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ASSOCIATIONS BETWEEN STRESS AND HEARING PROBLEMS

EPIDEMIOLOGICAL AND EXPERIMENTAL FINDINGS

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ABSTRACT

It is well established that long-term stress without sufficient recovery can induce plastic changes in certain brain regions by suppressing neural growth or by retraction of dendrites [1-4]. Many of these effects can be due to a dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis, which is the principal system controlling systemic stress response. While being a well known risk factor for several psychological disorders, e.g. depression, schizophrenia, and bipolar disease [5-7], little is known about the effects of long-term stress in relation to the auditory system. Therefore, the aim of this study was to explore the relationship between long-term stress and hearing problems. The specific aims of the study were to i) determine whether there is a relationship between hearing problems and different measures of health and work related stressors in the Swedish working population, ii) to determine whether the ability to hear speech in noise varies with emotional exhaustion (EE), before and after an acute stress task, iii) to validate a hyperacusis questionnaire (HQ) in different strata of EE, and iv) to validate a personal heart rate monitor (Polar RS800) against a traditional ECG-method for assessment of heart rate variability. Two different research approaches were used: a) an epidemiological questionnaire-based study involving 9,756 working Swedes, and b) an experimental study involving 348 individuals aged 23 to 71 years, with low, intermediate or high levels of EE. In the epidemiological study, stress and hearing problems were assessed with self-rating scales for hearing complaints, tinnitus and EE. In the experimental study, hearing in noise (HINT) and uncomfortable loudness levels (ULLs) were assessed before and after an acute stress task. Pure tone audiometry (PTA), tinnitus, heart rate variability (HRV) and EE were assessed at baseline only. The results of the epidemiological study demonstrated a statistically significant higher prevalence of hearing problems in individuals exposed to work-related stressors or threats, such as occupational stress, poorer self-rated health, long-term illness, poorer sleep quality, higher burnout scores, more symptoms of long-lasting stress, and higher performance-based self-esteem. The results revealed new risk factors for the auditory system that have not been described previously. The results from the experimental study demonstrated that, when adjusting for age and hearing loss, higher levels of EE were associated with a poorer ability to hear speech in noise in both men and women. The validation study of the HQ demonstrated significant correlations between the HQ and ULLs on both ears in those with intermediate and high EE but not in individuals with low EE. All correlations were negative, indicating that higher HQ-scores are correlated with lower ULLs. Taken together this thesis presents new evidence for associations between long-term stress and different types of hearing problems. In particular the results suggest that the potential role of long-term stress as an underlying factor in auditory pathology should be considered in clinical settings.

LIST OF PUBLICATIONS

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CONTENTS

LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
ANS	Autonomic nervous system
CAN	Central autonomic network
CVD	Cardiovascular disease
EE	Emotional exhaustion
HF	High frequency (heart rate variability)
HINT	Hearing in noise test
HPA-axis	Hypothalamic-pituitary-adrenal-axis
HQ	Hyperacusis questionnaire
HRV	Heart rate variability
ICC	Intraclass correlation
LF	Low frequency (heart rate variability)
LOA	Limits of agreement
MBI	Maslach Burnout Inventory
MBI-GS	Maslach Burnout Inventory General Survey
MBI-HSS	Maslach Burnout Inventory Human Services Survey
PFC	Prefrontal cortex
PNS	Parasympathetic nervous system
PTA	Pure tone audiometry
SCB	Statistics Sweden
SDNN	Standard deviation of normal R-peaks
SEM	Standard error of measurement
SES	Socio-economic status
SNHL	Sensorineural hearing loss
SNS	Sympathetic nervous system
SOC	Superior olivary complex
ULL	Uncomfortable loudness level

1 INTRODUCTION

Hearing problems are an increasing issue in today's society, with hearing loss alone affecting more than 250 million people worldwide [8]. In 2002, the WHO estimated hearing loss to be the 13th most frequent burden of disease in medium- and high-income countries [9], and it is projected to become among the top ten by the year of 2030. Epidemiological studies have reported the prevalence of hearing loss [9-10] and tinnitus [11-12] to be between 10 and 15 % in the general population, while 8 to 9 % of the Swedish population are estimated to suffer from hyperacusis [13]. In addition, a recent study found that approximately 31 % of the Swedish working population report hearing complaints, tinnitus or both [14].

The deleterious effects of mechanical stress (i.e. noise) on hearing have been studied extensively in both animal models [15] and human populations [16-17]. More recently, however, the idea of emotional or psychosocial stress as a modulator of the auditory system has received increased attention. A complex set of pathways of the stress response, involving both sympathetic stimulation of adrenergic α-receptors within the cochlea [18-19], have been identified. In addition, stress has been shown to affect the auditory system via neuro-endocrine hormones, e.g. cortisol, by engaging the hypothalamic-pituitary-adrenal-axis (HPA-axis) [20]. Animal studies have shown that acute stress may protect the sensory cells of the inner ear from noise trauma. This effect is, at least partially, mediated by the HPA-axis [21-24]. The best studied function of glucocorticoids is their role in immune system modulation and inhibition of inflammation. The basic mechanism through which glucocorticoids induce anti-inflammation is by stabilizing lysosomal membranes and prevent them from rupturing. Animals that are exposed to damaging levels of noise after exposure to restraint stress exhibit a decreased susceptibility to permanent threshold shifts, compared to animals that are not acutely stressed [22]. This can in part be explained by an increased expression of glucocorticoid receptors in the cochlea and in the paraventricular nucleus of the hypothalamus, providing additional docking sites for corticosteroid ligands [21].

Long-term stress, on the other hand, appears to make the organism more prone to auditory dysfunctions [25]. Research on orchestra musicians has demonstrated that self-reported hearing problems are associated with physiological and psychological measures of stress [26]. It has also been found that individuals suffering from tinnitus exhibit a lower salivary cortisol response after acute stress compared to healthy controls, implying a dysregulation of the HPA-axis [27]. Thus, there is accumulating evidence suggesting a link between long-term stress and different types of hearing problems; however this relationship has not been studied extensively in humans.

1.1 LONG-TERM STRESS AND DISEASE

1.1.1 The autonomic nervous system and the stress response

The autonomic nervous system (ANS) is generally considered to entail two separate and counteracting branches: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). While the activity of the SNS is associated with catabolism and mobilization of the organism, activation of the PNS is associated with anabolism and restoration of the organism. Theories of stress have traditionally

focused on physical stressors that too often or too long require an organism to mobilize and adapt, thereby causing strain.

In the late 1920s, Cannon suggested that emotional stress is associated with ill health and that it plays a key role in the development of physical disease [28]. The first attempt to explain how emotions are related to physical disease was made by Papez in 1937. Papez [29] proposed a model in which three main structures constitute the anatomical basis of emotions: the hypothalamus, the gyrus cinguli, and the hippocampus. Building on this work, MacLean [30], in 1952, put forth a new theoretic framework of a functional network for emotions which involves both the limbic system and cortical structures. In 1956, Selye introduced the term stress to describe the effects of environmental challenges on an organism. He proposed a three-stage model to describe the stress response: alarm reaction, resistance, exhaustion [31]. The model is still today commonly referred to in stress research.

Since this pioneering work, advances in the neurosciences have led to a better understanding of the processes and structures involved in maintaining autonomic balance. Benarroch [32], in 1993, put forth a model describing the *central autonomic network* (CAN) as a functional unit of the ANS, through which the brain regulates viscero-motor, neuro-endocrine, and behavioral responses. The model emphasizes the inhibitory processes within and between the prefrontal cortex (PFC) and the amygdala, suggesting them to be essential for organism flexibility, adaptability, and health.

Similar models representing a common central functional network have been suggested by others, the two most recognized perhaps being *the anterior executive region* [33] and the "*emotion circuit"* by Damasio [34]. Thayer [35-36] describes the sympatho-excitatory subcortical circuits to normally be under tonic inhibitory control by the PFC. In situations of perceived threat or uncertainty, the PFC becomes hypoactive which leads to a disinhibition of sympatho-exitatory circuits, ultimately resulting in a general mobilization reaction commonly referred to as the fight or flight response. One characteristic feature of the model is that there needs to be a dynamic balance between sympathetic and parasympathetic processes in order for the organism to remain healthy. This view is shared by several others, and today it is widely accepted that inhibitory processes within the central autonomic nervous system play an essential role for autonomic balance and health.

1.1.2 Homeostasis and allostasis

Most scientists today would agree that prolonged failure to inhibit stress responses at the cortical level leads to wear and tear of the system, eventually resulting in maladaptation of the organism and ill health. However, the traditional view of stress as a modulator of homeostasis has been elaborated on in contemporary stress research. McEwen [37], instead of speaking of homeostasis, uses the term allostasis to describe the cost of adapting to a demanding or threatening situation, and suggests that failure to effectively cope with stress eventually leads to allostatic overload. According to McEwen [37], allostasis denotes the ability of an organism to adapt physiologically and behaviorally to the demands of a situation. Contrary to the concept of homeostasis, which can be seen as coordinated physiological processes that must be kept within a narrow range (e.g. body temperature and pH), allostasis refers to the dynamic variation of certain systems to meet challenges. Examples of such adaptive responses are the release of stress hormones, the elevation of blood pressure and the increased synthesis

and release of cytokines when exposed to a demanding situation. While the adaptation of an organism to current demands can be seen as an important function of allostasis, it also plays an important role in maintaining homeostasis. An illustration of the allostasis model is presented in Figure 1.

When studying stress the most important organ is the brain, since it receives, integrates and interprets sensory input and generates the appropriate autonomic and behavioral responses. In an acute event, a rapid stress response that allows the organism to adapt to a threatening situation is essential for survival. The systemic release of cortisol via the HPA-axis and catechol-amines, via the sympatho-adreno-medullary-axis, enable fast mobilization while vegetative functions are suppressed. Cortisol also has anti-inflammatory actions, aiding in the repair of potentially damaged tissue. Adrenal steroids have been shown to exert biphasic effects on the immune system, stimulating the translocation of immune cells from the blood to the periphery where they may engage in wound healing and protect from infections [38]. Additionally, glucocorticoids and catechol-amines are involved in memory formation in emotionally charged events [39]. Conversely, overstimulation of this system leads to a dysregulation of the HPA-axis which controls cortisol release [38]. Chronically elevated levels of stress hormones have been shown to impair cognitive function and induce plastic changes in certain brain regions, such as suppressing neural growth in the dentate gyrus [3], as well as causing remodeling and retraction of dendrites in the hypothalamus, hippocampus, and the PFC [1-4]. It is thus conceivable that plastic changes in the central nervous system could also affect central auditory processing and interpretation.

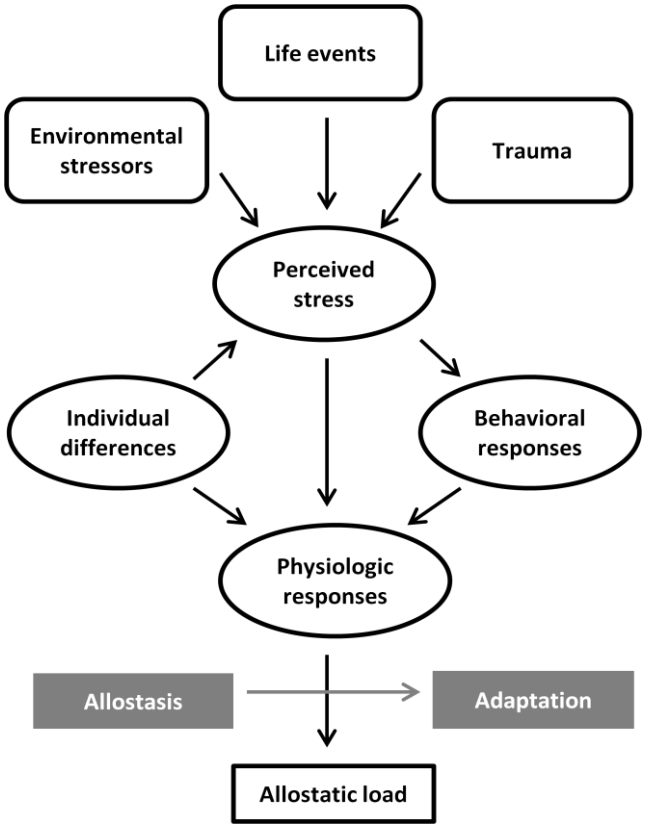

Fig 1. Environmental factors, life events and genetics influence how situations of daily life are perceived. Perceived stress induces behavioral and physiological responses that allow the individual to adapt to demands. When prolonged, this reaction may lead to allostatic load and eventually overload.

1.1.3 Heart rate variability

To study autonomic balance directly in humans is problematic since this would require invasive electrophysiological assessment of vagal activity. As an alternative, autonomic balance can be studied indirectly, by assessing heart rate variability (HRV). Operationally, measures of HRV are conceived to reflect the balance between sympathetic and parasympathetic processes of the autonomic nervous system (ANS) [40]. Due to the dual sympathetic and parasympathetic innervation of the heart, periodic changes in heart rate during relatively static conditions may be deduced to autonomic output. Parasympathetic activity is thought to be indirectly related, via vagal output, to respiratory sinus arrhythmia (RSA), a phenomenon characterized by the periodic up- and down regulation of the heart rate at the pace of breathing [41]. The fact that parasympathetic activity is dependent on the active inhibition of higher neural circuits makes it possible to measure this phenomenon by means of vagal activity.

RSA is commonly quantified in the high frequency (HF) domain (0.15 - 0.40 Hz) of HRV, where any variation is considered to be predominantly influenced by parasympathetic activity. However, more simple measures of HRV in the time domain (TD) have been found to correlate well with HF HRV. For instance, the standard deviation of interbeat intervals (SDNN), the root mean square of successive differences (RMSSD), and the percentage of interbeat intervals greater than 50 ms (pNN50), are all considered to reflect vagal activity [42].

Cyclic variations in heart rate are also evident at lower frequencies. Low frequency HRV typically occurs at a pace of 0.1 Hz and is thought to mainly be regulated by sympathetic activity. While sympathetic blockade abolishes most of the variability, a minor part of the LF-variability is considered to be accounted for by parasympathetic activity [43]. Additionally, fluctuations in heart rate can also be found in the ultra-low frequency domain (0.01 Hz). Even though the physiological basis for these very slow variations is not well understood, it has been suggested that they represent autonomic changes related to thermoregulation [44], cardiac chemoreceptor activity [45], and fluctuations within the renin-angiotensin-aldosterone-system [46].

HRV has been linked to a number of diseases, mental states and health factors. It is rather well established that higher variations of consecutive heartbeat intervals, as well as periodic changes over certain frequencies, are associated with positive health outcomes. Lower variations, on the other hand, are associated with negative health outcomes. Different measures of HRV have for instance been shown to predict cardiovascular disease (CVD), such as hypertension [47-49], cardiac dysfunction [50], progressive heart failure [51], and sudden cardiac death [51-52]. Furthermore, studies of elderly people [53] and the critically ill [54-55] have shown HRV to be a strong predictor of mortality. There have also been connections made to metabolic disorders, like obesity [56-57] and diabetes [58-60], as well as to several other co-morbidities [61-63]. Additionally, research within the field of psychiatry has linked HRV to a variety of psychological disorders, such as depression [64-65], anxiety disorders [66-67], bipolar disease [68], and schizophrenia [69-70].

Evidence from a range of medical fields suggests that mood disorders not only often coincide with a variety of diseases, e.g. CVD, stroke, diabetes, cancer, and epilepsy, but may also serve as etiologic factors of these outcomes [71-72]. A number of studies have found associations between improved health outcomes and increased levels of HRV, such as after the treatment of depression, anxiety, and stress [73-74].

High HRV-values have been related to healthy longevity [75]. Thus, there is ample support in the literature for the notion of HRV as a valid indicator for health and disease. An important factor to consider when assessing HRV is that acute stress may strongly influence the results, thereby making interpretations regarding long-term autonomic balance difficult. One way of handling this is to assess HRV over a 24-hour period or over several shorter periods and use the mean value. However, single 5-minute recordings have been shown to correspond well to 24-hour recordings [76].

1.1.4 Emotional exhaustion

The concept of burnout arose in the 1970s to describe the dysfunctional relationship between a worker and his workplace. Since then, several instruments have been proposed for assessing burnout, of which the Maslach Burnout Inventory (MBI) has become one of the most widespread. According Maslach and Jackson's model (2001) [77], burnout, defined as a prolonged response to chronic emotional and interpersonal stressors in the work-place, constitutes three core dimensions: emotional exhaustion (EE), cynicism (depersonalization), and inefficacy (reduced personal achievement) [77]. Within this context, burnout is viewed as a type of strain resulting from work-related stress.

To address differences between different work areas, three versions of the MBI have been developed. The first, called the MBI-Human Services Survey (HSS), is aimed at individuals working in human services and in health care. The second, called the MBI-Education Survey (ES) was developed to assess burnout in individuals who work in the education-sector, whereas the MBI-General Survey (GS) was developed for people in occupations that are less people-oriented [77].

According to Maslach et al [77], EE, or just exhaustion, is the core component of burnout. Importantly, EE reflects the stress dimension of burnout. It has been argued that EE is the only factor relevant for burnout, even though this view is controversial. Arguably, even if EE is the decisive factor for burnout, it does not necessarily cover all aspects of the work-person relationship. Recent studies attempting to determine the time-course of burnout have found that the order in which the three dimensions of burnout develop differs between men and women. Specifically, it has been found that in men, burnout is triggered by depersonalization, while it seems that EE is the trigger in women. Another important gender-difference repeatedly reported is that women in general score higher on EE than men [78].

1.2 AUDITORY FUNCTION AND DISEASE

1.2.1 Basic physiology of the auditory system

The peripheral auditory system

The physiology of hearing can be divided into peripheral and central components. The peripheral auditory system entails three functional parts: the external ear, the middle ear and the inner ear. Sound waves entering the ear are focused onto the tympanic membrane, where airborne sound energy is transduced across the bones of the middle ear - the malleus, incus and stapes. Two small muscles, m. tensor tympani and m. stapedius, connect to the malleus and the stapes, respectively, and are both innervated by cranial nerves V and VII. These muscles contract reflexively to loud or sudden sounds, thereby regulating the amplitude of sound entering the inner ear. From the middle ear, sound waves are transduced across the oval window into scala vestibuli that results in basilar membrane motion and a consequent depolarizing or hyperpolarizing response of the inner hair cells. Postsynaptic dendrites of spiral ganglion neurons transmit the generated impulses to the vestibulo-cochlear nerve.

The central auditory system

Electrical impulses from the auditory nerve transmit information to the cochlear nucleus in the brainstem. Here the nerve fibers innervate the anteroventral cochlear nucleus and the posteroventral and the dorsal cochlear nucleus, respectively. From the cochlear nucleus complex, ascending projections extend both ipsilaterally and contralaterally to the superior olivary complex. From here, postsynaptic axons connect, via the nucleus of the lateral lemniscus, to the inferior colliculus. The last synaptic junction in the auditory pathway, before reaching the auditory cortex, is located in the medial geniculate complex of the thalamus (Figure 2).

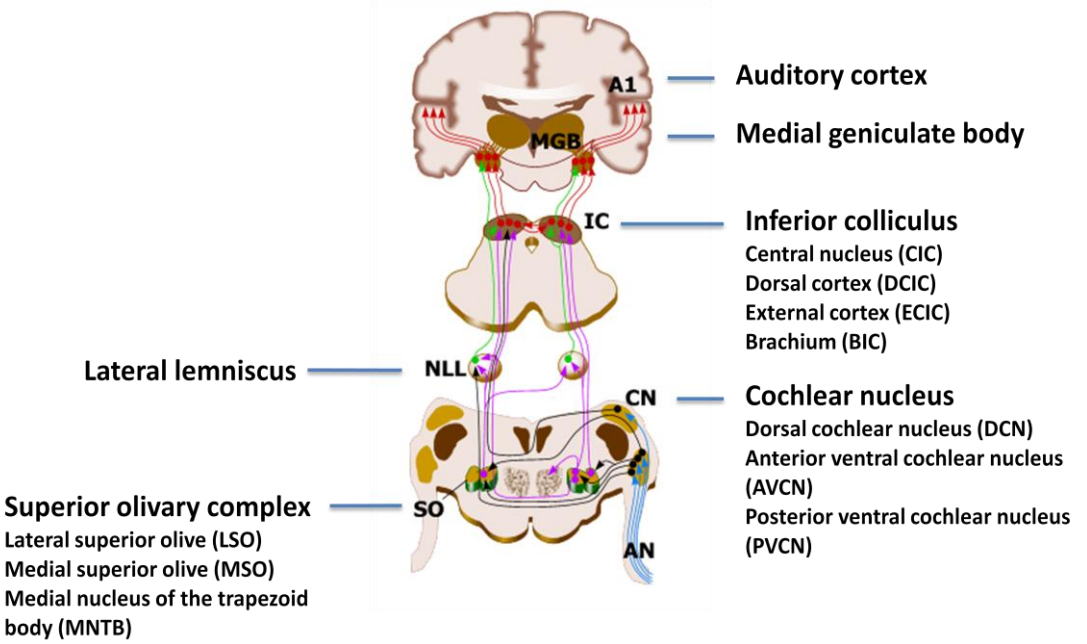

Fig 2. Illustration of the central auditory system and the main pathways (Artist: Sonia Charitidi).

The auditory cortex comprises two functional structures: the primary auditory cortex and the secondary auditory cortex. The primary cortex is situated in the medial transverse temporal gyrus called Brodmann's area 41. It is connected to the larger secondary area which encompasses Broadmann's areas 42 and 22, and even includes the lateral transverse temporal gyrus, spanning anteriorly and posteriorly into the superior temporal plane [79].

Autonomic control of the auditory system

Cochlear blood flow is regulated by the SNS [80]. The cochlea receives innervations from two sympathetic branches originating from the superior cervical ganglion and the stellate ganglia. Both branches enter the inner auditory meatus together with the cochlear artery and follow the spiral modiolar artery into the cochlea. Here one branch follows the arterioles and venules that extend throughout the lateral wall of the cochlea. The other branch forms synapses with afferent fibers of the spiral ganglion and with afferent and efferent neurons in Rosenthal's canal. Blood flow within the cochlea is regulated via tonic stimulation of α-adrenergic receptors situated on the vessels, stimulating local vasoconstriction [80].

The central auditory pathway is also under autonomic control. A descending sympathetic pathway between the midbrain and the cochlea that originates from the superior olivary complex (SOC) has been identified. Specifically, lateral olivo-cochlear neurons are connected to afferent dendrites adjacent to the inner hair cells, and medial olivo-cochlear neurons form synapses with outer hair cells [81-82]. These areas in the SOC are, in turn, innervated by noradrenergic neurons originating from the locus coeruleus [83]. Experimental evidence suggests that the central noradrenergic pathway modulates hearing by elevated hearing thresholds. Additionally, noradrenaline has been shown to interact with neurons in the SOC, acting mainly as an excitatory neurotransmitter in this area [84].

1.3 HEARING PROBLEMS

There are four different types of hearing problems that this thesis discusses: sensorineural hearing loss (SNHL), difficulties hearing speech in noise, tinnitus, and auditory hypersensitivity (hyperacusis). Each of these disorders is presented in more detail below.

Sensorineural hearing loss

Hearing loss can be either conductive or sensorineural in nature. While conductive hearing loss refers to an obstruction or pathology located in the external or middle ear (e.g. infections, otosclerosis or tumors), SNHL refers to the disruption of sensorineural signaling, or to pathology somewhere along the central auditory pathway. The distinction is important since most conductive issues are curable, while sensorineural damage is irreversible. An estimated 250 million people worldwide suffer from SNHL [9]. In western civilizations the prevalence of SNHL is estimated to be between 10 - 15 % in the adult population [9-10]. Among the known risk factors are noise exposure, smoking, diabetes, and age. Also, men are affected to a greater extent than women [85], a phenomenon that may in part be mediated by estrogen receptors. A hallmark of age-related hearing loss is that thresholds at higher frequencies are affected first. In comparison, accumulated noise exposure or acute noise trauma usually also

manifests as elevated thresholds at frequencies corresponding to speech sounds, i.e. between 1 - 4 kHz and up.

Difficulties hearing speech in noise

Most epidemiological studies use pure tone thresholds to describe the prevalence of hearing loss in a population. However, hearing in everyday life requires more than just being able to hear pure tones. The ability to understand speech is a far more complex task compared to the sensory perception of pure tones since it requires the synchronous interaction between auditory input and cognitive processes such as attention and memory. When adding background noise to speech sounds, the task becomes even more complex. For a listener to identify speech in background noise, an auditory object must be formed based on spectral and temporal cues. This is a necessary step in stream segregation, a process that allows the listener to focus on one particular sound source among many. In a process termed auditory grouping, certain vocal features are identified in the speaker's voice. This is a necessary step for being able to follow a conversation. The ability to form auditory objects and to separate multiple sound sources into distinct streams is mediated by top-down cognitive processes such as attention and working memory [86].

While simpler word repeating tasks mainly activate auditory and motor areas within the brain, the addition of noise activates linguistic, attentional, cognitive, working memory, and motor planning areas [87]. The process of selecting relevant auditory input from irrelevant auditory input, or any sensory input that is of subordinate relevance for the task being, largely takes place at the level of prefrontal areas 10 and 46. Brodmann's area 10, also known as the frontopolar area, is in particular known to be heavily activated in multimodal tasks. Areas 46 and 9, both part of the dorsolateral PFC, primarily engage in working memory functions. These areas are innervated by the anterior cingulate cortex (ACC) which strongly interacts with dorsolateral prefrontal areas during working memory tasks and with the frontopolar area when certain cognitive tasks need to be prioritized and others suppressed (for review see [88]). In contrast to the dorsolateral PFC, the ACC is bi-directionally connected to limbic structures and is involved in cognitive-emotional tasks [89]. The ACC also plays an important role for attentional control; however the mechanism through which this function is mediated remains unexplored.

Additionally, some evidence suggests that speech in noise is not exclusively processed at a central level, but that efferent pathways are involved via a medial olivo-cochlear feedback loop [90]. Failure at any level of sound processing hampers the possibilities of following a conversation in typical environments of everyday life. Indeed, it has been reported that that individuals with poor speech in noise thresholds may still display normal pure tone thresholds [91]. Thus, there are multiple levels at which processing of speech in noise may be compromised.

Tinnitus

Tinnitus is defined as a continuous perception of a sound in the absence of a physical source. It is estimated that about 8 % of the general population suffer from frequently occurring tinnitus, and about 1 - 2 % experience significant distress from it [92]. Since there is no physical source of the sound, tinnitus is considered to be a phenomenon similar to central neuropathic pain [93]. Electroencephalographic [94] as well as neuroimaging [95] studies have suggested that tinnitus is characterized by an abnormal

neural activity and reorganization of the central auditory nervous system. Specifically, tinnitus has been correlated with an increased neural firing within the central auditory pathway, where the thalamo-cortical connection in particular has been found to be dysregulated [94]. In animals, electrophysiological studies suggest that dorsal cochlear nucleus (CN) [96], as well as the inferior colliculus (IC) [97], are involved in tinnitus generation. However, neuro-anatomical correlates of tinnitus, measured either as increased excitation or decreased inhibition, have been found on almost every level in the central auditory pathway [98]. It has been suggested that in those cases when tinnitus is associated with sensorineural hearing loss, regions that were once represented by a damaged area become occupied by adjacent frequency regions. The cortical representation of these frequency areas will then be over-represented. In addition, since these regions become deafferented they lose the inhibitory control from the periphery that they normally are under, resulting in neural hyperactivity [99-100]. Interestingly, deafferentation has been reported in tinnitus patients even in the absence of a sensorineural hearing loss [100].

Moreover, it has been suggested that the neuropathological features of tinnitus change over time. While hyperactivity within the central auditory pathway is a main characteristic of tinnitus in the sub-chronic phase, chronic tinnitus patients display a diminished activity between these regions. At the same time, an increased activity within each individual region has been observed in the chronic state [95]. In addition, structural and functional differences between tinnitus patients and non-tinnitus controls have been reported in networks outside the auditory pathway, e.g. the anterior cingulate and the dorsal PFC, and in limbic areas such as hippocampus and amygdala [101-103], as well as nucleus accumbens [102], the ventromedial PFC [102, 104], and in frontal paralimbic areas [105].

In addition, increased activity in efferents projecting from nucleus accumbens to the medial geniculate nucleus of the thalamus has also been implied in tinnitus [102]. The increased firing of these neurons has been interpreted as a failure of the ventral striatum (nucleus accumbens) to cancel sound signals that are generated elsewhere. This failure is, in turn, thought to characterize the development of chronic tinnitus [102]. Some of these findings are however inconclusive, as illustrated by a recent neuroimaging study that could not find any abnormalities in subcallosal or thalamic areas in tinnitus patients as suggested above, but instead found increased activity in the right inferior colliculus and in the left hippocampus [106]. Thus, neuroimaging studies are somewhat inconclusive in identifying anatomical and functional correlates of tinnitus, suggesting that the pathophysiology of tinnitus is complex and heterogeneous.

Auditory hypersensitivity and hyperacusis

Hypersensitivity to sound is a complex phenomenon with several different origins. The causes can be due to pathology of the peripheral auditory system, the neural auditory system, and/or to hormonal or infectious diseases [107]. Hyperacusis, a special form of auditory hypersensitivity, is commonly defined as an abnormally high amplification of sounds that are within a normal loudness range. Individuals suffering from hyperacusis commonly have hearing thresholds within a normal range [108-109]. As in the case of tinnitus, the mechanisms behind hyperacusis are not well understood [110]. However, several authors have suggested that an abnormal increase in central gain, possibly due to a dysregulated auditory efferent system at the medial SOC nucleus [111],

may be implicated in hyperacusis (for review see [112]). Moreover, it has been suggested that emotional stress may play a role in the development of the disorder [107].

Hyperacusis differs from other similar phenomena associated with auditory hypersensitivity, e.g. phonophobia, misophobia, or recruitment of loudness [109]. While phonophobia refers to a fear of only certain sounds or to sounds that are associated with a particular situation, misophobia is characterized by a strong dislike of a particular sound. Misophobia may occur together with hyperacusis, and it may develop into phonophobia at a later stage [107, 109]. Recruitment of loudness, on the other hand, refers to an abnormal increase in perceived loudness associated with the degeneration of outer hair cells [113]. Hyperacusis can be assessed either with self-rating questionnaires or by measuring uncomfortable loudness levels (ULLs) using an audiometer. The association between self-rated questionnaires and audiological measures of hyperacusis has previously been found weak [114-115], which raises the question to what extent self-rated and audiometric instruments measure the same construct. The fact that hyperacusis is sometimes defined and operationalized differently between studies, makes it difficult to draw any firm conclusions about its prevalence. This fact is reflected in the varying prevalence figures reported for hyperacusis, with numbers ranging between 6 - 8 % [13] to 15 % [116]. This project includes a validation study of a hyperacusis questionnaire [117], where self-reported hyperacusis is correlated with ULLs in individuals with low, intermediate, or high levels of EE.

1.4 HOW LONG-TERM STRESS CAN AFFECT THE AUDITORY SYSTEM

There is growing evidence that stress can alter auditory function both peripherally and centrally. It has been suggested that one mode though which long-term stress may induce hearing problems is by compromising cochlear blood flow. From a physiological perspective, psychosocial stress causes vasoconstriction of the blood vessels supplying the cochlea via stimulation of adrenergic α-receptors. If sustained over a prolonged period of time, this reaction is thought to induce hypoxia, potentially resulting in hearing loss, tinnitus, or sudden deafness [118]. The rationale behind this hypothesis is the notion that vascular abnormalities in the cochlea are associated with several hearing disorders, including presbycusis, noise-induced hearing loss, tinnitus, and more (for review see [119]). Although rationally conceivable, the theory is difficult to test empirically.

Furthermore, indirect evidence suggests that long-term stress may not only affect the peripheral auditory system, but can also modulate central components that are involved in auditory processing at different stages. As outlined before, one area of particular importance for sensory processing is the PFC. Although heterogeneous and complex, one important task of the PFC is to selectively focus attention on stimuli that are relevant, while at the same time actively suppress distracting information. A functional system constituting the auditory associative cortex and the medial PFC has been identified [120]. This system is used as a model in neuro-scientific research to describe two modes of action for goal oriented information processing: focusing attention on relevant information while at the same time suppressing irrelevant information. The neuro-anatomical basis for this hypothesis is the identification of both excitatory and inhibitory neurons projecting from the auditory association cortex to the lateral PFC. These findings are in line with evidence from clinical research, demonstrating that schizophrenic patients and patients with dorsolateral PFC lesions

suffer from compromised auditory gating as evidenced by delayed or absent suppression of a secondary signal in a secondary auditory pulse pair test (for review see [121]).

Another brain area of particular interest for auditory research is the medial PFC which entails the ACC. The ACC has important connections with auditory association areas and is also involved in the control of attention and emotions. In addition, connections between the posterior orbitofrontal cortex (pOFC) and sensory cortices are closely associated with pathways involving the amygdala, which directs behavior within an emotional context [122]. The significance of intact connections between cortical and limbic structures cannot be overstated. In fact, disruptions of cortico-limbic connections have been implicated in several psychiatric diseases, such as schizophrenia and autism [122].

In light of this it is interesting to note that long-term stress is a well known risk factor for several neuropsychiatric conditions involving the PFC, including depression, affective disorders, schizophrenia, and anxiety [5-7]. Animal studies have shown that repeated restraint stress reduces the density of apical dendritic spines in medial PFC neurons [123-124], thereby decreasing the number of synapses to pyramidal cells by approximately one third [124]. In addition, a human experimental study recently demonstrated that chronic psychosocial stress disrupts PFC processing and attention control [2]. In accordance with previous research on rodents [4], the decline in performance was reversed after a recovery period of decreased stress. Together, these studies give support to McEwen's model of allostasis by demonstrating both structural and functional/behavioral changes following exposure to long-term stress. As a side note it should be mentioned that the exposure to chronic stress in the abovementioned study was relatively short (one month), and that care should be taken when extrapolating these results to other situations or populations. For example, the plasticity of the PFC has not been studied in emotionally exhausted or burned-out individuals. Nevertheless, together these studies indicate that long-term stress has deleterious effects on the PFC, a brain area essential for the ability to understand speech in noise, and in the extension, for the ability to communicate in everyday life.

Another line of research has demonstrated that chronically elevated levels of stress hormones exert degenerative effects on other brain regions as well, such as suppressing neural growth in the dentate gyrus [3], and causing remodeling and retraction of dendrites in the hypothalamus and hippocampus [1-4]. These studies offer plausible explanations to how long-term stress may induce plastic changes in the brain and affect function. Related to these findings are neuro-imaging studies that have found non-auditory brain regions to be activated in for example tinnitus [101]. These areas include the ACC and the dorsal PFC, as well as typical limbic areas such as the hippocampus, amygdala, nucleus accumbens, and the ventromedial PFC [102, 104]. One proposed mechanism for tinnitus refers to an increased activity in efferents projecting from nucleus accumbens to the medial geniculate nucleus of the thalamus [102]. The increased firing of these neurons is thought to derive from failed inhibition in the ventral striatum of sound impulses [102]. Involvement of sub-cortical structures in the pathophysiology of tinnitus may also in part explain why relaxation exercises and psychotherapy offer one of few effective therapeutic strategies in tinnitus patients. Finally, given that the dentate gyrus is the site for neural generation in the brain, and the role of the hippocampus in memory formation, it is likely that damage in these structures would compromise different aspects of hearing as well.

2 AIMS

The overall aim of this thesis was to explore possible associations between long-term stress and hearing problems. The specific aims were:

1) To determine whether there is a relationship between hearing problems and different health-and work related stressors in the Swedish working population.

2) To determine whether the ability to hear speech in noise varies with emotional exhaustion, before and after an acute stress task.

3) To validate a hyperacusis questionnaire in relation to different strata of emotional exhaustion.

4) To validate a personal heart rate monitor (Polar RS800) against a traditional ECG-method for assessment of heart rate variability as a measure of autonomic balance.

3 METHODS

3.1 DESIGN

The four papers of this thesis are based on two separate studies. *Paper I* is based on an epidemiological study, while *Paper II - IV* build on a clinical experimental study with a population derived from the first study.

3.2 PARTICIPANTS

Paper I

The Swedish Work Environment Survey (SWES) is conducted biennially by Statistics Sweden (SCB) and includes subsamples of gainfully employed Swedes, aged 16-64 years, from the Labor Force Survey. These individuals were sampled into the Labor Force Survey through stratification by country of birth, sex, citizenship, and occupation. The respondents of SWES 2003 and 2005 were invited to the Swedish Longitudinal Occupational Survey of Health (SLOSH) [125], which was initiated by the Stress Research Institute at Stockholm University in 2006. A second data collection was conducted in April 2008. In 2008, a total of 18,734 individuals were mailed self-completion questionnaires, out of which 9,756 (52 %) working individuals responded. When including individuals who were not working at the time, the total response rate was 11,441 (61 %). These individuals are not analyzed in the present study.

Papers II - IV

Participants were recruited from the 2008 SLOSH-cohort. The selection for the present study was based on the degree of EE (Maslach Burnout Inventory – General Survey [126]) assessed in the 2008 SLOSH study. Only individuals living in the greater Stockholm area were included in the selection. Three gender stratified groups were created, including those with the highest, lowest, and the most intermediate EE-scores.

In the first selection a total of 720 individuals matched the inclusion criteria. This number was reduced to 687 as 33 individuals were excluded due to participation in a concurrent study. Invitational letters were sent to 687 individuals in cooperation with Statistics Sweden. Sixteen of the 687 individuals who were initially invited did not have a valid address. Of the 687 individuals who received an invitational letter, 350 (51 %) agreed to participate. Two later withdrew, rendering 348 (51 %) final participants. A total of 341 participants (men = 139, mean age = 52; women = 202, mean age = 53) attended the experimental part of the study; the remaining seven only completed a web-based questionnaire. The distribution of EE-scores of the final sample was similar to that of the original selection. All gave their written consent to participate. The study was approved by the local ethical committee in Stockholm (protocol no 2009/493-31/3).

3.3 PROCEDURES

Paper I

Self-completion questionnaires were sent out by ordinary mail to the 18,734 individuals of the 2008 SLOSH cohort.

Papers II - IV

The study consisted of two main parts: a) a web-based questionnaire and b) an experimental part where hearing tests were performed before and after a 5 minute stress task. Participants were asked to complete the questionnaire 1 - 3 days prior to their appointment at the clinic. The questionnaire consisted of approximately 150 questions on their psychosocial and physical work-environment, lifestyle, and physical and mental health. A total of 348 individuals completed the questionnaire.

A schematic illustration of the procedure is presented in Figure 3. Participants attended the laboratory sometime between 07:00 and 11:30 AM. A battery of tests was assessed before and after a 5-minute stress task. At baseline the height, weight, waist- and hip circumference, blood pressure, and heart rate variability were assessed from all participants, and blood samples were collected. After the HRV-assessment, blood samples were collected.

Next, three clinical hearing tests were assessed: pure tone audiometry (PTA), a hearing in noise test (HINT), and uncomfortable loudness levels (ULL). Prior to the hearing tests the participants' ears were checked for obstructive wax. The hearing tests were followed by an acute stress test lasting for four minutes, after which the HINT and ULT hearing tests were re-assessed. Pure tone thresholds were assessed from all 341 individuals prior to the stress task. Four individuals were excluded from partaking in the stress test due to feeling nauseous (n = 2) or recently having experienced a stroke (n = 1) or a coronary event (n = 1), rendering a total of 334 sets of HINT-data for the left ear, and 334 sets for the right. The whole procedure for each individual (not including the web-based questionnaire) took 1½ - 2 hours.

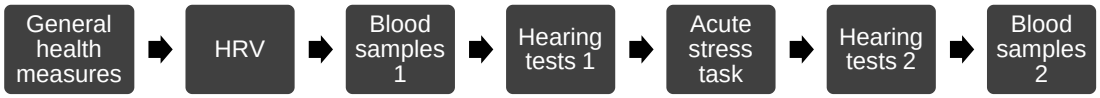

Fig 3. Schematic flow-chart of the experimental study.

3.4 INSTRUMENTATION

3.4.1 Assessment of long-term stress

Papers I - III

Emotional exhaustion was assessed via a web-based questionnaire with five items from the emotional exhaustion subscale of the Maslach Burnout Inventory general survey (MBI-GS) [126]. The scale consists of five items, derived from the Maslach Burnout Inventory human services survey (MBI-HSS) in unmodified form. Scorings reached from 1 (every day) to 6 (a few times a year or less/never), and an index was calculated to generate an EE index score. A minimum of three of five items were required for calculation of the index. The stability of the EE subscale has been reported to be satisfactory [126], and the construct validity of the Swedish translation of the

Maslach Burnout Inventory human services survey (MBI-HSS) has been found adequate [127].

Paper I

Work-related stressors/threats. Risk of being moved to another work/job against ones will, threats of getting fired were derived from the Swedish Labor Force Survey (LFS). Threats of bankruptcy were constructed for SLOSH 2008 to assess a threat particularly important for self-employed, a group who contacted the research group and expressed feelings of neglect in the SLOSH 2006 survey. The question was phrased: "Are you subjected to any of the following risks or threats in your work?". Response alternatives were yes/no.

Self-rated health was assessed with the single item "How would you rate your general health status?" This question has been used in research previously [128-130], and answer alternatives ranged from 1 (very poor) to 5 (very good) on a 5-graded Likert scale. Since only few participants reported very poor SRH, the categories quite poor and very poor were merged in the analyses.

Long-term illness, inconvenience after an accident, any handicap or other weakness were assessed with the question: "Do you have any prolonged sickness, accident-related complaints, a disability or other weakness?" This question was derived from the WOLFF (WOrk, Lipids and Fibrinogen – follow-up) [131-132] questionnaire and response alternatives were yes/no.

Sleep quality. Sleep quality was assessed with the single item: "On the whole, how do you feel that you sleep?" This item was derived from the Karolinska Sleep Questionnaire [133]. Response alternatives ranged from 1 (very poor) to 5 (very good) on a 5-graded Likert scale.

Long lasting stress (LLS) was assessed with 11 items reflecting stress arousal symptoms but not stress reactions. The participants were asked how they have been feeling during the last three months with regard to both physiological (e.g. "I sweat easily even though I do not exert myself physically") and cognitive - behavioral symptoms (e.g. "I have worrying thoughts"; "I often feel tense"). The four response alternatives reached from "Not at all" to "Nearly all the time".

Performance based self-esteem [134-135] was assessed with four items (e.g. "At times, I have to be better than others to be good enough myself") with five response alternatives ranging from "Fully disagree" to "Fully agree".

Papers II and III

Acute stress task. To elicit an acute stress response, participants were exposed to three stress-inducing tasks simultaneously. The first task consisted of an emotional Stroop-test, where participants were asked to identify the colors of rapidly alternating words on a computer screen. At the bottom of the screen were boxes with the words: blue, brown, grey, green, yellow, pink, red, black, and white, and the task was to click on the box corresponding to the color of the letters of the word currently displayed. In contrast to the traditional Stroop-test, emotionally charged and neutral words were used to elicit a greater stress response. The charged and neutral words were distributed equally and presented in random order. Examples of charged words were: death, hate, and enemy. Examples of non-charged words were rose, senior, and bread. To add to the difficulty, different interfering colors were displayed on the background of the screen, and additional colors were concurrently presented by a speaker voice via headphones.

The pace of the visual and auditory presentation was 40 words per minute, while the background color alternated 80 times per minute.

The second and third tasks constituted a combined cold-pressor test (hand in ice water; about 4°C) with a social evaluation element and were performed simultaneously with the Stroop-test. While the cold-pressor test has been extensively used in laboratory settings to induce a stress response, it has been demonstrated that adding a social evaluative task further enhances the stress response [136]. Hence, participants were asked to insert their non-dominant hand wrist-deep into a bowl of water and ice for the entirety of the Stroop-test, i.e. four minutes. Participants were instructed to remove their hand from the water if the pain became unbearable. A video camera was stationed approximately 40 cm behind the computer screen, and participants were told that their facial expressions would be recorded for evaluation by a professional. The recording started as soon as the headphones were properly equipped and one hand had been fully inserted the bowl of water. Participants were observed by a researcher during the assignment.

3.4.2 Hearing assessment

Hearing was assessed psychometrically, via self-rating scales, and psychophysically, via clinical auditory tests. All auditory testing was conducted inside a sound isolated booth by trained professionals. A 2-channel clinical audiometer (Orbiter 922, Madsen, Denmark) was used together with standard TDH-39 headphones (Telephonics Corporation, New York, USA). The equipment was calibrated in accordance with calibration standards ISO 389 and ISO 389-3.

Paper I

Hearing problems were assessed with three questions. *Tinnitus* was assessed with the question: "Have you during the most recent time experienced sound in any of the ears, without there being an external source (so-called tinnitus) lasting more than five minutes?" (No, Yes sometimes, Yes often, Yes all the time). *Tinnitus severity* was assessed with the question: "How much do you feel that the tinnitus sounds worry, bother or upset you?" (Not at all, A little, Moderately, Severely). The questions about tinnitus were adapted from Davis [137] and Palmer et al. [138].

Hearing complaints was assessed with the question: "How difficult is it for you to (without hearing aid) hear what is said in a conversation between several persons?" (Not difficult at all, Not very difficult, Quite difficult, Very difficult). In this study, hearing complaints reflects difficulties in communicating. The questions about hearing complaints were derived and adapted from Statistics Sweden and have been used in population studies for several years.

A new variable, "hearing problems", was computed based on the existence or non-existence of either tinnitus or hearing complaints or both. This consequently yielded three groups; those without hearing problems, those with either tinnitus or hearing complaints or those suffering from both. The cut-off for tinnitus was "yes, sometimes" or more often, and for hearing complaints "quite difficult" or "very difficult".

Papers II and III

Pure tone audiometry. Air conduction thresholds were determined by using a modified Hughson Westlake technique. Each ear was exposed to tones at 500, 1000, 2000, 4000, and 6000 Hz in the intensity range of -10 to 110 dB, and at 8000 Hz in the range of -10 to 100 dB. Testing started at 1000 Hz at an intensity of 40 dB. If the examiner received a response at this level, the intensity was reduced in 20 dB steps until the tone could not be perceived. The level was then increased in 5 dB steps until the tone became audible again. Once audible, the signal was decreased in 10 dB steps and increased in 5 dB steps until three responses were registered at the same level in the ascending phase. The same procedure was followed for all frequencies, proceeding from 1000 Hz to 8000 Hz in an ascending manner, and finishing with 500 Hz. Bone conduction was performed if the hearing threshold was 25 dB or higher on two or more frequencies between 500 and 4000 Hz. Hearing loss was defined as a pure tone threshold of 20 dB or higher at any frequency and ear.

Paper II

Speech reception thresholds in noise were assessed with a modified version of the Swedish HINT using a female speaker [139]. The original version of the test consists of 25 lists of 10 sentences each. Three protocols are suggested in the literature, constituting 7, 14, or 21 sentences. For time saving reasons, the seven sentence version was chosen. The two first lists were selected. The first four sentences of the first list served as practice sentences, and the following six sentences (no 5 - 10) together with the first sentence of the second list (no 11) constituted the presentation levels for the right ear. The subsequent seven sentences of the second list (no 12 - 18) were used for assessment of the left ear.

In accordance with standard procedure, speech intensity was set to a constant level while the intensity of the noise was adjusted to determine the threshold of speech reception. In the original Swedish HINT speech was set to 70 dB; here speech was set to 70 dB for 315 individuals and to 75 dB for 19 individuals. It has been previously demonstrated that noise-intensity does not influence performance as long as it is within normal hearing range [140]. It is therefore reasonable to assume that the 5 dB difference in presentation level had no significant impact on the results.

The intensity of the noise was elevated in 2 dB steps starting with 64 dB. However, after conclusion of the experiment, it was found that the audiometer produced a noise level approximately 3 dB too high on the left ear and approximately 8 dB too high on the right. The error was corrected for before the statistical analyses. This implies that the absolute HINT-scores should be interpreted with caution. However, the inferential statistics should not be affected by this error since it affected all participants.

During the procedure, each sentence constituted a minimum number of keywords that needed to be repeated in order to pass at that particular noise level. If the participant recalled half of the keywords accurately, the noise for the next sentence was increased by 2 dB, but if the participant failed to recall half of the keywords correctly, the noise level was decreased by 2 dB for the subsequent sentence. If the participant recalled precisely half of the keywords, the noise level remained unchanged for the next sentence. This alternative was only possible when keywords of a sentence had an equal number. The signal to noise ratio was calculated by subtracting the mean intensity of noise (dB) of all sentences, from the speech intensity (dB). There were no significant

differences between men and women on the HINT, neither at the first nor the second assessment.

Paper III

Uncomfortable loudness levels were determined according to the SAME-method [141]. Participants were instructed to announce through a microphone when the volume of the tone became uncomfortably loud. Testing started at 1000 Hz with an intensity of 70 dB. If this level was perceived as uncomfortably loud, the intensity was decreased by 10 dB, and the starting level on the following frequencies decreased to 60 dB. To determine the ULL, the intensity was increased in 5 dB steps until the participant responded. The tested frequencies were 500, 1000, 2000, and 4000 Hz. An index-score based on the average of the four frequencies was calculated for each ear.

Self-rated hyperacusis was assessed using the hyperacusis questionnaire by Khalfa et al [117]. The questionnaire consists of 14 items from three subscales: an attentional dimension (4 items), a social dimension (6 items), and an emotional dimension (4 items) [117]. The scores of the items within each dimension can be either summed and interpreted separately, or pooled together and interpreted as a total score. A total of 346 individuals provided complete answers on the HQ.

Paper IV

Heart rate variability was assessed in a supine position on a stationary bench. Three ECG-electrodes were placed over the left fifth interspace, the right fifth interspace, and over the manubrium, respectively. The ECG-signal was inspected for consistency and level of noise, and the electrodes were adjusted or replaced if the signal turned out to be noisy or abrupt. Once the ECG-signal was acceptable, the chest strap of the Polar RS800 was fixed around the chest of the subject according to the instructions of the user manual. The RS800 watch was set on standby and the heart rate compared with the heart rate displayed by the ECG for agreement.

Participants were informed that their heart activity would be recorded for five minutes, and were instructed not to talk or move excessively, but to relax as much as possible. They were also provided with ear protectors to reduce potential noise. Participants were in a supine position for 5 minutes prior to the start of the recording. The start of the recording was synchronized with both instruments, and a minimum 5 - minute recording was obtained with each system. The R-R-series of the Polar equipment was automatically stored in the watch, and later transferred to a laptop computer while the ECG-recording was directly stored on a laptop computer.

The ECG-registrations were recorded at a sampling frequency of 1000 Hz and stored on a computer. The first 300 second section of each recording was selected for analysis. Each ECG-recording was inspected for ectopic beats and artifacts, as well as for the correct identification of each R-peak by the software. Non-sinus beats and other artifacts were corrected by interpolation. After preparation of the data, SDNN and RMSSD in the time domain were computed. Spectral analyses utilizing an autoregressive method were performed to obtain HF and LF-power.

The PPT 5 software was used for error correction and computation of HRV-data obtained by the RS800-watch on a laptop computer utilizing the Microsoft Vista (32-bit) operating system. The first 300 second period of each recording was delimited and selected for analysis. Artifacts were corrected using the inbuilt error correction function at the standard setting. In this mode, filter power and the minimum protection zone are

by default set to moderate and 6 beats per minute, respectively. The proportion of excluded errors was obtained by dividing the total number of errors identified by the software during the 5-minute period, by the total number of beats for the same period.

3.4.3 Statistical analyses

The programs SPSS 18.0 and STATA 10 were used for statistical analyses. Statistical significance was set at $p < 0.05$ for all inferential analyses.

Paper I

Prevalence was calculated via frequency plots and crosstabs were used for calculation of $\chi 2$, Kendall's tau-b, and specific prevalence within different groups. Additionally, proportional odds (ordered logistic regression) were computed to estimate effect sizes, with and without control for age, gender and SES.

Paper II

Linear regression analyses were conducted in two steps to determine the association between EE and HINT-scores in the unchallenged state, after the acute stress task, and on the change from the unchallenged state to the post-stress assessment. The models were first analyzed for all participants, and thereafter stratified by gender. The factors age, audiometric hearing loss and sex are known to be associated with the ability to hear speech in noise and were therefore included as covariates in the first step of the regression analyses. Emotional exhaustion was included in the second step (enter). Paired samples t-tests were used to assess possible differences in mean values between the first and the second HINT.

Paper III

To determine the internal consistency of the HQ and each subscale (attentional, social, and emotional), Crohnbach´s alpha was calculated. To determine the factorial loading of the HQ, confirmatory factor analyses were performed on the HQ and each subscale. In accordance with Khalfa et al [117], a principal component analysis method was used [117]. The association between scores on the HQ and ULLs was determined using Pearson and Spearman correlations. Separate correlations were computed for each of the three groups of EE, both with and without control for audiometric hearing loss (pure tone threshold $\geq$ 20 dB on any frequency).

Paper IV

Chi2-tests were performed to test whether the number of correct exclusions (i.e. $\geq$ 5 % non-sinus beats) made by the PPT 5 differed significantly from the number of non-valid observations identified with the ECG. Only recordings with less than 5 % non-sinus beats were included in the subsequent analyses. Intraclass correlations with 95 % confidence intervals (CI) were obtained using a two-way mixed model. Essentially, the ICC provides a coefficient of relative agreement by dividing the between-subjects variance with the between-subjects variance plus the error.

Standard errors of measurement were estimated using the following formula: SD $\sqrt{}$(1-ICC) where SD = $\sqrt{}$SSTOTAL/(n-1). This variance was further expressed as a percentage of the mean, providing a coefficient of variation [142].

Agreement between the methods was additionally examined by means of Bland & Altman plots, which illustrate the difference between paired observations on the y-axis (method 1 - method 2), plotted against their mean value on the x-axis (method 1 + method 2 / 2). This provides a template with limits of agreement that allow for evaluating the agreement between the methods over different values of x, and to determine whether the range between the limits is clinically acceptable.

4 RESULTS

4.1 PAPER I

The results demonstrated a statistically significant increase in hearing problems among individuals with a higher exposure to work-related stressors or threats. Specifically, stressors such as occupational stress, poorer self-rated health, long-term illness, poorer sleep quality, higher burnout scores, more symptoms of long-lasting stress, and higher performance-based self-esteem were significantly associated with a higher prevalence of hearing problems. This was true for both men and women. The prevalence of hearing problems in relation to different employment-related threats is presented in Table 1. The odds ratios (derived from ordered logistic regressions) to suffer from hearing problems for individuals with the highest vs. the lowest exposure level to different stressors are presented in Table 2.

Table 1. Prevalence of hearing problems in relation to different work-related stressors.

Employment-related threats	Prevalence of hearing problems			Relationship between threats and hearing problems; Kendall's τ-b and p-value
	No problems N (row %)	Either tinnitus or hearing loss N (row %)	Both tinnitus and hearing loss N (row %)	
Risk of being moved to another work/job against ones will (N = 9,054)				0.076; p < 0.0001
Yes	997 (61)	514 (31)	126 (8)	
No	5,209 (70)	1,801 (24)	407 (6)	
Threats of getting fired (N = 8,616)				0.055; p < 0.001
Yes	714 (62)	345 (30)	85 (7)	
No	5,232 (70)	1,818 (24)	422 (6)	
Threats of bankruptcy (N = 8,385)				0.018; p = 0.105
Yes	247 (65)	106 (28)	25 (7)	
No	5,556 (69)	1,999 (25)	452 (6)	

Table 2. Odds ratios (OR), with and without adjustment for socio-economic status, gender and age, to suffer from hearing problems for individuals with the highest versus those with the lowest stress levels.

Exposure (level)	Women		Men	
	Crude OR*	Adjusted OR*	Crude OR*	Adjusted OR*
Occupational stress (Yes/No)	1.70	1.74	1.39	1.43
Self-rated health (High/Low)	3.81	3.49	3.89	3.29
Long-term illness (Yes/No)	1.72	1.64	1.92	1.76
Poor sleep quality (High/Low)	3.51	3.24	2.74	2.67
Burnout (High/low)	2.80	2.79	2.36	2.63
Long-lasting stress (High/Low)	2.61	2.79	2.06	2.42
Performance-based self-esteem (High/Low)	1.64	1.80	1.26	1.41

* All $p < 0.001$.

Taken together, with the only exception of 'threats of bankruptcy', the results consistently demonstrated an increased prevalence of hearing problems, i.e. hearing

complaints and/or tinnitus, in individuals who were exposed to a larger degree of stress/stressors.

4.2 PAPER II

The main finding of this study was that higher levels of EE were associated with a poorer ability to hear speech in noise in both men and women. This was true even after adjusting for age, hearing loss, and gender. Specifically, the results demonstrated significant associations between EE and HINT for the left ear, both when men and women were combined (Table 3), and separately in men (std. $\beta = 0.225$, 95 % CI = 0.087 - 0.654, $p = 0.01$, $R^2 = 4.1$ %), and women (std. $\beta = 0.151$, 95 % CI = 0.005 - 0.409, $p = 0.05$, $R^2 = 1.7$ %). Beta-coefficients were positive, indicating that higher values of EE were associated with increased difficulties in understanding speech in noise. The results were weaker for the left and right ear average scores, and non-significant for the right ear.

Table 3. Linear regression models predicting HINT at baseline on the left ear, right ear, and on the average of the left and right ears (L/R Average) for men and women combined.

Ear	Predictor	Adjusted R^2 %	Stand. β	95 % CI	F-value	p-value
Left	Full model	12.0			11.09	<.000
(n = 296)	Age	*	.319	.038- .079		<.000
	Hearing Loss	*	-.006	-.436 - .395		ns
	Gender	*	-.115	-.837 - (-.027)		.04
	Emotional Exhaustion	2.8	.181	.104 - .434		.001
Right	Full model	16.1			15.13	<.000
(n = 296)	Age	**	.377	.048 - .086		<.000
	Hearing Loss	**	.087	-.080 - .705		ns
	Gender	**	-.068	-.630 - .135		ns
	Emotional Exhaustion	.7	.099	-.013 - .298		ns
L/R Average	Full model	19.0			18.20	<.000
(n = 295)	Age	***	.406	.046 - .079		<.000
	Hearing Loss	***	.047	.190 - .483		ns
	Gender	***	-.106	-.664 - (-.009)		ns
	Emotional Exhaustion	2.3	.164	.072 - .339		0.03

* The aggregated adjusted R^2 for age, hearing loss and gender is 9.2 %. ** The aggregated adjusted R^2 for age, hearing loss and gender is 15.4 %. *** The aggregated adjusted R^2 for age, hearing loss and gender is 16.7 %.

After exposure to acute stress, EE was a significant predictor of poorer HINT-scores in men and on the left ear only. Taken together these results indicate that, in men, EE predicts a poorer ability to hear speech in noise both before and after an acute stress task. For women the results point in a similar direction but are not as pronounced.

4.3 PAPER III

The results demonstrated that the association between the HQ and ULLs was dependent on EE-level. Specifically, correlations were stronger with increasing levels

of EE. When controlling for hearing loss, moderate correlations were found for the intermediate and high EE groups on both ears. In contrast, no significant association between ULLs and the HQ were found on either ear in the low EE group. The strongest correlations were found for the social dimension in all subgroups of EE, indicating that social aspects of hyperacusis may correspond best to audiological parameters (ULLs) of hyperacusis.

Notably, the association between ULLs and the emotional dimension of the HQ did not reach statistical significance among individuals with low EE with either statistical method. At the same time, relatively strong correlations were found between ULLs and the emotional dimension for the intermediate and high EE groups. For these same groups, only weak associations were found between ULLs and the attentional dimension, indicating that the validity of the HQ and its subcomponents may differ between different strata of EE. The correlations between ULLs and the total score as well as each subscale of the HQ, with control for audiometric hearing loss, are presented in Table 4, by level of EE.

Table 4. Partial correlations between uncomfortable loudness levels and both the total HQ-score and the subscales of the Hyperacusis Questionnaire, with control for audiometric hearing loss. Results are presented separately for each level of emotional exhaustion (EE).

ULL	Hyperacusis Questionnaire	Attentional Dimension	Social Dimension	Emotional Dimension
Right ear				
All	-0.317****	-0.250****	-0.306****	-0.236****
Low EE	-0.204	-0.209*	-0.211*	-0.082
Intermediate EE	-0.328****	-0.273***	-0.330****	-0.216**
High EE	-0.349****	-0.198	-0.323**	-0.309**
Left ear				
All	-0.324****	-0.257****	-0.318****	-0.234****
Low EE	-0.196	-0.192	-0.234*	-0.055
Intermediate EE	-0.320****	-0.267***	-0.315****	-0.215**
High EE	-0.393****	-0.247*	-0.368***	-0.319**

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$

Taken together, significant correlations between HQ-scores and ULLs were found in individuals with intermediate and high levels of EE, but not in those with low EE. The results indicate that the validity of the HQ is in part dependent on EE-level.

4.4 PAPER IV

The most important finding was that the error correction function of the PPT 5 failed to recognize 18 out of 21 recordings that were excluded from the ECG-recordings due to an unacceptably high amount of non-sinus beats. A χ^2-test demonstrated the number of excluded observations to be significantly different between methods, $\chi^2 = 14.00_{df=1}$, $p<0.001$.

A total of 318 pairs of data had sinus rhythm > 95 % of the time and were included into the following statistical analyses. The ICCs demonstrated a difference in association between the methods that was dependent on gender, age, and

HRV-measure. Generally, the ICC coefficients were lower for women. The difference was most pronounced for SDNN, where interchangeable agreement was not reached for women in any of the three age categories. Women over 60 years did not reach the critical lower CI-value of 0.75 on any of the HRV-variables. In contrast, the ICCs of men were high for all HRV-variables, with most coefficients exceeding 0.9. The results from the *SEM*s were similar to the results of the ICCs.

The Bland & Altman plots further confirmed the results from the ICCs and *SEM* %, with wider ranges between limits on almost every HRV-measure for women (Figure 5). Moreover, the plots revealed that there was a higher discrepancy between the methods with increasing HRV-scores. In summary, when including recordings with less than 5 % non-sinus beats, the Polar system generally produced valid measures of HRV for men but not for women.

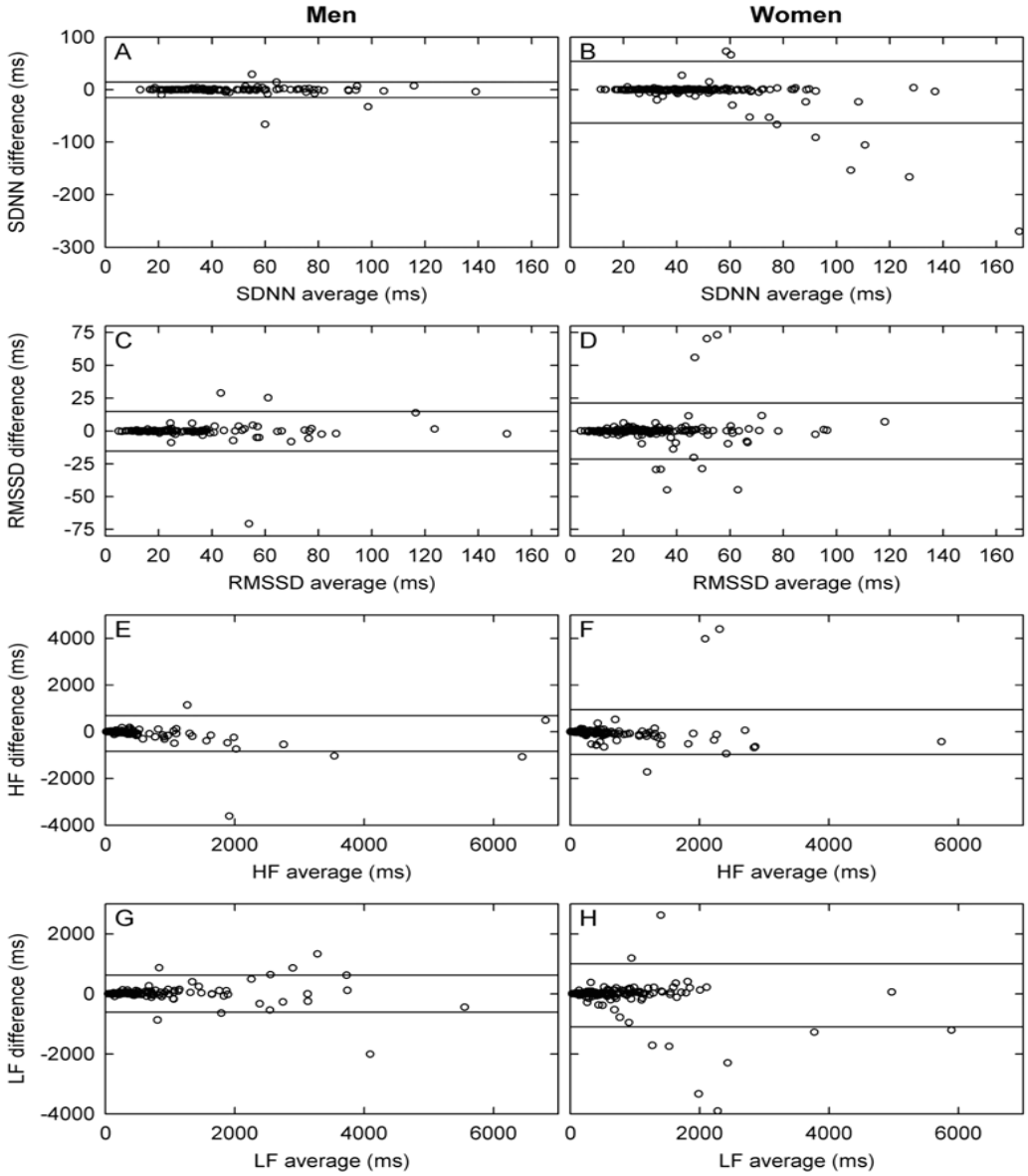

Fig 5. Bland & Altman plots of SDNN, RMSSD, HF-and LF- power for women and men separately. Wider limits imply poorer agreement.

5 DISCUSSION

The salient finding of this thesis is that hearing problems are more common in individuals showing more signs of long-term stress compared to those who are stressed to a lesser extent. The epidemiological study (Paper I) consistently demonstrated that higher levels of exposure to different work place stressors and negative health ratings were correlated with a higher prevalence of self-reported hearing complaints and/or tinnitus. The experimental studies both confirmed these findings and extended them, demonstrating that higher levels of EE are associated with a poorer ability to understand speech in noise (Paper II), and that hyperacusis scores are higher in individuals with higher EE-levels (Paper III). Importantly, the results from Papers II and III remained significant even after control for different confounding factors or covariates, such as audiometric hearing loss and age.

Taken together, both psychometric and audiometric data confirm that long-term stress is associated with different types of hearing problems, i.e. speech intelligibility in noise, hypersensitivity to sound, tinnitus and self-reported hearing complaints. These findings shed new light on the detrimental effects of long-term stress on different aspects of health. The results of each sub-study and their implications are discussed in more detail below.

5.1 PAPER I

Hearing problems are associated with different work-related stressors

The primary finding of the cross-sectional epidemiological study was that hearing problems were significantly more common among individuals who were exposed to work-related stressors or threats, such as long-lasting stress, poor sleep quality, high burnout-scores (EE-scores), low performance-based self-esteem, and risk of being moved to another job against ones will. This was true for both self-reported hearing complaints and tinnitus. The odds of having hearing problems were consistently larger for those who were more exposed to long-term stress compared to those who had less symptoms of long-term stress. These findings provide new evidence that stress may be an underlying factor in hearing problems and at the same time reveals new risk factors that have not been previously described for the auditory system. One of the main advantages of this study was the large study sample (n = 9,756) and that the sample is representative for the general Swedish working population. In line with previous reports on the prevalence of hearing loss, hearing problems in this study were more common in men, as demonstrated by lager absolute levels for hearing complaints, tinnitus and both. However, both men and women demonstrated an increased risk of having hearing problems with increasing levels of stress. Gender aspects are discussed in more detail below.

There is today an awareness of the damaging effects of loud and prolonged sounds that has led to the development of policies in work places and public places where sound levels are a concern. However, the potential dangers of long-term stress on hearing have not been emphasized. By identifying these new, stress related risk factors for the auditory system, this study reaffirms that not only the physical, but also the psychosocial work environment may play a role in maintaining healthy hearing. It is by now well established that stress-related disorders are related with different co-

morbidities, such as musculoskeletal pain and psychiatric disease [143-147]. The results of the present study add hearing problems to this list, indicating that long-term stress should be considered as a potential underlying factor for hearing problems in the clinic.

Even though these results identify new risk factors for hearing problems, they should be interpreted with some caution. Being a cross-sectional study, the causal direction cannot be established. In addition, the study relied solemnly on self-reported measures of hearing problems, i.e. hearing complaints and tinnitus. Even though there are advantages with self-reported instruments of hearing problems, e.g. tinnitus is subjective and hearing loss for speech is not always reflected in a pure tone audiogram, the association between long-term stress and hearing problems should be explored further using direct measures. Such studies will expand our understanding for the relationship between stress and hearing problems by revealing more precisely which auditory functions are compromised after long-term stress.

5.2 PAPER II

The ability to hear speech in noise is poorer with higher EE

The two-fold purpose of the experimental study was to determine whether HINT varies with level of EE and if an acute stress task modifies HINT performance. The salient finding was that, in the unchallenged state, higher levels of EE were associated with increased difficulties to hear speech in noise in both men and women. This study identified, for the first time, an association between EE and the ability to hear speech in noise. Gender-specific results were also implied, with men displaying stronger associations than women. These results expand on the previous epidemiological findings in Paper I, which demonstrated hearing problems to be associated with self-rated work- and health-related stressors. Unlike the previous study, a clinical HINT was utilized to assess hearing, demonstrating that higher levels of EE are associated with poorer hearing in noise. For men the associations were significant both in the non-challenged state and after acute stress, whereas significant associations were only found in the non-challenged state in women.

When studying the absolute HINT-values, a marked left-right ear difference was evident. However, this can likely be due to the technical issues with the audiometer. Previous studies have shown a right ear advantage when listening to speech, i.e. better hearing [148]. A right ear advantage would be theoretically conceivable, due to speech being predominantly processed in the left hemisphere [149]. However, it is possible that long-term stress could also affect this relationship. Given the aforementioned technical issues when assessing HINT, it is not possible to draw any conclusions about lateralization effects from the present results.

One major strength of this study was that hearing was operationalized as hearing in noise. The main advantage this is that the HINT more validly reflects an individual's ability to hear in everyday situations. In contrast, PTA lacks the ability to capture the complexity of hearing loss in everyday life under conditions with noisy background sounds. Indeed, previous work has demonstrated that individuals with normal audiograms may still have difficulties in understanding speech in noise, and it has been suggested that HINT be used as a complement to PTA [91].

Our results support this suggestion by showing that HINT varies with EE even after controlling for pure tone hearing loss and age. These results are in line with other studies showing that individuals with hearing problems demonstrate signs of increased

allostatic load as evidenced by a blunted cortisol reactivity [27], as well as difficulties to unwind from stress [26].

Moreover, previous research has shown that both auditory and non-auditory functions may explain HINT performance, e.g. spectral and temporal resolution, and cognitive skills [150]. However, no existing model has been able to fully explain the variance in HINT scores, suggesting that yet unknown factors are involved. The present study shows that EE can be added to the list of known predictors of the HINT. The potential role of EE as an underlying factor in auditory pathology should to be considered in future research and in clinical settings.

5.3 PAPER III

The validity of the Hyperacusis Questionnaire is dependent on emotional exhaustion

The main finding of this validation study of the HQ was that correlations between the questionnaire and audiometric uncomfortable loudness measurement were present in individuals with intermediate and high EE scores. In contrast, there was no correlation between the instruments for individuals with low EE scores. Controlling for audiometric hearing loss had no significant impact on the results, i.e. the correlations were largely unaffected when adding audiometric hearing loss as a factor. The direction of all correlations was negative, implying that higher scores on the HQ were associated with lower ULLs. Also, HQ-scores were significantly higher in groups with higher EE-level. However, the same was not true for the ULLs which did not differ significantly between EE-groups. These results further indicate that the two instruments do not fully measure the same construct.

To date, there is no established "gold standard" for measuring hyperacusis, and both self-reported tests as well as audiological methods are routinely used. This is also reflected in prevalence figures of hyperacusis that are inconclusive, with some studies reporting the prevalence to be somewhere between 6 - 8 % [13] while others report numbers as high as 15 % [116]. In the present study 1.1 % (three women and one man) met the critical value of a total HQ-score greater than 28 according to Khalfa et al. [117]. Given the fact that individuals with high EE-scores were (purposefully) over-represented in our study sample, this finding was unexpected. Since Khalfa et al. [117] used a study sample representing a more general population, a higher prevalence of hyperacusis would have been expected, especially for the group with high EE-level. The descriptive statistics indicated higher HQ-scores in individuals with higher levels of EE, both with respect to the total score and to the score of each subcategory. However, the mean total HQ-score even for the high EE-group was lower than the mean total scores reported by Khalfa et al. [117]. The cutoff for hyperacusis on the HQ has been questioned by others [114], since it failed to detect hyperacusis in a majority of individuals reporting hyperacusis complaints. Worth noting is that the same study used a sample specifically selected based on the diagnose of tinnitus - a patient group that has an increased risk of hyperacusis by approximately 40 % [151].

The validity of ULLs for measuring hyperacusis should also be discussed. While ULLs are perhaps seen as a more objective measure of hyperacusis than a questionnaire, it is important to point out that hypersensitivity to sound is highly subjective, and psychometric measures do not necessarily have to agree with audiometric findings. It is possible that individuals with lower than normal ULLs do not report complaints of hyperacusis in everyday life, and vice versa. Previous research

has found that while the intra-subject variability of ULLs is low, the inter-subject variability may be high, implying that the diagnostic value of ULLs may be limited [152]. For example, Sherlock and Formby [152] found that individuals who deny having sound tolerance problems and whose audiograms are normal may present ULLs as low as 70 dB.

Moreover, it has also been demonstrated that different instruments (i.e. earphones) may produce different sound pressure levels [153]. This warrants caution when comparing ULLs between studies or when re-assessing the same individuals with different types of equipment. Another limitation of ULLs lies in the external validity of the method, i.e. how well hypersensitivity to tones translates into hypersensitivity to sounds in everyday life. Thus, self-reported questionnaires constitute an important tool in the assessment of hyperacusis. From this also follows that care should be taken when interpreting the correlations between the HQ and ULLs observed in this study. The correlations only indicate the size of the associations; they do not determine how well the two methods measure the same construct.

Taken together, this study for the first time demonstrated significant correlations between a self-rated test of hyperacusis and ULLs, indicating that long-term stress may be an important factor to consider when assessing hyperacusis. The results emphasize the need for a clear definition of hyperacusis, which will serve as the basis for developing questions that are both sensitive enough to detect hyperacusis and specific enough to differentiate hyperacusis from other constructs associated with hypersensitivity to sound, e.g. phonophobia, misophobia, or recruitment of loudness.

5.4 PAPER IV

Traditional ECG-methods are recommended for assessment of HRV

Heart rate monitors offer a convenient and simple way of assessing HRV. However, the findings of this study discouraged their use in clinical studies. The most important drawback was that the PPT 5 did not accurately identify and exclude true errors. In total, the PPT 5 failed to identify 18 of 21 substandard recordings which suffered from ≥ 5 % non-sinus beats. This issue is problematic, since individuals with a high proportion of artifacts, instead of being excluded, will have highly overestimated HRV values [154].

Moreover, the combined results from the ICCs, SEMs and Bland and Altman plots demonstrated some uncertainty regarding the agreement between the Polar system and the ECG, where the validity of the Polar system appeared to be gender specific, such that women in general obtained lower ICC and SEM coefficients as well as wider LOA. Part of the poor results for women could be explained by partial interruptions of the Polar recordings, as evidenced by improved ICC coefficients when suspected interrupted recordings were excluded. However, the ICC coefficients for women over 60 years, who demonstrated the weakest agreement between methods, did not improve. This may have been due to even more discrete interruptions in the signal that cannot be detected upon visual inspection.

Taken together, the main problem with HRMs for HRV-measurement seems to be that the precise origin of each heartbeat cannot be determined, introducing potential biases into the data. The conclusion is therefore that, whenever possible, traditional ECG methods should be used for both gathering and editing of HRV data. While the Polar system did not meet the standards of this study, it may still have its place in

settings for which it was developed, where qualities such as flexibility, mobility and durability are of primary importance.

5.5 GENDER ASPECTS

Today it is well established that the auditory systems of men and women are different. A unique longitudinal study has captured the relationship between age, gender and hearing thresholds in 681 men and 416 women [85]. The authors found that pure tone thresholds in men were elevated from age 30, and then progressively continued to increase throughout life at a rate more than twice as fast compared to women. In women, on the other hand, the curve was relatively flat until approximately the onset of menopause, when thresholds rapidly increased and eventually caught up with the levels of men. Another difference was that women had better hearing than men at higher frequencies, while men had better hearing at lower frequencies. However, hearing at higher frequencies diminished most profoundly as age increased in both men and women, while lower frequencies were not affected to the same extent. In addition, tinnitus prevalence and severity has been reported to be higher in men than in women [155]. These differences are not easily explained, but may in part be due to different expression of estrogen receptors in both the cochlea as well as in the central auditory system. Interestingly, similar differences between men and women have been observed for the cardiovascular system. For instance, the incidence of CVD and hypertension is higher in men compared to age-matched, premenopausal women; however, when comparing with postmenopausal women the gender differences diminish (for review see [156]). Moreover, it is well established that women suffer negative consequences from long-term stress to a greater extent than men.

Given this background, this thesis rests on the assumption that the auditory systems of men and women differ to the extent that separate analyses are warranted. Hence, the aim was to determine associations between stress and hearing problems for each gender, rather than to determine possible differences. Even though the effect of gender was not assessed statistically in any of the studies, different results were observed for women and men in several aspects. The separate analyses demonstrated that EE was a predictor of HINT both in the unchallenged state and after acute stress in men. In women, EE was only a predictor of HINT in the unchallenged state. In contrast, the preliminary results demonstrated an interaction between EE and acute stress in women only, suggesting that women who are long-term stressed become more sound-sensitive when challenged, while men are not affected to the same extent. Both these findings may have implications for the clinical setting when assessing HINT and sound hypersensitivity in women and men. Previous research has shown that both auditory and non-auditory functions may explain HINT performance, e.g. spectral and temporal resolution, and cognitive skills [150]. However, no existing model has been able to fully explain the variance in HINT scores, suggesting that yet unknown factors are involved. Having shown that EE is a predictor of HINT opens new avenues for the evaluation and interpretation of speech-reception-in-noise tests. Importantly, future studies aiming to explain HINT performance should assess women and men separately.

5.6 CAUSALITY

Although not explicitly tested, the evidence presented in this thesis suggests that long-term stress may affect different hearing functions in humans, including the ability

to understand speech in noise and sensitivity to sounds. However, the relationship most probably also goes the other way around, i.e. hearing problems may cause distress and induce a vicious circle of more stress-related consequences. The effects of acute stress on auditory function have been studied in animals, showing that restraint stress, a form of emotional stress, affects the physiology of the animal both systemically, via expression of hormones, and locally, via regulation of receptor sensitivity in the auditory system. These effects are protective in the short term. However, there is a void of studies on the long-term consequences of stress on hearing in both humans and animals.

Despite continuous work to better understand and characterize tinnitus and hyperacusis in both animal and human studies, many questions regarding the pathophysiology of these disorders remain. While most scientists agree that tinnitus is generated centrally, often (but not always) due to damage peripherally, the exact localization or precise mechanisms are inconclusive. Evidence for the involvement of limbic structures in tinnitus and hyperacusis is accumulating. According to a recently proposed auditory-limbic model for tinnitus, sensory input generated subcortically enters auditory and limbic circuits via the medial geniculate nucleus (MGN) in the thalamus. In healthy individuals, the limbic system successfully identifies and inhibits irrelevant signals at the MGN via neurons from the ventromedial PFC, a limbic structure, projecting to the auditory thalamic reticular nucleus. In the pathological state, however, this inhibition in the ventromedial PFC is compromised, leading to a failed inhibition of irrelevant signals, i.e. tinnitus [102]. Thus, limbic structures seem to play a role in tinnitus; however the extent to which long-term stress is responsible for pathology manifested as tinnitus or hyperacusis in these areas has not been studied.

Several authors have suggested that long-term stress can negatively affect different aspects of hearing, even though most such claims rely on anecdotal evidence. As an example, Alpini and Cesarini have recently, based on their clinical experience, suggested tinnitus to be an alarm bell for stress [157]. Assuming the three stage stress theory by Selye (alarm reaction, resistance, exhaustion), they argue that tinnitus may become chronic if the cause for the alarm, i.e. tinnitus, is not addressed in time. The stress signals need to be identified during the alarm reaction phase in order to prevent the development of resistance and eventually exhaustion [157]. Moreover, indirect evidence suggests an association between stress and tinnitus. For instance, a study on 40 patients suffering from sudden hearing loss and tinnitus found that they experienced a larger number of stressful daily hassles and had fewer coping abilities compared to a group of 28 healthy controls [118]. In addition, a study on a large sample of the elderly (n = 10,216) found significant associations between tinnitus, poor sleep quality, and daytime sleepiness [158].

However, no-one has studied directly how long-term stress affects structures in the classical auditory pathway. While it has been demonstrated that chronically elevated levels of stress hormones may suppress neural growth and cause remodeling of dendrites in the hypothalamus and hippocampus [1-4], the effect of long-term stress on typical auditory structures is unknown. If, and to what extent, there are plastic changes in the auditory system following long-term stress, and how these changes may affect hearing, is a task for future research to explore. Another important step to further our understanding for the mechanisms underlying long-term consequences of stress on auditory function will be to characterize the expression of glucocorticoid-and mineralocorticoid receptors throughout the auditory pathway, both in the unchallenged

state and after chronic stress. Finally, longitudinal studies with repeated measurements are needed to improve our understanding of how different types of hearing problems develop as a consequence of long-term stress, and vice versa.

5.7 CONCLUSIONS

The salient features of the present study can be summarized as follows:

- The prevalence of self-rated hearing loss and tinnitus is higher among individuals who are exposed to long-term stress compared to those who are less stressed. This is true for both women and men.

- Individuals with higher emotional exhaustion exhibit higher difficulties in understanding speech in noise than those with lower emotional exhaustion-scores. Men seem to be more sensitive than women in this respect.

- Psychometric and audiometric measures of hypersensitivity to sound correspond better in individuals who exhibit higher levels of emotional exhaustion than in those with lower levels.

- When measuring hypersensitivity to sound it is important decide precisely what construct is to be measured and use an instrument that is both sensitive and specific.

- Commercial HRMs do not provide valid measures of HRV due to inadequate editing possibilities. Hence, it is recommended that, whenever possible, conventional ECGs, allowing manual detection and editing of ectopic beats and other artifacts, to be used.

- Taken together, these findings indicate that long-term stress should be taken into consideration when characterizing hearing problems, e.g. difficulties hearing speech in noise, tinnitus and hyperacusis. Future studies are needed to determine the causal direction between long-term stress and hearing problems via longitudinal data collection.

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