpha_{total} = 0.94$).

The Tinnitus Functional Index (TFI [41]; German version [42]) measures negative tinnitus impact. It consists of 25 items that are answered on a 10-point Likert scale with scores ranging from 0 to 100. For the current sample, internal consistency was excellent (Cronbach's $\alpha_{total} = 0.97$).

2.6.2. Perceived Stress

Subjective stress was measured using the Perceived Stress Questionnaire (PSQ [43]). The scale consists of 30 items that are rated on a 4-point scale (1 = "almost never", 2 = "sometimes", 3 = "often", and 4 = "almost always") across three internal (tension, worries, and [lack of] joy) and one perceived external stress dimension (demands). All scores are summed up to a total score for which "joy" is recoded. Each score is linearly transformed to range from 0 to 100. For the current sample, internal consistency was excellent (Cronbach's $\alpha_{total} = 0.91$).

2.6.3. Psychological Epiphenomena

The Hospital Anxiety and Depression Scale (HADS) is a screening instrument for self-reported anxiety and depression [44] (German version [45]). The scale features two independent subscales with seven items each that relate to anxious/depressive symptoms during the last week (0 = "not at all" to 3 = "mostly"). For the current sample, internal consistencies were good and excellent, respectively (Cronbach's $\alpha_{anxiety} = 0.85$; $\alpha_{depression} = 0.90$).

The ICD-10-Symptom-Rating (ISR [46]) is a questionnaire that aims to evaluate emotional distress across six subscales (depressive syndrome, anxiety syndrome, obsessive-

compulsive syndrome, somatoform disorder syndrome, eating disorder syndrome, and supplementary scale). The ISR consists of 29 items that are answered on a 5-point-scale (0 = "does not apply", 1 = "hardly applies", 2 = "somewhat applies", 3 = "considerably applies", and 4 = "completely applies"). All item values are averaged to a total score that weighs the supplementary scale score twice. Each score ranges from 0 to 4. For the current sample, internal consistency was excellent (Cronbach's $\alpha_{total} = 0.93$).

2.7. Statistical Analyses

Sociodemographic information was summarized using descriptive statistics. As expected, given the stratification and randomization protocol, the IIG and DIG did not differ on age, gender, and previous use of hearing aid use at pre-treatment. Step 1: Separate two-way analyses of variance (ANOVA) investigated the effects of Terzo© hearing therapy on [a] tinnitus-related distress, [b] perceived stress, and [c] psychological epiphenomena. We specified "group" [IIG vs. DIG] as between factor, "time" [IIGt_1-t_2 vs. DIGwait-t_1] as within factor and "tinnitus-related distress" [TQ, THI, TFI], "perceived stress" [PSQ], or "psychological epiphenomena" [HADS, ISR] as dependent variables. Cohen's *d* quantified significant effects where indicated (0.20–0.49 small effect, 0.50–0.80 medium effect, and >0.80 large effect). Step 2: In order to investigate the stability of the identified treatment effects, separate three-tiered repeated-measures ANOVAs were conducted on the significant outcome measures identified in Step 1. For these analyses, data for the IIG and DIG were pooled ($n = 150$). Pooling was possible because computations revealed that [a] the IIG and DIG did not differ on any of the defined outcome variables at their respective pre-treatment timepoint [t_1], [b] there were no significant "group" [IIG vs. DIG] $\times$ "time" interaction effects for any of the outcome measures when considering all three treatment-related measurement timepoints [pre-treatment, post-treatment, and follow-up], and [c] there were no significant covariate effects of previous hearing aid use or hearing aid use during treatment. Where significant, age or hearing ability (PTA) were included as covariates. Post hoc paired-samples *t*-tests investigated between-timepoint differences, given a significant main effect of time. Again, Cohen's *d* quantified effect sizes. All reported results did not differ for participants with or without previous hearing aid use. See Figure 2 for a visualization of analysis protocols.

3. Results

3.1. Psychological Variables

Upon inclusion in the study, participants reported (1) low-to-moderate levels of tinnitus-related distress and (2) normal levels of [PSQ-measured] perceived stress, [ISR-measured] anxiety-, depression-, obsession-, somatoform-, and eating-related symptoms, as well as [HADS-measured] anxiety- and depression-related symptoms. By contrast, [ISR-measured] overall psychological epiphenomena levels showed mild elevation.

3.2. Effects of Terzo© Hearing Therapy on Tinnitus-Related Distress, Perceived Stress, and Psychological Epiphenomena: Immediate Intervention Group vs. Wait (Delayed Intervention Group)

Participants in the IIG used the hearing aids for 9.33 h/day ($SD = 4.08$). Participants who previously wore hearing aids did not differ in their hearing aid use from the remaining subjects (9.66 [$SD = 4.06$] vs. 9.10 [$SD = 4.20$] hours/day; not significant).

Significant "group" $\times$ "time" interaction effects emerged for all three tinnitus questionnaires. Relative to the DIG that yielded stable measurements, the IIG showed significant improvements of tinnitus-related distress (TQ: $F(1, 158) = 21.21$, $p < 0.001$, $d = -0.304$ [small effect]; THI: $F(1, 158) = 5.02$, $p = 0.026$, $d = -0.137$ [negligible effect]); and TFI: $F(1, 158) = 34.40$, $p < 0.001$, $d = -0.525$ [medium effect]). There were no significant interaction effects for perceived stress and psychological epiphenomena; however, significant main effects of time emerged for anxiety and emotional distress ($HADS_{anxiety}$, and $ISR_{total,\ anxiety}$). See Table 2 for an overview of results.

Table 2. Means, standard deviations, and significant main effects of "time" or "group" × time interaction effects for tinnitus-related distress, perceived stress, and psychological epiphenomena in the immediate vs. delayed intervention groups.

	Group	**Timepoint**				**Group × Time Interaction Effect**	***d***	**Main Effect of Time**	***d***
	n_{IIG} = 79 n_{DIG} = 81	t_{1IIG}; t_{wDIG}		t_{2IIG}; t_{1DIG}					
Measure		***M***	***SD***	***M***	***SD***				
TQ	IIG	31.11	15.72	24.71	15.46	$F_{group \times time}(1, 158) = 21.21$, $p < 0.001$	−0.304		
	DIG	33.05	17.09	31.67	16.14				
THI	IIG	30.61	22.09	26.20	21.41	$F_{group \times time}(1, 158) = 5.02$, $p = 0.026$	−0.137		
	DIG	34.17	23.68	32.91	22.06				
TFI	IIG	40.38	21.46	27.85	21.61	$F_{group \times time}(1, 158) = 34.40$, $p < 0.001$	−0.525		
	DIG	41.87	21.83	40.75	21.68				
PSQ_total	IIG	28.12	19.00	26.60	18.85				
	DIG	30.07	19.59	29.42	19.66				
PSQ_w	IIG	23.46	19.91	20.59	20.18				
	DIG	26.75	23.39	26.58	23.18				
PSQ_t	IIG	34.01	25.41	30.72	23.98				
	DIG	35.12	26.08	34.40	23.70				
PSQ_j	IIG	57.05	27.67	57.62	26.18				
	DIG	57.12	27.37	56.21	28.44				
PSQ_d	IIG	31.98	21.60	31.05	22.39				
	DIG	32.67	22.45	33.00	24.40				
HADS_a	IIG	6.09	4.06	5.30	4.10			$F_{time}(1,158) = 7.98$, $p = 0.005$	−0.114
	DIG	6.40	4.55	6.20	4.18				
HADS_d	IIG	5.19	4.44	4.94	4.46				
	DIG	5.73	5.07	5.86	4.91				
ISR_total	IIG	0.59	0.49	0.54	0.52			$F_{time}(1,158) = 8.67$, $p = 0.004$	−0.094
	DIG	0.66	0.62	0.61	0.57				
ISR_ds	IIG	0.88	0.95	0.82	0.96				
	DIG	0.98	1.01	0.96	0.97				
ISR_as	IIG	0.90	0.84	0.68	0.73			$F_{time}(1,158) = 13.83$, $p < 0.001$	−0.186
	DIG	0.84	0.91	0.75	0.81				
ISR_ocd	IIG	0.49	0.70	0.54	0.85				
	DIG	0.64	0.84	0.58	0.77				

Table 2. *Cont.*

	Group	Timepoint				Group × Time Interaction Effect	*d*	Main Effect of Time	*d*
ISR_sds	IIG	0.33	0.51	0.27	0.52				
	DIG	0.48	0.70	0.40	0.67				
ISR_eds	IIG	0.51	0.60	0.54	0.68				
	DIG	0.48	0.73	0.47	0.73				
ISR_sup	IIG	0.52	0.44	0.47	0.42			$F_{time}(1,157) = 9.21$, $p = 0.003$	−0.098
	DIG	0.62	0.59	0.58	0.56				

Notes: TQ = Tinnitus Questionnaire—German version; THI = Tinnitus Handicap Inventory; TFI = Tinnitus Functional Index; PSQ = Perceived Stress Questionnaire; PSQ_w = PSQ, worries subscale; PSQ_t = PSQ, tension subscale; PSQ_j = PSQ, joy subscale; PSQ_d = PSQ, demands subscale; HADS_a = Hospital Anxiety and Depression Scale; Anxiety Subscale; HADS_d = HADS, Depression subscale; ISR = IDC-10 Symptom Rating; ISR_ds = ISR, depressive syndrome subscale; ISR_as = ISR, anxiety syndrome subscale; ISR_ocd = ISR, obsessive-compulsive syndrome subscale; ISR_sds = ISR, somatoform disorder syndrome subscale; ISR_eds = ISR, eating disorder syndrome subscale; ISR_sup = ISR, supplementary subscale; IIG = immediate intervention group; DIG = delayed intervention group; *M* = mean; and *SD* = standard deviation. *d* = Cohen's *d* (0.20–0.49 small effect, 0.50–0.80 medium effect, and > 0.80 large effect).

3.3. Stability of Treatment Effects [Pooled Sample]

The stability of treatment-related effects was investigated in the pooled dataset (see also '2.7. Statistical Analyses'). Terzo-fitted hearing aids were used for 9.49 h/day during the follow-up period (during the intervention period: 9.26 h/day, $SD = 4.14$; $t(145) = -0.48$, not significant). The three-tiered rmANOVAs [pre, post, and follow-up] confirmed significant improvements in tinnitus-related distress (TQ: $F(1.79, 267.35) = 49.75$, $p < 0.001$, $d = -0.363$ [small effect]; THI: $F(1.73, 257.13) = 23.61$, $p < 0.001$, $d = -0.268$ [small effect]; TFI: $F(1.59, 236.48) = 84.61$, $p < 0.001$, $d = -0.570$ [medium effect]). As hypothesized, post hoc comparisons revealed significant improvements from pre- to post-treatment and pre-treatment to follow-up with no significant differences between post-treatment and follow-up. Pre-to-follow-up TQ change comprised 5.8 ($SD = 8.2$), THI change 4.9 ($SD = 10.9$), and TFI 12 ($SD = 14.6$) points. In the context of the overall mild rates of tinnitus-related distress, clinically relevant change (defined as $TQ_{Follow\text{-}up\text{-}Pre} \geq 12$; $THI_{Follow\text{-}up\text{-}Pre} \geq 7$ and $TFI_{Follow\text{-}up\text{-}Pre} \geq 13$) was obtained for 0.7 (TQ), 10.7 (THI), and 2.7% (TFI) of participants, respectively. See Figure 3 for a visualization of results.

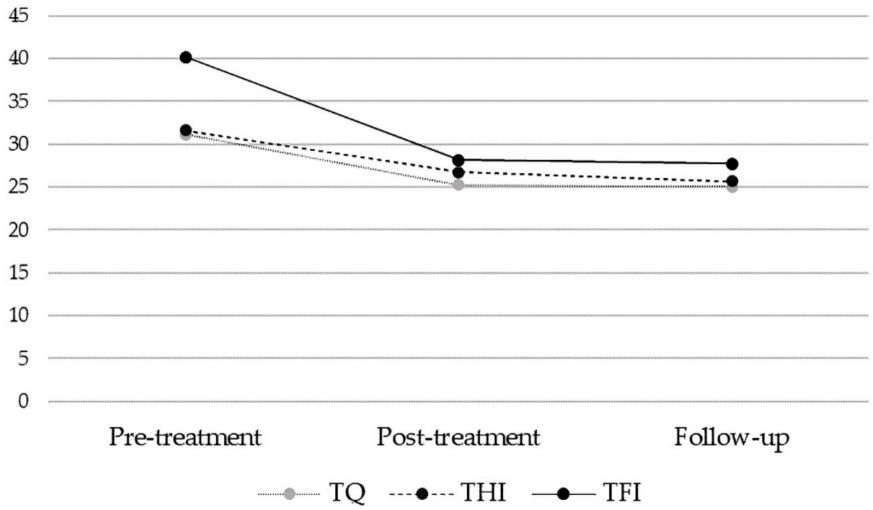

Figure 3. Treatment-related effects on three tinnitus-related distress measures in the pooled total sample ($n = 150$) at pre-treatment, post-treatment, and follow-up. All measures significantly improve from pre- to post-treatment and pre-treatment to follow-up with small (TQ, THI) or medium effect sizes (TFI).

3.4. Exploratory Analyses: Uncontrolled Effects from Pre-Treatment to Follow-Up [Pooled Sample]

Significant, yet uncontrolled, pre- to follow-up changes emerged for indices of perceived stress (PSQ_total: $F(1.91, 284.39) = 5.98$, $p = 0.003$, $d = -0.152$; PSQ_t: $F(1.78, 265.62) = 5.07$, $p = 0.009$), $d = -0.165$; and PSQ_d: $F(1.88, 274.30) = 3.70$, $p = 0.029$, $d = -0.122$) and emotional distress, notably depressive symptoms and anxiety (HADS_d: $F(2, 298) = 4.30$, $p = 0.014$), $d = -0.080$; HADS_a: $F(2, 298) = 4.50$, $p = 0.012$), $d = -0.110$; ISR_total: $F(1.89, 278.94) = 3.92$, $p = 0.023$, $d = -0.109$; ISR_d: $F(1.84, 273.56) = 3.90$, $p = 0.025$, $d = -0.115$; and ISR_sup: $F(1.75, 259.29) = 3.79$, $p = 0.029$, $d = -0.100$). Whilst statistically significant, the effect sizes for these changes were 'negligible' (<0.2). See Table 3 for an overview.

Table 3. Means, standard deviations, and significant pairwise comparisons investigating [a] the stability of identified treatment effects (t_{2}- t_{3}) and [b] exploratory uncontrolled pre- to follow-up changes in the pooled total sample (t_{1}- t_{3}).

Group *n* = 150	Timepoint Pre		Post		Follow-Up		Paired Samples *t*-Tests		
	$t_{1IIG\ and\ DIG}$		$t_{2IIG\ and\ DIG}$		$t_{3IIG\ and\ DIG}$		t_{2}- t_{3}	t_{1}- t_{3}	*d*
Measure	***M***	***SD***	***M***	***SD***	***M***	***SD***			
TQ [a]	31.09	16.16	25.27	15.80	25.07	17.02		$t(149) = 7.67$, $p < 0.001$	−0.363
THI [a]	31.64	22.36	26.75	22.03	25.65	22.42		$t(149) = 5.50$, $p < 0.001$	−0.268
TFI [a]	40.18	21.67	28.14	21.22	27.69	22.16		$t(149) = 10.02$, $p < 0.001$	−0.570
PSQ_total [b]	28.80	19.85	27.12	19.95	25.84	19.16		$t(149) = 3.13$, $p < 0.01$	−0.152
PSQ_w	25.20	22.14	23.16	22.32	23.24	22.73			
PSQ_t [b]	34.31	25.16	30.80	23.79	30.18	25.01		$t(149) = 2.60$, $p < 0.05$	−0.165
PSQ_j 2[b]	57.20	28.49	59.19	28.49	60.31	28.29			
PSQ_d 1[b]	32.36	23.36	31.29	23.58	29.56	21.97		$t(149) = 2.21$, $p < 0.05$	−0.122
HADS_a [b]	6.04	4.19	5.58	4.42	5.55	4.69		$t(149) = 2.35$, $p < 0.05$	−0.110
HADS_d [b]	5.47	4.78	5.02	4.85	5.09	4.71		$t(149) = 2.15$, $p < 0.05$	−0.080
ISR_total 2[b]	0.60	0.54	0.56	0.56	0.54	0.56		$t(149) = 2.79$, $p < 0.01$	−0.109
ISR_ds [b]	0.93	0.97	0.87	0.98	0.82	0.94		$t(149) = 2.45$, $p < 0.05$	−0.115
ISR_as 2[b]	0.83	0.84	0.67	0.75	0.69	0.82			
ISR_ocd	0.51	0.73	0.53	0.81	0.49	0.75			
ISR_sds	0.35	0.58	0.34	0.58	0.30	0.58			
ISR_eds	0.48	0.68	0.47	0.71	0.48	0.74			
ISR_sup 2[b]	0.55	0.52	0.51	0.54	0.50	0.53		$t(149) = 2.62$, $p < 0.05$	−0.100

Notes: TQ = Tinnitus Questionnaire—German version; THI = Tinnitus Handicap Inventory; TFI = Tinnitus Functional Index; PSQ = Perceived Stress Questionnaire; PSQ_w = PSQ, worries subscale; PSQ_t = PSQ, tension subscale; PSQ_j = PSQ, joy subscale; PSQ_d = PSQ, demands subscale; HADS_a = Hospital Anxiety and Depression Scale; Anxiety subscale; HADS_d = HADS, Depression subscale; ISR = IDC-10 Symptom Rating; ISR_ds = ISR, depressive syndrome subscale; ISR_as = ISR, anxiety syndrome subscale; ISR_ocd = ISR, obsessive–compulsive syndrome subscale; ISR_sds = ISR, somatoform syndrome subscale; ISR_eds = ISR, eating disorder syndrome subscale; ISR_sup = ISR, supplementary subscale; *M* = mean; *SD* = standard deviation. *d* = Cohen's *d* (0.20–0.49 small effect, 0.50–0.80 medium effect, and > 0.80 large effect). [a] Identified controlled treatment effects and [b] exploratory uncontrolled pre- to follow-up changes. [1] Significant covariate "age" included in model. [2] Significant covariate "mean pure tone audiometry" included in model.

3.5. Exploratory Analyses: Hearing Ability and [Pre-to-Follow-Up Change in] Psychological Variables [Pooled Sample]

At pre-treatment [IIG: t_1; DIG: t_1], small positive correlations (Pearsons $r < 0.02$) emerged between participants' hearing ability and emotional distress ($r_{PTA\_ISR\_Total} = 0.154$, $p = 0.04$), as well as depression ($r_{PTA\_ISR\_d} = 0.154$, $p = 0.03$). No correlations were found between PTA indices and change across those psychological variables that were found to improve over time.

4. Discussion

The present study investigated the effects of Terzo© hearing therapy on tinnitus-related distress and accompanying psychological parameters. The intervention combined binaurally-fitted hearing aids with a 14-day, CD-enhanced Terzo self-study program.

Using a randomized-controlled cross-over design, an immediate (vs. delayed) intervention group showed significantly greater improvements in tinnitus-related distress. This finding demonstrates for the first time that the 14-day Terzo© hearing therapy bears the potential to improve self-reported psychological aspects of tinnitus symptomatology in patients with chronic tinnitus and mild-to-moderate high-frequency hearing loss. Importantly, however, the effects sizes of the observed effects differed according to the respectively used questionnaire (TQ: small effect size; THI: negligible effect size; and TFI: medium effect size) highlighting the importance of matching the content and targets of interventions with respectively applied measurement choices [7].

The study joins previous research on self-reported symptom-relief following hearing aid fittings in patients with hearing loss [19,20,47] with possible mechanisms involving enhancements of individuals' tonal environments [21,48,49], tinnitus masking [19], reduced tinnitus awareness and improved communication opportunities [22] or possible psychological effects such as, for some patients, enhanced senses of self-efficacy, control, or social inclusion. In the present study, the majority of participants (68%) wore the hearing aids between 5.25 and 13.41 h/day, which is broadly consistent with the previously reported times in the literature (e.g., 3.67–11.93 h/day [50], 5.49–11.77 h/day [51], or 1.20–11.00 h/day [52]).

Because the intervention primarily aimed to improve executive and attention-related processes in their interaction with participants' hearing ability, it follows that the observed improvements were primarily reflected in the TFI, which, unlike the TQ and THI, emphasizes audiological and functional aspects of chronic tinnitus [7,53].

Whilst the Terzo training was not directly aimed at addressing psychological parameters, we expected indirect psychological benefits, possibly through ameliorating sensory contributions that have been well established in their impact on emotional distress [54]. Contrary to this expectation, we found that emotional distress slightly improved in both groups. By contrast, perceived stress and depressive symptoms did not change in either group. Crucially, upon inclusion in the study, participants showed overall low levels of psychological distress, and the resulting floor effects may limit the possibilities to effect or detect changes with treatment [55,56]. Nonetheless, time-related improvements in anxiety might be attributable to the anticipation of treatment, natural fluctuations in symptoms, coping mechanisms, or self-monitoring skills, as well as - in the immediate intervention group—a possible response–shift bias [57]. Natural improvements in anxiety with time have been previously observed across different patient populations [57–59]. However, research on such fluctuations of expectation-based effects has yielded mixed results, and the listed reasons for the observed effects remain speculative at this point. In the present study, we observed no beneficial effect of hearing aids on the indices of depression or perceived stress, which were, however, low upon commencing treatment. Whilst hearing loss has been associated with depression, anxiety, or stress in some studies [25,60,61], but not others [62,63], our findings suggest a small association between mild-to-moderate hearing loss and emotional distress or low mood, albeit within a context of overall low distress

and symptom severity. Similarly, evidence for hearing aid-associated improvements in depression is mixed with some studies [64,65], but not others [60,66], reporting hearing aid or auditory-training-related improvements in mood. However, 'depression' labels a heterogeneous syndrome cluster that involves interacting cognitive, affective, behavioural, and physiological symptoms [67], and the present study's findings need to be replicated in study populations with varying levels of low mood - using multidimensional depression measures, that capture experiential as well as physiological aspects of depression-related symptom presentations [68].

Examining treatment effects within the pooled sample, the improvements of tinnitus-related distress remained stable at follow-up. Stable improvements following hearing-focused interventions have been previously reported after cochlear implantation [69–72] or hearing aid fittings [73], and the present study provides first promising evidence in favour of the here-investigated intervention in this regard.

Finally, exploratory analyses revealed statistically significant, yet negligible, improvements of perceived stress and emotional distress indices between pre-treatment and follow-up that were further unrelated to participants' hearing ability.

4.1. Limitations

Participants in the present study yielded only mild levels of hearing impairment and tinnitus-related, as well as broader psychological distress. Future studies need to investigate the helpfulness of the approach for more severely impaired populations that were excluded in the present study. Moreover, a Terzo employee conducted the hearing aid fittings and the explanatory introduction to the hearing therapy. Whilst this may constitute a source of bias, it is transparently highlighted in the study's Conflict of Interest section, and all data collection and analysis procedures were conducted independently. Terzo© hearing therapy consists of a combination of hearing aid fitting and auditory training. Future studies might wish to investigate the specific effects of the hearing aids or auditory training components in order to maximize the effects for different subgroups of patients at various levels of distress or (hearing) impairment.

4.2. Clinical Implications

The present study offers the first support of the hypothesis that a combination of binaural hearing aid fittings and auditory training (the Terzo© hearing therapy) can improve tinnitus-related distress in patients with chronic tinnitus and mild-to-moderate hearing loss. Whilst methodologically exploratory, the observed benefits of this intervention on psychological indices warrant further investigation, particularly across samples with varying levels of emotional distress.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Charité Universitätsmedizin Berlin (EA1/114/17).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: As per Charité Universitätsmedizin Berlin's ethics committee, unfortunately, we cannot make the data public without restrictions because we did not obtain patients' consent to do so at the time. Nevertheless, interested researchers can contact the directorate of the Tinnitus Center Charité Universitaetsmedizin Berlin with data access requests (birgit.mazurek@charite.de).

Conflicts of Interest: All authors complied with APA ethical standards in the treatment of participants and in the setup of the study. Although the developers of the intervention funded the study, data collection and analysis were performed completely independently. The potential conflict of interest is transparently addressed throughout the manuscript.

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Paper 6: Psychological Effects on Hearing Amplification

Having determined psychological benefits *of* hearing amplification on TRD, **Study 6** [162] examines psychological effects *on* hearing amplification. It demonstrates for the first time, that psychological factors causally influence hearing aid use-time and – thereby – the psychological benefit of hearing amplification.

'***Background****: Hearing aids (HAs) can improve tinnitus-related distress (TRD) and speech comprehension (SC) in silence or at 55 dB noise-interference (SC_55 dB) in patients with chronic tinnitus and mild-to-moderate hearing loss. However, the role of HA use-time in relation to psychological, audiological, or self-reported tinnitus characteristics is under-investigated.* ***Methods****: We examine 177 gender-stratified patients before (t_1) and after an intervention comprising binaural DSLchild algorithm-based HA fitting and auditory training (t_2) and at a 70-day follow up [t_3]. HA use-time was retrospectively retrieved (at t_2) for the pre-post- and (at t_3) post-follow up periods. General linear models investigated HA use-time in relation to (1) general audiological, (2) tinnitus-related audiological, (3) tinnitus-related self-report, and (4) distress-related self-report indices before and after treatment, where applicable. Receiver operator characteristic analyses identified optimal HA use-time for hereby-mediated treatment changes.* ***Results****: At t_1 and t_2, psychological, but not audiological indices causally influenced prospective HA use-time—except for SC_55 dB at t_1, which, however, correlated with patients' anxiety, depressivity, and psychological distress levels. Correlations did not differ between patient subgroups defined by categorical tinnitus-related audiological or self-report indices. HA use-time partly mediated treatment-related improvement in TRD, but not SC. Optimal use amounted to 9.5–10.5 h/day.* ***Conclusions****: An awareness of psychological influences may help clinicians facilitate HA use and, thereby, TRD improvement with hearing amplification.*' [162(p1)]

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Hearing Aid Use Time Is Causally Influenced by Psychological Parameters in Mildly Distressed Patients with Chronic Tinnitus and Mild-to-Moderate Hearing Loss

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Abstract: Background: Hearing aids (HAs) can improve tinnitus-related distress (TRD) and speech-comprehension (SC) in silence or at 55 dB noise-interference (SC_55 dB) in patients with chronic tinnitus and mild-to-moderate hearing loss. However, the role of HA use time in relation to psychological, audiological, or self-reported tinnitus characteristics is under-investigated. Methods: We examine 177 gender-stratified patients before (t_1) and after an intervention comprising binaural DSL_{child} algorithm-based HA fitting and auditory training (t_2) and at a 70-day follow up [t_3]. HA use time was retrospectively retrieved (at t_2) for the pre-post- and (at t_3) post-follow up periods. General linear models investigated HA use time in relation to (1) general audiological, (2) tinnitus-related audiological, (3) tinnitus-related self-report, and (4) distress-related self-report indices before and after treatment, where applicable. Receiver operator characteristic analyses identified optimal HA use time for hereby-mediated treatment changes. Results: At t_1 and t_2, psychological, but not audiological indices causally influenced prospective HA use time—except for SC_55 dB at t_1, which, however, correlated with patients' anxiety, depressivity, and psychological distress levels. Correlations did not differ between patient subgroups defined by categorical tinnitus-related audiological or self-report indices. HA use time partly mediated treatment-related improvement in TRD, but not SC. Optimal use amounted to 9.5–10.5 h/day. Conclusions: An awareness of psychological influences may help clinicians facilitate HA use and, thereby, TRD improvement with hearing amplification.

Keywords: hearing aids; usage time; use time; mild-to-moderate hearing loss; tinnitus-related distress; psychological epiphenomena

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1. Introduction

Tinnitus denotes "the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source" [1]. While psychological, audiological, or medical factors can facilitate tinnitus onset or maintenance, hearing loss (HL) is an important risk factor for many—though not all—tinnitus presentations [2–4]. Accordingly, current guidelines suggest the provision of hearing aids (HAs) as first-line intervention for individuals with HL and chronic tinnitus, alongside psychological interventions for those who experience high levels of psychological distress preceding or following symptom onset [5].

Both HL [6] and chronic tinnitus can contribute to difficulties with speech comprehension (SC), especially in contexts involving noise distractors [7]. Initial evidence suggests that HA use may benefit SC over time [8,9], potentially through individual levels of hearing loss linearly influencing HA use as a mediator of benefit [10]. However, neuropsychological mechanisms underlying these effects are likely complex [7,11–17], and research findings in this regard are limited to date.

Despite its putative importance and comparatively easy influenceability, research at the junction of HA use time and associated psychological influences in adults is sparse [18]. The majority of studies focuses on audiological predictors of HA use [19] and psychological influences on HL that are either unsusceptible to HA use [20] or improve following hearing amplification [21]. "Previously identified psychological predictors of HA nonuse include 'perceived stigma', 'cosmetic concerns', 'disappointment with HA', 'oversold expectations', or 'family pressure to get HAs' [22]. By contrast, HA use is influenced by '[positive] attitudes towards HAs', '[realistic] expectations of benefit', and individuals' 'perception- and acceptance of their hearing difficulties' [23]. Only one study specifically examines the impact of psychological factors on HA use time - and reported a negative association between depressivity and HA use time [24]. Dawes et al. [25], however, failed to find such an association in a large cross-sectional sample.

Against the background of interacting influences of HL, chronic tinnitus symptomatology, psychological distress, and SC difficulties, few studies have investigated the effectiveness of HAs on tinnitus-related distress (TRD) or SC in silence or noise in patients with chronic tinnitus and mild-to-moderate HL. Two recent studies from our group aimed to fill this gap and reported beneficial effects of a 21-day hearing therapy on TRD [26] and SC in silence for patients with mild or moderate, and 55 dB noise-interference for patients with mild HL only [27]. Treatment involved binaural Desired Sensation Level $(DSL)_{child}$ algorithm-based HA fittings and auditory self-study training. At 65 dB noise-interference, SC did not improve with treatment in either patient group.

Expanding these investigations, the present study has two aims: First, to examine psychological distress levels across general audiological (hearing ability, speech comprehension in silence and at 55 dB or 65 dB noise-interference), tinnitus-related audiological (tinnitus type, location, pitch), and tinnitus-related self-report data (perceived pitch, onset, duration, as well as perceived fluctuations of sound and loudness). Second, to examine HA use time in relation to these four variable groups and herewith-associated treatment benefits on TRD or SC, respectively. We hypothesized that both audiological and psychological variables would influence HA use time and, thereby, the intervention's benefit.

2. Materials and Methods

2.1. Participants

Expanding on the above-reported results [26–28], we use data from the original randomized controlled crossover study that investigated the effects of a hearing therapy protocol on TRD and SC. The present study examines pooled data from the crossover study's two intervention arms and includes $N = 177$ patients with chronic tinnitus and mild-to-moderate HL ($age_{mean} = 59.61$ years; $SD = 7.46$) who were examined at screening (t_0), pre- and post-treatment ($t_1 - t_2$), and at a 70-day follow up timepoint (t_3) (see also [27]). The study was conducted according to the principles of the Declaration of Helsinki and approved by the Charité's Ethics Committee (EA1/114/17).

2.2. Data and Measures

Briefly, obtained data comprised four groups of variables: (1) general audiological data (hearing ability [Pure-Tone-Audiometry, PTA, t_0]; SC in silence and at 55 and 65 dB noise-interference, t_1, t_2, t_3); (2) tinnitus-related audiological data (tinnitus type, location, pitch, t_0); (3) tinnitus-related self-report data (perceived pitch, onset, duration, as well as perceived sound-and loudness fluctuations, t_0); and (4) distress-related self-report data (Tinnitus Questionnaire, TQ, [29]; Tinnitus Handicap Inventory, THI [30]; Tinnitus Functional Index, TFI [31], Perceived Stress Questionnaire, PSQ [32]; Hospital Anxiety and Depression Scale, HADS [33]; and ICD-10 Symptom Rating, ISR [34,35], t_1, t_2, t_3).

Overall, the sample was characterized by low-to-mild (TFI) or mild-to-moderate levels of TRD (TQ, THI), respectively; normal levels of perceived stress (PSQ), anxiety, and depression (HADS), and mildly elevated general psychological distress (ISR).

2.2.1. Hearing Therapy

The hearing therapy combined binaural DSL_{child} algorithm-based HA fittings and a 14-day auditory self-study program (terzo© Hearing Therapy). For detailed information on sample characteristics at screening [28] as well as study design, sample characteristics at baseline, the examined hearing therapy, and the obtained self-report measures, readers are referred to the current study's predecessor papers [26,27].

2.2.2. Hearing Aid Use Time

The present study used Mood 16 G4 HAs. HA use time (h/day) was retrospectively retrieved (at t_2) for the pre-post- and (at t_3) for the post-follow up periods, thus allowing for a causal interpretation of correlation coefficients at pre- or post-treatment respectively.

2.3. Statistical Analyses

First, descriptive analyses and univariate comparisons (independent-samples *t* tests and analyses of variance, ANOVAs) examined tinnitus-related audiological and tinnitus-related self-report indices relative to general audiological- and distress-related self-report variables.

Second, Pearson correlation coefficients *r* investigated (1) associations between general audiological as well as distress-related self-report indices at pre- and post-treatment and HA use time, as well as (2) possible differences in any such associations for patient subgroups who differed on factors identified in Step 1. Here, similar to our approach in [27], coefficients were compared using MedCalc (https://www.medcalc.org/calc/comparison_of_correlations.php; accessed on 19 August 2022), where applicable. Correlational effects were interpreted according to Cohen [36] ($r \geq 0.10$ = small effect, $r \geq 0.30$ = moderate effect, $r \geq 0.50$ = strong effect).

Third, Hayes' PROCESS macro [37] calculated simple mediation models that examined 'true' mediation [38] of pre (x)-to-post (y)-treatment changes in SC or distress-related variables via (retrospectively quantified) HA use time (m). For significant indirect effects, Receiver operator characteristic (*ROC*) analyses further aimed to quantify the optimal HA use time associated with treatment-related 'improvement' (vs. 'no improvement'), pragmatically defined as any pre-to-post-treatment change to the positive (SC) or negative (TQ, THI, TFI, PSQ, HADS_a, HADS_d, ISR), respectively. Here, the 'area under the curve' statistic (*AUC*) reflects HA use time's poor ($0.50 < AUC < 0.70$), acceptable ($0.71 < AUC < 0.90$), or outstanding ability ($AUC > 0.91$) to perform this distinction [39,40].

All analyses were computed using SPSS statistical software version 27 (SPSS Inc., Chicago, IL, USA). Of note, analyses revealed no significant effects for the post- to follow up period—likely owing to the relative stability of all treatment-related effects (cf. [26,27]). The present paper thus limits itself to reporting findings for the t_1-t_2 intervention period.

3. Results

3.1. Tinnitus-Related Audiological and Tinnitus-Related Self-Report Indices in Relation to General Audiological and Distress-Related Self-Report Data

Table 1 reports between-group differences in general audiological- (Panel a) and distress-related (Panels b and c) variables across categorical tinnitus-related audiological and tinnitus-related self-report indices, where applicable.

Table 1. Sample descriptors and univariate comparisons for general audiological (a), tinnitus-related (b), and other distress-related indices (c). PTA = pure tone audiometry; SC = speech comprehension; TRD = tinnitus-related distress; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; TFI = Tinnitus Functional Index; PSQ = Perceived Stress Questionnaire; HADS_a = Hospital Anxiety and Depression Scale_anxiety subscale; HADS_d = depression subscale; ISR = ICD-10 symptom rating. *Italicised numbers* denote significantly differing contrasts. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

General Audiological Indices				**Hearing Ability [PTA]**			**SC_0 dB**			**SC_55 dB**			**SC_65 dB**		
Descriptors		*n*	%	*M*	*SD*	*F*	*M*	*SD*	*F*	*M*	*SD*	*F*	*M*	*SD*	*F*
Gender															
	male	81	45.8												
	female	96	54.2												
Previous psychotherapy															
	no	124	70.1							73.75	13.16	(1171) = 3.96 *			
	yes	53	29.9							69.34	14.08				
Previous hearing aid use															
	no	123	69.5	35.82	7.36	(1170) = 4.89 *	98.55	2.62	(1174) = 13.57 ***						
	yes	53	29.9	40.11	6.41		95.88	12.72							
Tinnitus type															
	pure-tone	121	68.4				98.63	2.59	(1167) = 5.97 *						
	narrow-band	52	29.4				95.61	12.94							
Tinnitus location															
	right	15	8.5												
	left	31	17.5												
	both	131	74.0												
Tinnitus pitch															
	very high	-	-												
	high	104	58.8												
	middle	37	20.9												
	low	7	4.0												
Perceived tinnitus pitch															
	very high	37	20.9							*66.71*	*11.17*	(3169) = 3.11 *	*18.16*	*13.58*	(3169) = 2.72 *
	high	104	58.8							*74.28*	*14.35*		*27.55*	*20.02*	
	middle	32	18.1							72.76	12.14		21.72	17.33	
	low	3	1.7							77.50	3.54		22.50	3.54	
Perceived tinnitus onset															
	gradual	92	52.0	37.92	6.79	(1163) = 4.78 *									
	sudden	73	41.2	35.48	7.51										
Perceived tinnitus duration															
	<1/2 year	5	2.8												
	1/2–1 year	9	5.1												
	1–2 years	23	13.0												
	2–5 years	24	13.6												
	>5 years	107	60.5												

Table 1. *Cont.*

General Audiological Indices				**Hearing Ability [PTA]**			**SC_0 dB**			**SC_55 dB**			**SC_65 dB**		
Descriptors		*n*	%	*M*	*SD*	*F*	*M*	*SD*	*F*	*M*	*SD*	*F*	*M*	*SD*	*F*
Perceived sound intermittence															
	intermittent	22	12.4												
	permanent	155	87.6												
Perceived loudness fluctuation															
	constant	71	40.1												
	variable	105	59.3												

(**a**)

Tinnitus-related distress indices		**TQ**			**THI**			**TFI**		
Descriptors		*M*	*SD*	*F*	*M*	*SD*	*F*	*M*	*SD*	*F*
Gender										
	male							36.90	19.73	(1171) = 4.03 *
	female							43.35	22.01	
Previous psychotherapy										
	no	28.97	14.33	(1171) = 7.97 **	27.40	19.41	(1171) = 15.43 ***	38.08	19.59	(1171) = 4.96 *
	yes	36.30	18.62		41.32	25.61		45.78	23.80	
Previous hearing aid use										
Tinnitus type										
Tinnitus location										
Tinnitus pitch										
Perceived tinnitus pitch										
	very high	*37.89*	*17.15*	(3171) = 3.76 *	*42.81*	*23.76*	(3.171) = 5.64 **	*50.85*	*24.34*	(3171) = 5.62 **
	high	30.32	15.94		*30.25*	*21.69*		*39.23*	*20.04*	
	middle	*26.00*	*12.48*		*22.90*	*17.41*		*31.30*	*15.20*	
	low	20.00	12.73		12.00	14.14		26.86	8.57	
Perceived tinnitus onset										
	gradual				28.09	20.67	(1.160) = 5.41 *			
	sudden				36.45	24.93				
Perceived tinnitus duration										
Perceived sound intermittence										
	intermittent							30.25	18.37	(1172) = 5.67 *
	permanent							41.85	21.23	
Perceived loudness fluctuation										

(**b**)

Table 1. *Cont.*

Other psychological distress-related indices		**PSQ**			**HADS_a**			**HADS_d**			**ISR**		
Descriptors		*M*	*SD*	*F*	*M*	*SD*	*F*	*M*	*SD*	*F*	*M*	*SD*	*F*
Gender													
	male	25.33	15.37	(1171) = 6.53 *	5.50	3.81	(1171) = 4.63 *				0.52	0.45	(1171) = 4.50 *
	female	32.77	21.64		6.84	4.27					0.69	0.57	
Previous hearing aid use													
Previous psychotherapy													
	no	23.67	14.03	(1171) = 42.89 ***	5.12	3.33	(1171) = 35.09 ***	4.48	4.13	(1171) = 25.42 ***	0.48	0.38	(1171) = 29.19 ***
	yes	42.43	23.29		8.81	4.59		8.15	4.93		0.91	0.67	
Tinnitus type													
Tinnitus location													
Tinnitus pitch													
Perceived tinnitus pitch													
	very high				*7.92*	*4.83*	(3170) = 3.57 *	*7.78*	*5.52*	(3170) = 4.30 **	*0.87*	*0.61*	(3171) = 4.89 **
	high				5.99	3.92		*5.28*	*4.45*		*0.57*	*0.51*	
	middle				*4.97*	*3.20*		*3.97*	*3.63*		*0.42*	*0.35*	
	low				3.50	0.71		4.00	1.41		0.43	0.15	
Perceived tinnitus onset													
	gradual	26.64	16.56	(1160) = 4.50 *									
	sudden	33.45	22.86										
Perceived tinnitus duration													
Perceived sound intermittence													
Perceived loudness fluctuation													
	constant	25.14	16.67	(1170) = 5.52 *	5.26	3.89	(1170) = 6.58 *						
	variable	32.14	20.64		6.88	4.17							

(**c**)

Results revealed that patients' PTA-measured hearing ability was lower for patients reporting previous hearing aid use and gradual tinnitus onset.

SC in silence was aggravated for patients reporting previous hearing aid use and narrow-band tinnitus perception. At medium noise-interference (SC_55 dB), patients with a history of psychotherapeutic support reported higher SC difficulties. At 55 and 65 dB noise-interference, higher SC difficulties were further accompanied by a 'very high' (vs. high) self-reported tinnitus pitch.

Significantly higher levels of psychological distress were reported by patients who were female (TFI, PSQ, HADS_a, ISR), had a history of psychotherapeutic support (TQ, THI, TFI, PSQ, HADS_a, HADS_d, ISR), described a 'very high' (vs. middle: TQ, HADS_a; or vs. high vs. middle: THI, TFI, HADS_d, ISR) self-reported tinnitus pitch, reported sudden tinnitus onset (THI, PSQ), experienced no intermittence (TFI), and reported fluctuations in perceived loudness (PSQ, HADS_a).

The majority of patients reported a 'high' tinnitus pitch. Yet, despite comparable proportions of patients in PTA-measured vs. self-reported tinnitus frequency ranges, statistical agreement between the two variables was only "slight" (Cohen's $\kappa = 0.12$; $p < 0.05$, [41]), indicating an importance of independent measurement and conceptualization.

3.2. Hearing Aid Use Time and General Audiological, Tinnitus-Related Audiological, Tinnitus-Related Self-Report-, and Distress-Related Self-Report Data

Participants' average daily HA use time amounted to 9.26 ($SD = 4.14$) for the t_1-t_2 period and 9.49 ($SD = 4.25$) h for the t_2-t_3 period, respectively. It did not differ between any patient subgroups who were characterized by differences in categorical tinnitus-related audiological or tinnitus-related self-report indices.

Table 2 reports Pearson's r correlations between general audiological as well as distress-related self-report indices and subsequent HA use time. At pre-treatment, small-to-moderate causal effects emerged for psychological, but not audiological variables. An exception was found for SC_55 dB, which was further associated with both patients' hearing ability, $r = -0.40$, $p < 0.001$ ('moderate'), and indices of anxiety, $r = -0.18$, $p < 0.05$; depression, $r = -0.20$, $p < 0.01$; and general psychological-, but not tinnitus-related distress, $r = -0.26$, $p < 0.01$ ('small'). At post-treatment, psychological variables continued to causally influence prospective HA use time during the follow up period in the small-to-moderate range.

Table 2. Significant correlation coefficients between HA use time ($t_1 - t_2$) and general audiological as well as distress-related indices at pre- and post-treatment. Patients' hearing ability was measured at a preceding screening timepoint. PTA = pure tone audiometry; SC = speech comprehension; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; TFI = Tinnitus Functional Index; PSQ = Perceived Stress Questionnaire: HADS_a = Hospital Anxiety and Depression Scale, anxiety; HADS_d = depression; ISR = ICD-10 Symptom Rating; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

t_1 ***n* = 155**	**HA Use Time** **[$t_1 - t_2$]**	**t_2** ***n* = 150**	**HA Use Time** **[$t_2 - t_3$]**
Hearing ability [PTA]			
SC_0 dB			
SC_55 dB	−0.17 *		
SC_65 dB			
TQ	−0.30 ***		−0.32 ***
THI	−0.26 ***		−0.29 ***
TFI	−0.29 ***		−0.42 ***
PSQ	−0.19 *		−0.20 *
HADS_a	−0.17 *		−0.23 **
HADS_d	−0.23 **		−0.19 *
ISR	−0.20 *		−0.27 **

SC in silence and at 65 dB noise-interference did not influence HA use time. SC_0 dB was associated with patients' hearing ability, $r = -0.19$, $p < 0.05$, TRD (THI: $r = -0.16$, $p < 0.05$; TFI: $r = -0.19$, $p < 0.05$) and perceived stress, $r = -0.17$, $p < 0.05$ ('small'). SC_65 dB was associated with patients' hearing ability, $r = -0.28$, $p < 0.001$, depression, $r = -0.17$, $p < 0.05$, and general psychological distress, $r = -0.17$, $p < 0.05$ ('small').

Linking findings from Sections 3.1 and 3.2, additional analyses investigated, whether correlation coefficients between HA use time and influencing parameters (cf. Table 2) differed between patient subgroups who were characterized by differences in categorical tinnitus-related audiological or tinnitus-related self-report indices (cf. Table 1). For example, because (1) TQ-measured TRD causally influenced subsequent HA use time (cf. Table 2), and (2) TQ scores significantly differed for participants with vs. without previous psychotherapy (cf. Table 1), correlation coefficients $r_{\text{TQ HA use time}}$ were compared between these patient subgroups.

Overall, results revealed no between-subgroup differences in correlational strengths. An exception was found for $r_{\text{SC\_55 dB\_HA use time}}$, which only emerged in patients with a 'high', $r = -0.31$, $p < 0.01$ (but not 'very high', $r = 0.10$, *n.s.*) tinnitus pitch ($z = 2.07$, $p < 0.05$).

3.3. Mediation Analyses

Simple mediation analyses examined effects of HA use time (m) on treatment-related changes in SC and distress-related variables between t_1 (x) and t_2 (y). Results indicated that HA use time partly mediated pre- to post-treatment change in TRD as measured by the TQ (path a: −0.07, SE = 0.02, $p < 0.001$; path b: −0.36, SE = 0.16, $p < 0.05$; ab = 0.03, SE = 0.02) and TFI (path a: −0.05, SE = 0.015, $p < 0.001$; path b: −0.85, SE = 0.28, $p < 0.01$; ab = 0.05, SE = 0.02). Here, higher TRD levels at baseline negatively affected subsequent HA use time and, thereby, TRD-related improvement with treatment. By contrast, HA use time did not mediate changes in THI scores, SC indices, or other distress-related variables.

Receiver Operator Characteristics Analyses

Following up on the identified indirect effects, ROC analyses aimed to identify the optimal HA use time that distinguished pre- to post-treatment 'improvement' (from 'no improvement') on the TQ or TFI. While point estimates were not significant, trend significant AUC statistics within poor-to-acceptable confidence intervals suggested minima of 9.5 (TQ; 0.47–0.75, $p < 0.10$) and 10.5 h/day respectively (TFI; 0.48–0.77, $p < 0.10$).

4. Discussion

The present study demonstrated that HA use time (1) is causally influenced by psychological parameters and (2) partly mediates tinnitus distress-related, but not speech comprehension improvements in mildly distressed patients with chronic tinnitus and mild-to-moderate hearing loss.

One-hundred seventy-seven gender-stratified patients with chronic tinnitus and mild-to-moderate HL were binaurally fitted with DSL_{child} algorithm-based HAs and completed auditory training exercises over a 21-day period. Measurements in TRD, anxiety, depressivity, general psychological distress, and SC in silence as well as at 55 or 65 dB noise-interference were obtained at screening (t_0), before (t_1) and after the intervention (t_2), and at a 70-day follow up (t_3). Previously published studies that examined this dataset reported controlled improvements in TRD (TQ, THI, TFI) alongside uncontrolled small improvements in anxiety and psychological distress levels (HADS_a, ISR) [26], as well as HA-related improvements in SC in silence (for patients with mild or moderate HL) and at 55 dB noise-interference (for patients with mild HL only) [27].

4.1. Patients' Self-Report and Audiological Data

First, the present study examined differences in general audiological ([PTA-measured] hearing ability, SC) or psychological distress indices (TQ, THI, TFI, PSQ, HADS, ISR) across patient subgroups characterized by tinnitus-related audiological (tinnitus type, location,

pitch) or tinnitus-related self-report indices (perceived tinnitus pitch, onset, duration, as well as perceived sound- and loudness fluctuations).

Here, self-reported 'sudden' tinnitus onset was associated with proportionately higher levels of perceived stress and THI-measured TRD. Previous research has highlighted links between sudden tinnitus and 'stress' or, relatedly [42,43], sudden hearing loss in patients' own tinnitus narratives [44] as well as emotional difficulties in patients with experiences of traumatization [45]. By contrast, a reported history of 'gradual' onset was associated with lower PTA-measured hearing ability. For some patients, gradually developing hearing loss might parallel the perception of tinnitus [46], emphasizing a need for preventative or early-onset hearing protection measures that might delay both clusters of difficulty [47–49] alongside associated broader emotional difficulties [50,51].

The dissociation between self-reported sudden vs. gradual tinnitus onset and observed psychological vs. hearing ability-related influences may reflect a particular importance of stress-related factors for the former type of onset [52,53], particularly within a broader psychological context of pre-existing vulnerability [54,55]. For the chronification or maintenance of TRD, however, psychological factors may contribute to the appraisal of the tinnitus sound regardless of onset trajectory, potentially explaining varying TRD levels across both psychologically or audiologically mediated onset patterns [56].

Moreover, patients with higher levels of perceived stress and anxiety reported fluctuations in perceived tinnitus loudness, and patients with higher psychological distress levels or SC-in-noise difficulties reported a 'very high' tinnitus pitch. In keeping with some previous findings, audiometric frequency matching did not mirror this association [57,58]. Thus, rather than high-pitched noise being perceived as aversive, psychological distress likely shapes the appraisal and experience of the tinnitus sound [59]. Previous research has suggested 'emotional tension' or 'worry' as transdiagnostic factors that potentially underlie TRD [60]. Because patients' emotional states likely mediate the appraisal and experience of the tinnitus sound [61,62], it is crucially important to understand and conceptualize patients' distress experiences holistically, i.e., beyond the influence of the tinnitus symptom [63]. Any such accounts, however, are necessarily complex and idiosyncratic, thus necessitating person- (not symptom-) focused psychological formulations and treatment plans [64–66]. Clinically, patients who report sudden tinnitus onset or loudness fluctuations may particularly benefit from clinicians' awareness and consideration of psychological influences beyond tinnitus as the presenting index symptom, as well as their own emotional reactions to respective patient presentations [67–70]. Ideographic associations between patients' psychological distress levels and experienced characteristics of the tinnitus sound remain uninvestigated.

Patients' PTA-measured hearing ability correlated moderately with their SC abilities. Interestingly, SC_55 dB further correlated with patients' anxiety, depressivity, and general psychological, but not tinnitus-related distress levels. By contrast, SC_0 dB yielded a roughly inverse pattern. Moreover, SC_55 dB was lower in patients with a history of psychotherapeutic support, who further reported higher levels of distress across all psychological indices.

Patients with chronic tinnitus commonly report difficulties with SC, which can (but does not have to) be associated with hearing difficulties, potentially reflecting a 'functional' component in some patients [71]. Psychologically, SC is underlain by a multitude of cognitive processes such as inhibitory control, processing speed, allocation of attentional resources, or working memory [72,73], all of which are also known to interact with affective states such as anxiety or mood [13,74–82]. In a recent study, Tai and Husain [83] suggested that SC in noise may be influenced by interactions of ongoing tinnitus perception, cognitive control of emotion (involving the perception of, orientation towards, appraisal of, and reaction to the tinnitus sound), and cognitive control of attention.

Speculatively, SC might follow an inverse U-curve characterized by inversely proportional ratios of hearing- vs. emotion-related influences under circumstances of increasing noise-interference [84–87], with emotion-related influences reaching their proportionate

maximum at medium noise-interference. Future studies might wish to test this possibility by measuring patients' SC across linearly increased noise-interference levels in patients at varying levels of HL and psychological distress.

In keeping with previous findings, female patients reported higher levels of tinnitus-related [88–91] and general psychological distress [92–96]. Studies aiming to explain this gender discrepancy suspect the existence of gender-specific (hormonal [97]) phenotype clusters [98] or high numbers of emotionally stressed men who do not access available support options, potentially influenced by masculine gender norms [99–104].

Moreover, intermittent perception of the tinnitus sound was associated with lower levels of TFI-measured TRD, supporting some [105,106], but not all previous findings [107]. Underlying factors likely include both cognitive or behavioral processes such as higher attentional control [108], or individuals' distress-related (in)abilities to distract themselves from the tinnitus percept [56,109]. Alternatively, however, the finding may reflect an artifact owed to some of the TFI's item phrasings (e.g., "What percentage of your time awake were you consciously aware of your tinnitus?").

4.2. Hearing Aid Use Time

Second, we examined the four obtained variable groups (general audiological, tinnitus-related audiological, tinnitus-related self-report, and distress-related self-report indices) in relation to HA use time and associated treatment benefit. Owing to the retrospective retrieval of HA use time, correlation coefficients could be interpreted causally. Results revealed small yet significant causal influences of both tinnitus-related and broader psychological distress on HA use time at both pre- and post-treatment.

Relatedly, HA use time partly mediated treatment-related change in TRD as measured by the TQ and TFI, with higher TRD levels at baseline reducing prospective HA use time - thereby lowering treatment benefit as measured by these indices. According to Van der Wal et al. [110], the TQ captures the "psychological", and the TFI the "body functions" and "activity and participation"-related impact of chronic tinnitus symptomatology. A similar suggestion was made by Boecking et al. [111], who discussed "psychological" vs. "audiological" characteristics of TRD as measured by the TQ or TFI, respectively. Associations between pre-existing psychological distress, HA use, HA use time, and subsequent psychological, hearing-related or participation-based benefits are, however, likely bidirectional and closely interrelated. Notwithstanding, while HA-related benefits on TRD have been previously demonstrated in patients with chronic tinnitus and HL [5,112–115], our study is the first to demonstrate a vicious cycle wherein TRD at baseline likely decreases the use of the very intervention likely to benefit it.

Supplementary analyses revealed at trend level that an average use time of 9.5-to-10.5 h/day best distinguished between patients who showed improvement (vs. no improvement) on the TQ or TFI, respectively. Although these results necessitate replication due to a lenient definition of 'improvement' and rather broad confidence intervals around the AUC statistics, they do suggest that HA use time partly influences TRD improvement (in context of DSL_{child} algorithm-based HA fittings for patients with mild-to-moderate HL) – yet by no means exclusively so. Clinicians may wish to emphasize or review associations between baseline TRD, likely effects on HA use time, and resulting improvements for individuals with chronic tinnitus and mild-to-moderate HL.

By contrast, HA use did not mediate changes in anxiety, depressivity, or general psychological distress. Mirroring previous observations [116], this finding likely reflects the multifactorial, non-audiological origin and breadth of peoples' emotional experiences [117] as well as the overall only mild distress levels in the present sample [26].

Interestingly, HA use time did not mediate changes in patients' SC levels either: Neither patients' PTA-measured hearing ability nor SC levels at 0 or 65 dB noise-interference causally influenced prospective HA use time. By contrast, SC_55 dB *did* do so; however, HA use time did not predict treatment-related change on this index—which was therefore influenced by other, unmeasured variables. We further observed indications of a double

dissociation wherein SC_55 dB was associated with general psychological, but not tinnitus-related distress, and a roughly inverse pattern emerged for SC_0 dB. Future studies might wish to experimentally study the effects of people's affective states on SC at varying levels of HL, noise-interference, or amplification.

Overall, the observed mediation pattern appears to reflect both the psycho-audiological nature of TRD in patients with chronic tinnitus and HL [5] and the clinical need to conceptualize and address psychological influences on hearing- as well as SC difficulties beyond amplification alone [118].

4.3. Limitations

The present study has important limitations. Most notably, the interpretability and generalizability of results is inconclusive, owing to overall 'mild' psychological distress levels, a primarily amplification-based treatment protocol, and dual 'index symptoms' (chronic tinnitus symptomatology and mild-to-moderate HL) that may independently or interactionally affect both SC and psychological distress as outcomes of interest. Future studies might wish to examine chronic tinnitus patient samples with dimensionally distributed rates of hearing loss, speech comprehension difficulties, noise-interference levels, and psychological distress levels.

4.4. Conclusions

In summary, the present study highlights the importance of psychological factors in motivating HA use time for patients with chronic tinnitus and mild-to-moderate HL, with direct effects on TRD-improvements following amplification-based hearing therapy. To this end, certain self-reported tinnitus characteristics may serve as tentative markers of psychological distress that ought to be conceptualized holistically within patients' broader life contexts [54,64,119–121]. Clinicians might wish to counsel individuals sensitively about links between baseline TRD, HA use time, and realistically expectable amplification benefits. The influence of psychological factors on SC difficulties is currently unclear and warrants further examination, particularly in circumstances of medium noise-interference.

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Data Availability Statement: As per Charité—Universitätsmedizin Berlin's ethics committee, unfortunately, we cannot make the data public without restrictions, because we did not obtain patients' consent to do so at the time. Nevertheless, interested researchers can contact the directorate of the Tinnitus Center at the Charité—Universitätsmedizin Berlin with data access requests (birgit.mazurek@charite.de).

Conflicts of Interest: All authors complied with APA ethical standards in the treatment of participants and in the setup of the study. The developers and distributors of the here-investigated intervention funded the study and were partly responsible for audiological data collection. Data analyses were performed independently. This important potential conflict of interest is transparently addressed throughout the manuscript.

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Das ganze Leben ist ein ewiges Wiederanfangen.
Hugo von Hofmannsthal, Der Schwierige

Chapter 5 [General Discussion]

Outset

The present habilitation thesis set out to examine chronic tinnitus (and 'tinnitus-related' distress, TRD) as both a symptom and psychosomatic phenomenon. Anchored within a vulnerability-stress-coping framework, the thesis examined (1) potential biomarkers that index a vulnerability for tinnitus symptomatology or TRD, (2) personality variables as psychological vulnerability factors and vulnerability-stress interactions for TRD, and (3) the roles of psychological factors such as perceived stress as transdiagnostic, superordinate constructs of interest. Last, focusing on intervention effects, the thesis demonstrated psychological benefits of psychological and amplification-based treatment programmes - and identified causal psychological predictors of hearing aid (HA) use-time as mediators of treatment benefit in the latter. Overall, the portfolio of the here-presented studies argues in favour of (1) dimensional operationalizations of psychological factors within a transdiagnostic vulnerability-stress-coping framework, (2) the crucial importance of psychological factors in conceptualizing and treating TRD with or without HL, and (3) the consideration of psychological variables in audiology and hearing amplification research and practice.

The following sections will briefly summarize the main findings of each paper, embed them into a broader literature context and finally outline ensuing theoretical and clinical implications of the joint findings of the thesis.

Overview and Discussion of Main Findings

Vulnerability

Paper 1 ('Boecking B, Klasing S, Walter M, et al. Vascular–Metabolic Risk Factors and Psychological Stress in Patients with Chronic Tinnitus. Nutrients. 2022;14(11):2256.').

In this paper, $N = 200$ patients with chronic tinnitus were screened for an array of common blood index values linked to vascular-metabolic risk, immune function and redox processes. In addition, participants completed questionnaires measuring TRD and perceived stress. The study yielded two main outcomes: First, a substantial percentage of patients showed elevated levels of vascular-metabolic risk factors – suggesting a potential role of inflammatory processes in tinnitus symptom onset. Second, whilst some correlations emerged, the screened blood index values were largely unrelated to self-rated perceived stress levels. Strengths of the study comprised a comparatively large patient sample size and a broadly indexed array of blood parameters. The study contributes to a growing body of evidence that investigates vascular risk factors as non-specific, though modifiable risk factors for tinnitus symptomatology [163,164] – possibly through their impact on inner-ear damage and, thereby, hearing loss (HL). Because of the often-reported independence of

the tinnitus symptom and TRD, it is not surprising that only few associations emerged between the measured parameters and perceived stress levels.

Overall, vascular-metabolic risk factors may increase the risk of vascular damage that, once involving the inner ear, may lead to HL, which, in turn, might heighten the risk for tinnitus symptomatology. By contrast, TRD is likely associated with psychological risk factors that predispose individuals to interpret neutral stimuli in a threatening manner (e.g. distress-related memories [66]), health anxiety [165–167], or maladaptive (i.e. distress-perpetuating) ways of reacting to emotional distress or physical symptomatology [143].

Future studies may wish to integrate HL, tinnitus symptomatology, TRD, vascular-metabolic risk (as measured by metabolic markers) as well as behavioural expressions of risk factors within a holistic vulnerability-stress-coping framework.

Following the investigation of biomedical vulnerability factors for the tinnitus symptom and (unsuccessfully) TRD, Study 2 examined (1) personality variables as psychological vulnerability factors as well as (2) vulnerability-stress interactions for TRD.

Paper 2 ('Biehl R, Boecking B, Brueggemann P, Grosse R, Mazurek B. Personality Traits, Perceived Stress, and Tinnitus-Related Distress in Patients With Chronic Tinnitus: Support for a Vulnerability-Stress Model. Front Psychol. 2020;10.')

In this paper, $N = 100$ patients with chronic tinnitus completed the revised version of the Freiburger Persönlichkeitsinventar (FPI-r) alongside the perceived stress questionnaire. The study yielded two main outcomes: (1) Compared to the general population, patients with chronic tinnitus tended to interpret and respond to stimuli (including, but not limited to the tinnitus symptom) in a manner characterized by easy irritation, high levels of subjective overload, inner conflict, and ruminative tendencies. Concurrently, patients tended to feel inhibited to express their emotions or needs and experienced guilt-associated tendencies to orientate themselves towards others' needs. Further, (2) mediation analyses demonstrated that these personality dimensions interacted with perceived stress in the here-and-now in explaining TRD. Notably, most interaction effects involved patients' *internal* stress reactions (such as worry and emotional tension) – with only few effects involving patients' representation of external demands.

Results of the study support the validity of Lazarus and Folkman's work [65,168] and strongly suggest that psychotherapeutic approaches for 'stress reduction' ought to focus on the idiographic psychological *meanings* that people assign to stressors and experiences - rather than mechanistic 'work-load reduction' programmes. The study may further explain some of the literature's heterogeneity in personality factor research and chronic tinnitus [97,103,166]. For example, parts of the literature (1) used rather mechanistic univariate views on stimulus interpretation tendencies, (2) did not distinguish between bothersome and non-bothersome tinnitus presentations with or without HL, and (3) did not differentiate again between 'stimulus' (biomedically mediated symptom criteria) and 'interpretation' (psychologically mediated stimulus processing criteria - within a larger, symptom-independent psychological context). Moreover, TRD is not only a function of personality factor expressions 'per se', but also results from interactions between stimulus processing

propensities and relevant or 'activated' internal stress experiences in the here-and-now for some individuals [152].

Future studies ought to distinguish between symptom and distress dimensions with or without HL and understand TRD within a broader context of personality factors and subjective internal appraisals of life stressors and resources.

Following the examination of psychological vulnerability factors for TRD, Study 3 examined the role of perceived stress as potential driver (or component) of TRD further.

Stress

Paper 3 ('Boecking B, von Sass J, Sieveking A, et al. Tinnitus-related distress and pain perceptions in patients with chronic tinnitus–Do psychological factors constitute a link? PLOS ONE. 2020;15(6):e0234807.')

Paper 3 adopted a transdiagnostic approach and examined a dataset of $N = 1238$ patients with chronic tinnitus and pain symptomatology who completed questionnaire measures of TRD and affective and sensory pain perceptions alongside various psychological variables including anxiety, depression and perceived stress. The rationale for the study was set on theoretical considerations about phenomenological similarities between chronic tinnitus and pain experiences [66,125,126] as well transdiagnostically relevant psychological factors [169]. In this large patient sample, TRD and affective as well as sensory pain perceptions were significantly associated. Associations between TRD and affective pain experiences were mediated by the examined superordinate psychological constructs (perceived stress, depressivity, and attitudinal factors [self-efficacy/optimism/pessimism]). The findings strengthened the role of perceived stress as transdiagnostic treatment target for pervasive, symptom-linked distress experiences.

Generally, the important role of psychological factors in maintaining both chronic tinnitus and pain experiences is largely unrefuted [24,159,170–174]; however, our study was the first to demonstrate psychological constructs as mediators of both symptom clusters in a large sample of patients with chronic tinnitus.

Unfortunately, the above study did not feature a control group. It could thus not be concluded, that perceived stress and other psychological constructs actually drove the co-occurrence between both symptom clusters. To consolidate the study's findings, Paper 4 investigated the effect of a transdiagnostic psychological treatment approach on different psychosomatic symptom clusters.

Coping

Paper 4 ('Boecking B, Rose M, Brueggemann P, Mazurek B. Two birds with one stone.–Addressing depressive symptoms, emotional tension and worry improves tinnitus-related distress and affective pain perceptions in patients with chronic tinnitus. PLOS ONE. 2021;16(3):e0246747.')

Following Study 2 and 3's findings that emotional tension and worry (1) interacted with personality factors in predicting TRD and (2) partly explained associations between TRD and pain-related experiences,

treatment-related effects remained unexplored. We thus investigated whether treatment-related *changes* in depressivity, emotional tension and worry mediated changes in TRD (and pain perceptions). Treatment comprised a psychologically anchored multimodal treatment programme that combined medical assessment and care for potential otological influences with psychological single, and group sessions. The study yielded two main outcomes. First, treatment was associated with small effect sized-improvements in TRD, affective (but not sensory) pain perceptions, depressive symptoms, emotional tension and worry. Second, depressive symptoms, emotional tension and worry emerged as key predictors of this treatment response and – as such – transdiagnostic treatment targets for alleviating TRD and affective pain perceptions.

Tinnitus and TRD are largely independent constructs – that are likely influenced by different sets of risk factors leading to their onset and maintenance. At the junction of psychosomatic influences on TRD, HL is the main medical risk factor for tinnitus symptomatology – and in itself thus both vulnerability factor (for tinnitus symptom onset) and psychological stressor (potentially contributing to TRD). Having established the effect of a *psychologically* anchored multimodal treatment programme, Paper 5 examined the effects of a *somatically* focused, hearing amplification-based intervention on TRD.

Paper 5 ('Boecking B, Rausch L, Psatha S, et al. Hearing Therapy Improves Tinnitus-Related Distress in Mildly Distressed Patients with Chronic Tinnitus and Mild-to-Moderate Hearing Loss: A Randomized-Controlled Cross-Over Design. J Clin Med. 2022;11(7):1764.vel')

Beneficial effects of HAs on both hearing ability and, secondarily, tinnitus symptom perception were previously established. To this end, current treatment guidelines unanimously suggest amplification-based treatments for individuals with HL (and chronic tinnitus symptomatology) [18,175]. However, potential effects of HAs on *TRD* are much muss less equivocal. The heterogeneity of study results to this regard is likely owed to a mismatch between amplification-based interventions on the one hand and complex, multivariate distress experiences on the other hand. The latter may comprise, but not be limited to, distress linked to HL and/or the tinnitus symptom. To expand on the scarce available evidence, Paper 5 used a randomised controlled crossover design. It assigned $N = 177$ patients with chronic tinnitus and mild-to-moderate HL to a delayed or immediate intervention condition comprising binaural HA fittings. Participants further completed a 14-day CD-based self-learning programme designed to improve attention and auditory skills. Psychological and audiological measurements were obtained at baseline, post-treatment and 70-day follow-up. Results revealed that overall levels of TRD were mild. Against this background, the intervention was associated with significant improvements in this key outcome measure – that were maintained at follow-up.

Results of this work were in keeping with previous findings distinguishing between HA-effects on HL and tinnitus symptomatology on the one – and TRD on the other hand. For example, Wallhäusser-Franke and colleagues reported that HAs improved subjectively perceived tinnitus loudness in individuals with low, but not high TRD-levels [176]. There is a growing consensus in the literature that it is necessary to distinguish between the tinnitus symptom and psychological distress. The latter may include but not be limited to the tinnitus symptom - and therefore be only partially responsive to amplification-based interventions.

Neither the risk factors nor the theoretical research literature is well advised to operationalise TRD as a symptom-specific construct. Instead, research should establish somatic influencing factors (such as HL) as biomedical, symptom-associated risk factors on the one hand; and interpret both these risk factors and symptoms as psychological *stressors* that are processed psychologically within idiographic psychological vulnerability-stress-coping frameworks.

Having examined the effect of psychological and audiological interventions on TRD, Study 6 finally examined psychological influences *on* amplification-based treatment success. To this end, it was of particular interest to investigate (1) if variability in HA-use-time was explained by psychological variables and, if so, (2) whether any such psychological influences might mediate the effectiveness of the HAs on ameliorating TRD.

Paper 6 ('Boecking B, Psatha S, Nyamaa A, et al. Hearing Aid Use Time Is Causally Influenced by Psychological Parameters in Mildly Distressed Patients with Chronic Tinnitus and Mild-to-Moderate Hearing Loss. J Clin Med. 2022;11(19):5869.evel 3.')

Focusing on HA-use-time as both outcome and mediating variable, Paper 6 expanded Paper 5's analyses and studied HA-use-time with regard to psychological influences at baseline and post-treatment or follow-up respectively. Because HA-use-time was retrospectively and objectively retrieved from the HAs at the post and follow-up timepoints, the study could demonstrate that psychological, but not audiological variables causally influenced HA-use-time at the pre- and post-intervention timepoints.

'True' mediation analyses further demonstrated that TRD at baseline influenced HA-use-time, which in turn influenced changes in TRD with treatment. While HA-related benefits on TRD had been previously demonstrated in patients with chronic tinnitus and HL [177–179], Paper 6 was the first to demonstrate a vicious cycle wherein TRD at baseline likely decreased the use of the very intervention likely to benefit it.

Strengths and Limitations

The here-presented studies feature several strengths and limitations. They extend previously available evidence adopting a psychosomatic, rather than primarily audiological perspective on chronic tinnitus: Paper 1 links commonly screened blood indices to vulnerability factors for both tinnitus symptom onset and perceived stress. Paper 2 extends mixed previous findings on the role of personality factors on TRD by adopting an interactional vulnerability-stress perspective. Paper 3 highlights the role of superordinate psychological constructs that overlie different somatic symptom expressions. Paper 4 corroborates these findings by demonstrating that psychological treatment of the overlying factors is associated with improvement across different symptom domains. Paper 5 contributes to as-yet scarce evidence on beneficial effects of amplification-based treatments on (low levels of) psychological distress; and Paper 6 finally demonstrates that such effects are also strongly linked to psychological variables. Overall, the thesis strengthens a psychosomatic narrative wherein biomedical and psychological perspectives complement each other in operationalizing and researching tinnitus risk factors and symptom presentations.

All studies feature considerable clinical sample sizes. Importantly, however, most papers (except for Paper 5) did not feature control groups – and thus disallow for conclusive interpretations, because their results may also have been explained by the passing of time or unmeasured third variables. The reported cross-sectional findings (Papers 1-3) ought to be replicated in controlled longitudinal studies. Similarly, prospectively identified effects (Papers 4, 6) are potentially confounded by the passage of time, spontaneous recovery, non-specific effects or unknown or unmeasured third variables and thus need replicating within randomized controlled designs.

Theoretical Implications

Investigate Biomedical Correlates of the Tinnitus Symptom and Tinnitus-Related Distress

Over the last decade, the medical sector has seen a paradigm shift from symptom-, syndrome-, or diagnosis-based medicine towards personalized medicine that aims to centre on *patients* (rather than *conditions*). This so-called P_4 medicine (personalized, predictive, preventive and participatory) [180] adapts Big Data technologies to identify aetiologically relevant networks of biopsychosocial influences that underlie given patient presentations. Research strands either aim to identify multivariate biopsychosocial phenotypes [181] or argue for dimensional conceptualizations of influencing factors [182].

For chronic tinnitus presentations, P_4 medicine is still in its infancy. As discussed previously, the onset of the tinnitus symptom is likely linked to inner-ear pathologies, whilst psychological appraisals of the symptom likely drive symptom chronification. These appraisals, in turn, occur within a broader context of stimulus processing which, by itself, is dependent upon complex and multivariate vulnerability-stress-coping interactions.

Big Data technologies aim to identify both psychological, behavioural and biomedical correlates of the (onset of the) tinnitus sound as well as associated emotional experiences – with the latter, however, having to be interpreted within a holistic psychological context. Both sets of processes can be examined on the biomedical or psychological level. For example, anxious appraisal of the tinnitus symptom in context of activated aversive memories would be reflected in overlapping neural networks pertaining to attentional, mnestic and emotional processes.

Overall, future research ought to generate and analyse large datasets that map and combine biomedical, psychological and social variables – that are each operationalised from a physiological *and* psychological perspective. To this end, careful variable selection and definition is key – given that any prospective knowledge gain is limited by the variables initially deemed relevant.

Identify and Implement Individualized Biopsychosocial Treatment Pathways

Due to a multitude of (1) biomedical influences that facilitate HL, (2) other biomedical influences that may facilitate tinnitus-symptom onset, (3) biomedical and neurophysiological correlates of psychological distress, and (4) psychological factors that contribute to psychological distress within a holistic and idiographic frame of reference, the identification of individualized treatment pathways is key in offering optimal patient care. These pathways ought to combine medical, psychological and social components that

should be anchored within a meaning-based case conceptualization-, rather than mechanistic problem-solution framework.

For example, a patient's given set of experiences involves

1. biographical experiences and – associated – personality predispositions,
2. dynamic appraisals of intrapersonal and interpersonal stressors (including, but not limited to HL or the tinnitus symptom),
3. dynamic appraisals of intrapersonal and interpersonal resources (including, but not limited to social support networks, educational level, or financial stability), and
4. dynamic intrapersonal and interpersonal coping strategies that are – context dependently - adaptive or maladaptive.

All of these processes are mirrored in dynamically changing neurophysiological networks. Overall, individualized treatment would need to consider this ever-changing system of vast metabolic, neurophysiological and psychological diversity.

To date, advocates of individualized treatment models weigh hitherto 'fruitless' efforts against 'promising' future outlooks [183]. Overall, the translational road from data collection and analysis to translation and clinical implementation remains challenging – mainly due to a need for improved construct definition, psychosomatic operationalization of underlying mechanisms, dimensional, rather than categorical investigation frameworks, and longitudinal study designs.

Use Dimensional Conceptualization Frameworks of (Psycho-)Pathology

A traditional, categorical medical nomothetic assigns symptoms to established diagnoses – which subsequently guide intervention. Medical diagnosis is often based on knowledge of the pathomechanism of symptoms or 'conditions'. Once the medical model is applied to pervasive emotional difficulties, categorical symptom combinations are listed in Chapter F of the 'International Statistical Classification of Diseases and Related Health Problems' (ICD-10) [184], or the 'Diagnostic and Statistical Manual of Mental Disorders' (DSM-5) [185]. The categorical model is well established in somatic medicine. In mental health contexts, however, there are serious conceptual disadvantages to this approach [46]. For example, most symptoms are not disorder-specific [186], and the lack of reliability, validity and clinical usefulness of the diagnostic categories has been convincingly criticised for over 40 years [187–189].

Newer developments in medical nomothetics argue to replace distinct disorder categories with dimensionally operationalised, 'systems medicine' models [180]. These approaches do not understand diseases as 'entities', but as changing expressions of dynamic interplays of continuously distributed biological, psychological and social factors. In a recent opinion piece, Mazurek et al. [190] argue that chronic tinnitus ought to be investigated within such a systems medicine framework. The authors cite an initial study, which used a comparatively large dataset to identify clinical phenotypes that, limited by the nature of the initially provided questionnaires, differed according to physical or behavioural expressions of psychological strain [191].

Analogously, clinical psychology has begun to make a strong scientific case for empirically-supported, dimensional operationalisations of mental distress rather to replace traditional nosologies [192,193].

In future, dimensional conceptualization frameworks may help structure accumulating empirical evidence in a way that is likely to benefit interpretability of heterogeneous results, disciplines, methods and research strands.

Move towards Transdiagnostic Psychological Treatment Approaches

As indicated in Paper 3, dimensionally distributed psychological factors (1) underlie different symptom expressions and thus (2) offer promising foci for both problem conceptualization and treatment planning. Empirically, transdiagnostic psychological treatment presents with a solid empirical evidence base – that lends further support to move 'beyond' 'disorder-' or 'symptom-specific' psychological treatment approaches [194–196]. Future research ought to expand this research base – and combine transdiagnostic nomothetic research with new developments in the psychotherapy field.

Combine Nomothetic Findings with Idiographic, Process-Focused Psychological Theory and Practice

Process-oriented treatment frameworks ('*the future of intervention science*' [197]) offer an interesting and promising new development in how to outperform traditional symptom-focused psychological approaches by considering both 'the general' and 'the unique' [197,198].

Current research consensus states that both chronic tinnitus and TRD are maintained by biological, psychological and social influences. To this regard, Randomized Controlled Trials (RCTs) represent the gold standard of effectiveness research and suggest that psychological treatment approaches can help improve TRD [199]. These studies compare standardised, disorder-specific treatment methods with one or more control conditions. Ideally, this approach results in proof-of-efficacy for a syndrome- or symptom-specific standardised treatment protocol.

Despite the merits of this rigorous scientific approach, researchers, clinicians and patients have begun to question its relevance for nuanced individual experiences. In particular, results from quantitative nomothetic research designs are limited to group mean averages – which cannot reflect interindividual differences in both experience and behaviour. However, it is especially these interindividual differences, that are crucial for a psychotherapeutic understanding of complex vulnerability-stress-coping networks [200] and thereon based treatment plans [201]. Thus, findings from quantitative research do not necessarily apply to individuals 'at all'. Rather, they may offer empirical anchors of potentially relevant 'themes' or 'factors' that may or may not be of importance for any given individual. Therefore, whilst nomothetic frameworks for operationalizing psychopathology and quantitative research designs are important in identifying 'the general' amidst 'the special', these approaches ought to be complemented by idiosyncratic, process-based scientific methods as well as idiographic clinical case conceptualizations.

Summary

The thesis' studies expand on existing literature in the field. Future studies ought to develop this work by using the latest data-analytical technologies to model multidimensional dynamic systems that reflect both biomedical, as well as behavioural and psychological variable networks. Psychotherapeutically, research ought to move towards an integration of nomothetic quantitative findings with idiographic research and

intervention strategies in a bid to (1) increase overall psychological treatment response rates and (2) appreciate the subtlety and nuance in the psychological profiles of individuals with chronic tinnitus.

Clinical Implications

Aim to Prevent Hearing Loss – And Integrate Psychological Factors into Audiological Treatment Approaches

HL continues to be the best established risk factor for initial tinnitus symptom onset [72]. Consequently, particular attention should be paid to associated preventative measures [202–204]. Arguing for a targeted prevention approach, Brown et al. [203] argue for prevention strategies linked to known aetiological factors such as congenital, infection-, nutrition-, noise-exposure-, medication, age-, trauma-, or immune-related influences. They further differentiate between primary (aiming to prevent the development of HL), secondary (aiming to slow the progression of existing HL or limit disability), and tertiary prevention strategies (aiming to successfully treat existing HL). The authors advocate for (1) global vaccination strategies to reduce vaccine-preventable infections such a rubella or meningitis, (2) conservative prescription guidelines for ototoxic medication such as aminoglycosides, and (3) occupational and social prevention of noise-induced HL – most importantly through the (a) routine use of hearing protection and (b) regular, employer-mandated screenings for HL. Because HL is often unnoticed, (4) early detection measures in both children and elderly people are crucial to use interventional windows as early as possible. Lastly, (5) treatment strategies for HL include (a) hearing aids, (b) assistive listening devices, (c) sign language instruction, (d) auditory rehabilitation programmes, or (e) cochlear implants. Genetic or pharmacological treatment options remain largely unsuccessful to date [205,206].

Importantly, however, audiological constructs such as speech comprehension are not mechanistically resolved using sound amplification devices alone. Regarding chronic tinnitus, there is some evidence demonstrating that patients with HL and chronic tinnitus may benefit from HAs as regards their hearing ability and some tinnitus-related parameters [207]. The effect of hearing amplification on emotional *distress* (including TRD), however, is mixed – likely owed to the multivariate nature of emotional distress that involves, but is not limited to HL or the tinnitus symptom respectively [161].

Overall, measures that aim to prevent HL may substantially lower the risk of tinnitus symptom onset – alongside other associated difficulties such as prospective cognitive [208] or psychological difficulties [209]. Notwithstanding, efforts to prevent HL should not mechanistically limit themselves to hearing alone. Rather, HL occurs in context of a broader network of psychological cognitive-emotional and behavioural influences (such as social stigma [210], loneliness [211], increased risk of drug-use [212,213] or potentially heightened levels of frustration and aggression [214]) that equally present as important target points for preventative or interventional measures.

Identify and Support Emotionally Vulnerable Individuals at the Acute Stage to Prevent Symptom Chronification

Current treatment guidelines highlight the multimodal origin of the tinnitus symptom and its emotionally mediated chronification. Indeed, prospective studies assign a key role to depressive or anxious

processing styles for symptom chronification [23,24,215,216]. Thus, early identification of individuals who are expected to process the tinnitus symptom in a psychologically unhelpful manner may lower both cost [217] and symptom chronification rates.

Analogous to preventative measures for HL; primary, secondary and tertiary prevention measures ought to focus on psychological factors known to predispose individuals to or maintain emotional distress in order to prevent symptom chronification. In this vein, measures of psychological support should become accessible across school, occupational and private settings. For example, Wainberg et al. [218] argue for global means to diminish pervasive mental health stigma, build mental health system treatment and research capacity, implement prevention programs to decrease the incidence of mental disorders, and establish sustainable scale ups of public health systems to improve access to mental health treatment.

Curiously, although current guidelines unanimously highlight the role of psychological therapy in successfully ameliorating TRD [18,175], recent publications on the prevention, assessment and management of tinnitus omit psychological prevention measures [219]. Whilst counselling (i.e. de-catastrophizing psychoeducational measures that address myths and potential fears about the tinnitus symptom) is well evidenced and recommended in routine care [18,175], the field may further benefit from establishing and researching low-threshold psychological services – possibly aimed at building psychological resilience [220]. Alternatively, early intervention programmes might wish to provide support during sensitive periods, which have a significant influence on human brain, neuroendocrine, cognitive or psychosocial development respectively [221].

Understand and Conceptualize 'Tinnitus-Related Distress' within a Broader Psychological Context – And Do Not Confuse Correlation and Causation

TRD reflects emotional distress that is attributed to (and not necessarily caused by) the tinnitus symptom – often in context of previously existing vulnerability or other concurrent sources of emotional distress. Indeed, ecological momentary assessment measures recently demonstrated that fluctuations in TRD ratings paralleled general emotional distress levels [135]. As such, the idea of 'tinnitus-related' distress might be misleading, as it may prove difficult for individuals to 'allocate' their distress experiences to a clearly defined univariate 'cause'. Thus, it is clinically crucial to assess and formulate psychological distress within idiographic vulnerability-stress-coping frameworks that do not limit themselves to 'tinnitus' as 'the problem', but aim to conceptualize interactions between patients' complex and dynamic outer and inner psychological environments.

Whilst patient narratives often suggest a causal relationship between 'tinnitus' and 'distress', clinicians must always consider broader influences on the reported emotional distress experiences. In particular, medical attributions of emotional distress must be sensitively formulated – as organic causal beliefs have been associated with higher levels of unnecessary medical examinations, symptom expression, feared illness consequences, and other psychological maintaining factors such as bodily scanning [222].

Integrating psychological research and clinical observations, TRD is best explained by considering (1) an individual's past experiences, (2) resulting beliefs about self and others-to-self, (3) external and internal

stressors and resources and, importantly, (4) their subjective appraisals, as well as (5) intra- or interpersonal coping strategies aimed at stabilising self-image, regulating emotion, or achieving motivational goals.

Because both TRD and subjective symptom intensity fluctuate parallel to individuals' general emotional states [135,223,224], it is crucial to formulate relevant influencing factors idiographically [121,225–230]. Only when a person's emotional experience (and TRD as part thereof) has been explored in the context of a detailed psychosomatic assessment, can a psychological case conceptualization be formulated and a treatment plan derived.

Treat Chronic Tinnitus Multimodally – and Target Audiological Tinnitus-Symptom-Related and Broader Distress-Related Psychological Factors

Once chronified, current treatment guidelines suggest a stepwise approach that includes hearing amplification measures [18,175] alongside psychotherapeutic treatment options for individuals with high levels of emotional distress prior to or following symptom onset [199]. Here, case conceptualisation approaches are ideally suited for mapping and interpreting biopsychological interdependencies from both medical and psychological perspectives.

Understand and Conceptualize the Idiographic Meaning of the Tinnitus Symptom and Tinnitus-Related Distress

A comprehensive understanding of TRD is often hampered by (1) its nomenclatural mingling with the tinnitus symptom (e.g. 'tinnitus severity' implying *symptom*-, whilst actually referring to *distress* severity [231]) as well as (2) largely linear and unidimensional modelling of influencing factors in the research landscape to date.

Much has been said about tinnitus being 'heterogeneous' – referring to a mix-up of tinnitus symptom and distress, indiscriminate patient populations with varying underlying or not-yet-identifiable (inner-ear) pathologies, and a generally self-limiting application of a categorical medical, rather than dimensional biopsychosocial understanding of its phenomenology [232].

Psychologically, part of this heterogeneity is owed to the fact that nomothetic research largely ignores idiographic contexts wherein the tinnitus symptom occurs as part of a much broader psychological landscape [233]. In order to understand the self-maintaining nature of TRD from a psychological point-of-view, relevant psychological variables ought to be assessed and integrated using psychological case conceptualization frameworks. These frameworks can account for individual differences in psychological experiences that are difficult to capture in nomothetic research designs.

A decade ago, Richard Hallam, a pioneer of tinnitus research, also advocated for the use of individual case conceptualization frameworks [234] and suggested comprehensive training programmes for individual case conceptualization skills [235]. Idiographic case conceptualisation forms the basis of psychological problem understanding and treatment planning. It relates feedback loops between a person's experiences and behaviours to their biography as well as to each other [236] – thereby explaining the maintenance of emotional distress [19,237]. Psychological case conceptualisation understands the symptom level

of mental health difficulties not as ‘the problem’, but as ‘maladaptive coping attempt’ as part of broader, psychologically complex problem constellations [238].

Consequently, psychological treatment plans are not anchored at diagnoses or symptoms of ‘a disorder’, but at the *meaning* and *function* of the reported symptoms for relationships, needs, identity, emotions, and a person's self-image [239–241]. Case conceptualisation can thus be understood as a dynamic ‘process of ongoing collaborative meaning-making’ between psychotherapist and patient that places a person's experiences within a meaningful psychological context [242].

Target Transdiagnostic Psychological Mediators of Treatment Change and – if psychiatrically minded – their Neurobiological Correlates, not ‘Symptoms’ or ‘Diagnoses’

The here-presented papers suggest psychological variables as transdiagnostically relevant treatment targets. Transdiagnostic psychological approaches [169,228,243,244] appear helpful in effecting psychological benefit across a variety of symptom domains. Moreover, dimensional conceptualization frameworks appear helpful in identifying nomothetic psychological constructs that may underlie a variety of different symptom patterns [192,245]. Equally, psychiatric research has also begun to focus on biomedical correlates of transdiagnostic psychopathology constructs to promising effect [246,247].

Summary

In summary, the present thesis has several clinical implications, which directly translate into patient care. Treatment approaches should

1. Continue to address both HL and psychological distress experiences within audiological and psychologically anchored treatment models
2. Normalize and de-catastrophize symptom onset as well as initial distress experiences – and provide psychological support following initial symptom onset to emotionally vulnerable individuals
3. Conceptualize TRD experiences idiographically within a broader context that considers early experiences, current stressors and resources, internal psychological symptom representation, and individually meaningful intrapersonal or interpersonal coping strategies, and
4. Investigate the effectiveness of interventions, which emphasize holistic case conceptualizations and use contemporary paradigms of transdiagnostic, emotion-focused psychological treatment strategies [248,249].

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Statutory Declaration / Eidesstattliche Versicherung

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Datum: 22.01.2024

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