Association Between Stress and Tinnitus—New Aspects

Birgit Mazurek, Benjamin Boecking, and Petra Brueggemann

Tinnitus Center, Charité – Universitätsmedizin Berlin, Germany

This contribution focuses on the relationship between stress and tinnitus. While the causal and directional pathways between these constructs continue to remain unclear, this paper uses an allostasis-based framework to discuss associations between physiological stress responses, individuals' idiosyncratic experiences of the tinnitus percept, and psychological treatment approaches. **Key Words:** Auditory system—Stress—Tinnitus.

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STRESS

There are numerous scientific and colloquial definitions of *stress*. Traditionally, the literature distinguishes between 1) external or internal ''*stressors,*'' i.e., stimuli that disrupt cellular ''homeostasis'' or, on the organismic level, form ''a real or interpreted threat to physiological and psychological integrity'' and 2) a ''*stress response,*'', i.e., an individual's biopsychosocial reaction to such triggers—often involving physiological arousal and negative affect (1).

Psychological approaches have highlighted the role of emotions and—perceived—coping abilities in describing an individual's stress response. For example, stress-coping theory (2) defines stress as an affective response resulting from an interaction of stressors being perceived as personally relevant and coping abilities being appraised as insufficient (3). In humans, a stress response can be triggered by minor environmental influences (daily hassles) or serious life events, including trauma (4). An individual's stress response is influenced by genetic, cognitive, and behavioral components (5,6). For example, a stressor can be perceived and experienced as positive (a challenge), tolerable (a nuisance), or aversive (a catastrophe). This idiosyncratic response depends both on the magnitude of the stressor and an individual's perceived resources that are in turn influenced by their learning histories, self-esteem, sense of mastery and control, available social and emotional support, and early life experiences (7).

Stress responses affect various psychophysiological networks. For example, when stressed, blood pressure, pulse, glucose metabolism, gluconeogenesis, lipolysis, proteolysis, and insulin resistance increase as part of the stress response. So do gluconeogenesis, lipolysis, proteolysis, and insulin resistance. By contrast, gastrointestinal activity, appetite, and need for sleep are reduced (8).

Hormonally, the hypothalamic–pituitary–adrenal (HPA) axis is the main neuroendocrine system involved in an individual's stress response. It is a self-regulating system involving the release of hormones in the hypothalamus (corticotrophin-releasing hormone), the pituitary gland (adrenocorticotropic hormone), and the adrenal glands (glucocorticoids [corticosterone, cortisol] or mineralocorticoids [aldosterone]).

Activation of the autonomic nervous system (ANS) triggers the release of adrenaline/noradrenaline from the adrenal medulla as well as acetylcholine and neuropeptides from the spiral ganglion neurons (9–12).

Key components of the stress response comprise the release of cortisol, adrenaline, and noradrenaline (13). There are two types of cortisol-binding receptors: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). MR and GR receptors are located on the cell membranes (''membrane-associated'') while GR receptors are also found in the cytoplasm (''cytoplasmic''). Binding at the cortisol receptors results in genomic and nongenomic effects (14,15). In particular, glucocorticoid binding at the cytoplasmic receptors induces translocation of the ligand-receptor complex to the nucleus where the transcription of selected genes is either induced or suppressed (16). Nongenomic effects are triggered by the activation of the membrane-associated receptors and effect yet-unclear changes in synaptic communication (17).

It is further important to distinguish between *acute* and *chronic stress*. While short-term stress responses can be adaptive and trigger excitement and increased motivation, chronic stress can lead to numerous changes in the central nervous system and contribute to the development of illness including depression, hypertension, or coronary

Address correspondence and reprint requests to Birgit Mazurek, M.D., Ph.D., Tinnitus Center, Charité – Universitätsmedizin Berlin, Luisenstrasse 13, 10117 Berlin, Germany; E-mail: birgit.mazurek@charite.de

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heart disease (18–20). For example, chronic stress has been shown to trigger changes in neural plasticity via glutamate neurotransmission (21,22). It has further been shown to effect morphological changes such as the size of neurons (23,24), and lead to a reduction of links between CA3-pyramidal apical dendrites thereby reducing synaptic binding potential (25–27). Other effects comprise reductions in MR and GR receptor expression and GR translocation (28), reductions in neurogenesis, atrophy of hippocampal cells, and increased responses of N-methyl-D-aspartate receptors (29). Increased glucocorticoid release has further been associated with neural changes in emotion-processing and associated neural networks (30).

HOMEOSTASIS, ALLOSTASIS, AND ALLOSTATIC LOAD

Homeostasis is a fundamental principle of biological systems and refers to an organism's preservation of stability by keeping a range of variables within an acceptable range (31). It operates across organismic (including psychological functions) and cellular levels.

Once this equilibrium is changed through exposure to stressors, *allostasis* occurs—which refers to an organism's adaptive attempt to retain or recreate homeostasis through adaptation (32). Within allostatic systems, the parameter values of certain variables are thus in constant flux informed by adaptive change. *Allodynamic adaptation*—and thereby the process of and ability to cope with stressors—is coordinated by a complex neural network involving the hippocampus and the amygdala that mediate between lower order systems such as the brainstem and hypothalamus and higher order systems such as the prefrontal cortex. Importantly, this neural allodynamic adaptation system influences the interpretation of a stimulus as threatening and motivates responses to recreate homeostasis (''coping'') (32).

Chronic deregulation of the allostatic process can lead to a maladaptive process referred to as *allostatic load* that is associated with negative physiological and behavioral consequences including neuronal atrophy, reduction in immunity, bone demineralization, or mood disorders (33,34). Similarly, allostatic load has been associated with premature hypertension, atherosclerotic heart disease, habitually increased cortisol levels, sustained blood-pressure elevation, and chronic fatigue or fibromyalgia (32).

INFLUENCES OF STRESS ON THE AUDITORY SYSTEM

Some research has begun to focus on the effects of stress on the auditory system in both animals and humans. Supporting a possible stress-sensitivity hypothesis of hearing, mineral- and glucocorticoid receptors have been identified in the inner ears of both animals (35–37) and humans (38); however, research is mainly focused on animals at the time being.

In animals, the stress response has been found to be associated with the stimulation of GR receptors in the cochlea, as well as hormonal responses alongside the HPA axis (1,39). Similarly, in animal research, prenatal stress has been associated with postnatal low-frequency hearing loss, dysregulation of the HPA axis, increased baseline corticosterone levels, and generally increased corticosterone concentrations (40–42). Canlon et al. (43) demonstrated that rats that were prenatally treated with dexamethasone—an artificial glucocorticoid—developed stronger hearing loss after exposure to noise than untreated controls.

Interestingly, *acute short-term* stress (heat, isolation, or sound) has been shown to *protect* the cochlea in animal models (44–46). Similarly, a 4-hours isolation period (stressor) has been associated with an increase in corticosterone levels that in turn appears to protect against noise-induced hearing loss (47).

By contrast, *chronic* stress exposure seems to be detrimental to hearing (39) thus possibly inducing allostatic load. For example, exposure of Sprague-Dewley rats to isolation for 2 hours per day over a period of 10 days was associated with significant atrophy of the inferior colliculus and a stronger impairment in avoidance conditioning upon confrontation with an aversive acoustic stimulus (48). Similarly, Mazurek et al. (49,50) demonstrated that psychological stress (24-h stress exposure with regularly occurring, intermittent aversive audiological stimuli) was associated with significant temporary reductions in evoked auditory potentials and an increase in expression of inflammation genes in the inferior colliculus.

In the Sprague-Dawley rat studies where the animals were exposed to chronic stress through isolation (10 d, 2 h per day), significant atrophy of the inferior colliculus and a stronger impairment in acoustic conditioning was demonstrated. Active avoidance conditioning was trained with the presentation of an auditory −2800 Hz tone or a visual −28 V light stimulus after a foot shock (48) and of the medial geniculate body (51).

Although this body of research is still in its infancy, it appears that 1) the auditory function of animals appears to be influenced by acute stressors such as immobilization, heat, and hypoxia; 2) pretraumatic increase of glucocorticoids via activation of the HPA axis appears to provide some inner-ear protection against hearing loss after acoustic trauma; 3) posttraumatic administration of glucocorticoids (dexamethasone) appears to provide protection against further hearing loss, and, conversely; 4) pharmacological disruption of the HPA axis is associated with increased posttraumatic hearing loss (52–54).

STRESS AND TINNITUS

Tinnitus is defined as the subjective perception of sound in the absence of an external source. It is the most common chronic auditory disorder, and it is increasingly recognized as a global health problem (55–57). Its prevalence ranges between 10 and 15% in adult populations (55,58). If people experience the sound as *distressing*, tinnitus can be defined as a ''negative and emotional auditory experience associated with actual or potential physical or psychological harm'' (59).

Tinnitus is commonly associated with prolonged noise exposure, aging, and stress and occurs alongside various otologic, neurologic, infectious, or drug-related conditions (1,60,61).

Onset and persistence of tinnitus have been associated with both peripheral and central neural structures (62). For example, animal studies identified reduced spontaneous firing rates in the auditory nerve, and increased firing rates in the cochlear nucleus, inferior colliculus, and auditory cortex (63). Moreover, increases in neuronal synchronicity between the colliculus inferior and auditory cortex were identified in both animals and humans. By contrast, tonotopic reorganizations were identified in the auditory cortex of animals, but not humans (64,65).

Several models have attempted to conceptualize and integrate neurological findings in tinnitus for humans. For example, Georgiewa et al. (66) suggest that the tinnitus noise is generated in the cochlea, auditory nerve, or brain stem. The auditory cortex then contributes to the persistence of the auditory experience, with attention and emotion-associated limbic networks consequently interacting in the maintenance of tinnitus-related distress. See Figure 1, for an illustration of this model.

Other models postulate possible vicious cycles between an increase in arousal and resulting selective attention (67). Zenner (68) postulates that a neurophysiological sensitization of cognitive areas may mediate a lowering of perceptual thresholds thus making tinnitus audible and triggering compensatory overreactions in cognitive, emotional, or somatic/motoric systems. Vulnerability-stress models (69,70) postulate that tinnitus is a stressor that interacts with pre-existing psychological vulnerability to result in disproportionately heightened stress levels.

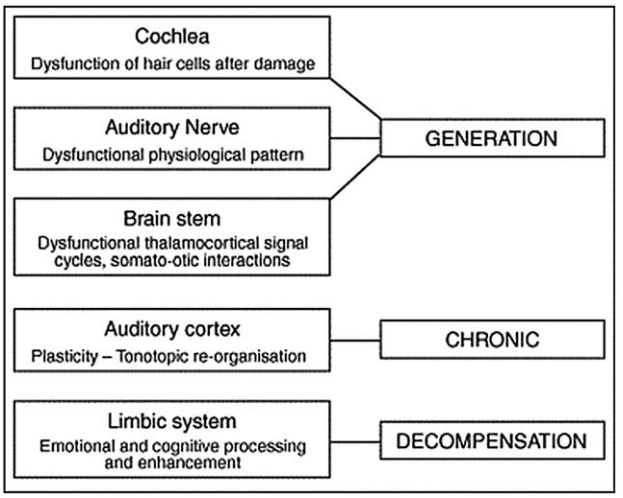

FIG. 1. Model of tinnitus generation, chronicity and decompensation. Reprint from Georgiewa P, Klapp BF, Fischer F, Reishauer A, Juckel G, Frommer J, Mazurek B. An integrative model of developing tinnitus based on recent neurobiological findings. *Medical Hypotheses* 2006 66:592–600 with permission.

CLINICAL ASPECTS

Somewhat unsurprisingly, tinnitus frequently occurs alongside mental health difficulties such as depression, anxiety, and somatoform disorders (71) as well as other conditions such as hyperacusis, Menière's syndrome, and vertigo/dizziness (72–74).

While the correlation of tinnitus and emotional distress is well established (75,76), the direction, causes, and underlying mechanisms of this effect are much more unclear. Observational studies report that up to 60% of tinnitus patients report longstanding emotional distress and about 25% of tinnitus sufferers in a German sample consider chronic stress as the main reason for their tinnitus (77). Hasson et al. (78) demonstrated a correlation between tinnitus and the duration of stress, while a large environmental study with $n = 9{,}756$ participants demonstrated that the probability of developing tinnitus was equal for people with high sensitivity to environmental noise and high levels of stress (79). Although it did not investigate the role of possible third variables, the study did demonstrate that an interaction of high distress and environmental noise exposure doubled the incidence of tinnitus. Seydel et al. (80) demonstrated that severe tinnitus was associated with higher levels of ''worries'' and ''tension'' than mild tinnitus, as measured by the Perceived Stress Questionnaire (PSQ) (81). Similarly, Hébert et al. (82) demonstrated that emotional exhaustion predicted tinnitus, self-reported hearing problems, or both while Brueggemann et al. (83) demonstrated that hearing loss, perceived stress-related tension, pessimism, and concentration predicted tinnitus-related distress.

Investigating mediators of tinnitus-related distress, one study showed that the effect of tinnitus loudness on tinnitus distress was mediated by individuals' emotional states (84,85); two other studies identified anxiety, somatization tendencies and, in particular, depression as possible mediators of tinnitus-related distress (86,87).

While these studies allow no inference of either direction or causality, an individual's emotional processing of stimuli seems to strongly influence the experience of the tinnitus sound. The emotional stress response may be mediated by hormonal and limbic responses that are influenced by a multifactorial network of individual genetic and psychological factors that interact with acute or chronic environmental stimuli (88).

PATHOPHYSIOLOGICAL ASPECTS

Both stress responses and tinnitus have been associated with hormonal (HPA axis), vegetative (ANS), and immunological dysregulation.

Patients with tinnitus have been demonstrated to show signs of impaired stress responsivity via inhibited HPA axis activation (89–91). Hébert et al. demonstrated that, completing a social stress task, tinnitus patients with high levels of stress had higher blood cortisol levels and higher subjective feelings of stress and tinnitus severity than tinnitus patients with low levels of stress and control

subjects at several time-points after stress exposure. In patients with chronic tinnitus, exposure to an acute social or auditory stressor induced sustained cortisol levels or a reduced cortisol response as well as subjective experiences of higher stress.

These experiments suggest that chronic stress may contribute to the development of chronic tinnitus via changes in HPA axis-related activity.

Although there is some evidence for the involvement of parts of the ANS with stress and tinnitus (92), respective findings have been limited and mixed. For example, tinnitus-related distress has been shown to positively correlate with sympathetic (93) and negatively with parasympathetic tone (94). Similarly, successful suppression of tinnitus has been associated with an increase in parasympathetic tone (95). A recent pilot study with n = 10 tinnitus patients and 10 healthy controls (96) compared salivary α-amylase (as a marker of ANS activity), salivary cortisol (as a marker of HPA Axis activation), and salivary neopterin (as immunological marker) before and after stress exposure using the Trier Social Stress Test. Following stress exposure, tinnitus patients showed a decrease in α-amylase, but not cortisol or neopterin levels compared with healthy controls suggesting ANS involvement in moderating the stress response of tinnitus patients. Studies using heart rate variability (HRV) as a marker for ANS activity in chronic tinnitus report mixed results with two studies reporting reduced HRV in patients with tinnitus compared with control subjects (93,94) and one study reporting no difference (97). Using heart rate (HR) and HRV as proxies for autonomous stress reactivity, an elegant study by Betz et al. (98) exposed n = 19 patients with chronic tinnitus and 19 matched healthy controls to two stress tasks (a mental arithmetic tasks and an instruction to focus on ear noise) that were alternated with three resting conditions. Across all conditions, HR, HRV, and subjective stress measurements were obtained. Compared with healthy controls, patients with tinnitus showed an overall decrease in HR, a reduced response to acute stress and more subjective stress, and increased awareness of tinnitus after the mental arithmetic task. HRV measurements did not differ between the two groups. Moreover, a correlation of HR and HRV was observed in healthy controls, but not tinnitus patients suggesting possible ANS dysfunction in response to acute stressors.

In summary, while there is some evidence of ANS dysfunction in chronic tinnitus, it is yet unclear whether these changes are systematic and specific to tinnitus or associated with interacting systems commonly correlated with tinnitus onset, maintenance, or distress.

Immunological factors, in particular cytokines, have also been associated with both stress responses and tinnitus. Given their involvement in numerous physiological processes, including the regulation of immune and inflammatory responses (99), cytokines are of interest in investigating physiological stress reactions in patients with tinnitus within a broader allodynamic stress-reactivity framework. Tinnitus, in particular, has been associated with abnormalities in—among others—IL-1, IL-6, IL-10, or TNF-α. For example, Szczepek et al. (100) analyzed blood and psychological parameters in a sample of n = 30 tinnitus patients and demonstrated a positive correlation between TNF- α and perceived tinnitus loudness, perceived stress as measured by the PSQ (81) and, on a subscale, ''tension.'' In keeping with this finding, ''Joy'' – another PSQ subscale—correlated negatively with TNF-α levels. Investigating changes in cytokine levels following a psychological intervention, a study by Weber et al. (101) investigated the effects of a 10-week relaxation training on TNF- α, IL-6, and IL-10 serum concentration levels by comparing tinnitus patients who had completed the intervention with patients without the invention and healthy controls. Compared with the control groups, patients who had completed the intervention reported reduced perceived stress levels, reduced tinnitus severity, and increased quality of life. Compared with controls, they further showed significantly lower levels of TNF-α.

Taken together, TNF-α might be a promising indicator of sensitively assessing stress reactivity, level of emotional distress, and therapeutic impact; however the current evidence base is small and further research needs to investigate the specificity of TNF- α concentration for tinnitus and stress and its specificity for and sensitivity to measuring responses to treatment.

PSYCHOLOGICAL TREATMENT APPROACHES

There are numerous pharmacological and medical treatment approaches for tinnitus, very few of which have shown systematic effects (102). Recent developments such as the therapeutic application of repetitive transcranial magnetic stimulation failed to result in functional connectivity changes relative to a sham condition (103), although further research might expand the therapeutic applicability of this approach.

From an allodynamic point of view, the negative affective and cognitive responses triggered by the tinnitus percept motivate coping behaviors aiming to reduce negative affect and increase senses of well-being, mastery, and control. However, depending on an individual's pre-existing vulnerabilities, such behaviors can maintain or worsen emotional distress thus leading to a downward spiral ultimately resulting in the development of psychological comorbidities, i.e., allostatic load.

Psychological interventions thus aim to increase subjective well-being, reduce perceived distress and—within an allodynamic framework—reinstate allostasis through 1) changing negative interpretations of the tinnitus percept, 2) facilitating processing of negative affect, 3) increasing adaptive coping behaviors and 4) reducing maladaptive, or 5) increasing adaptive coping responses (67). Cognitive behavioral treatments aim to address these factors and constitute a well-evaluated treatment approach for tinnitus to date (104). A Cochrane meta-analysis that included n = 8 studies reported significantly higher improvements in quality of life (standard mean

difference = 0.64–0.91) and depression (standard mean difference = 0.37), but not tinnitus loudness, in patients completing cognitive behavioral treatments compared with ''no treatment'' or an ''other intervention'' (105).

Multimodal therapy concepts that combine informational, cognitive behavioral, and auditory stimulation approaches also demonstrated medium-large effect sizes for improvement in quality of life ($d = 0.24$), tinnitus degree ($d = 0.43$), and tinnitus-related impairment ($d = 0.45$) (106).

Currently, psychological approaches are the treatments of choice for distressing tinnitus—with respective intervention frameworks focusing on cognitive, emotional, and behavioral sequelae of predisposing and tinnitus-related distress (102,104).

FUTURE DIRECTIONS

Overall, effective treatments for tinnitus exist, yet focus on the cognitive, emotional, and behavioral sequelae of the tinnitus percept. Recent developments focus on advances in molecular and cellular therapy and targeted pharmacological therapies (107). Such research aims to protect or repair vulnerable structures of the auditory, limbic, or attention-related brain networks (108). In addition, such research aims to modulate the stress response associated with the tinnitus percept.

Future developments in psychological approaches may begin to provide and evaluate the effectiveness of emerging psychological approaches such as Mindfulness-Based Stress Reduction, Acceptance and Commitment Therapy, Compassion Focused Therapy , or Schema Therapy (109). Cognitive behavioral treatment approaches may further be refined and evaluated using individually adapted, formulation-based models to maximize idiosyncratic relevance and optimize outcome (110,111).

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