Agnieszka J. Szczepek
Birgit Mazurek
Editors

Tinnitus and Stress

An Interdisciplinary Companion for Healthcare Professionals

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Agnieszka J. Szczepek
Charité Universitätsmedizin Berlin
Berlin
Germany

Birgit Mazurek
Charité Universitätsmedizin Berlin
Berlin
Germany

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AJS: For Roger and Rysio

Preface

"A young lady from the city, affected with tinnitus, in consequence of the death of her brother by drowning, is very low spirited…."

John Harrison Curtis (*Surgeon to the Royal Dispensary for Diseases of the Ear) TINNITUS AURIUM; The Lancet; Volume 36, Issue 940, 4 September 1841, Pages 828–829.*

The observation about heavy emotional burden being connected with tinnitus made by John Harrison Curtis almost two hundred years ago is made by the tinnitus practitioners also today. In fact, majority of patients affected by tinnitus report heavy emotional burden either proceeding the onset of their tinnitus, worsening their existing tinnitus or both.

Dealing with the mental status of a tinnitus patient or measuring the emotional burden inflicted by tinnitus is not an easy task for general practitioners, ENT surgeons, or the audiologists. Most of the time, it is outside the scope of their training, and this is precisely why we wrote this book. Our first intention was to gather the latest knowledge about tinnitus and stress, to show mutual interactions between the two, to offer methods for measurement of the emotional burden in tinnitus patients, to demonstrate the importance of such measurements for the therapeutic outcome, and to propose some stress-related therapeutic solutions.

Interdisciplinary diagnosis and therapy of tinnitus are growing increasingly. To be most effective in their clinical efforts, the specialists attending tinnitus patients should understand each other's jargon. This was our second reason for creating this book, as our invited specialists wrote their chapters in a special, discipline-characteristic way. We hope that this book will help you—regardless of who you are: a physician, audiologist, physiotherapist, or perhaps psychologist—to better understand your colleagues.

Dr. Tony Fields, who was a director of Cross Cancer Institute at the University of Alberta during the times when I studied there, used to hold instructional talks for the new coworkers, students, and volunteers. During these lectures, he always stressed that "…we are here *because of* our patients and we are here *for* our patients…." It stayed with me all these years. The third and most important reason for writing this book was our commitment to the patients who suffer from tinnitus.

Berlin, Germany — Agnieszka J. Szczepek

Acknowledgments

We are grateful to our home institution Charité University Hospital Berlin for giving us the opportunity to perform the basic, translational, and clinical research regarding tinnitus and stress. Special thanks to the director of the Department of ORL, Head and Neck Surgery—Prof. Heidi Olze—for her personal and professional support. We thank the staff members from the Tinnitus Center and ORL Research Laboratory for their excellent work.

We are deeply indebted to the late Burkhard F. Klapp, Professor in Psychosomatic Medicine, for his long-standing advice regarding the role of stress and psychosomatics in diagnosing and treating tinnitus.

Many thanks to Heinz and Heide Dürr Foundation (*Heinz und Heide Dürr Stiftung*) for their continuous generous funding of our basic and clinical research. Likewise, we thank the Sonnenfeld Foundation (*Sonnenfeld Stiftung*) for financing several indispensable pieces of equipment in the ORL Research Laboratory.

We also thank our families and friends for their love, understanding, and support. A large chunk of work on this book was done in a beautiful Ośno Lubuskie, Poland; special thanks to all friends there and to the wonderful staff in the hotel "Afrodyta".

Lastly, many thanks to the patients who suffer from tinnitus for their cooperation and participation in various clinical trials - without you, this book would not exist.

Contents

Introduction

1

Agnieszka J. Szczepek and Birgit Mazurek

Dear Reader,
You have in your hand a book containing years of experience and summarizing the work of many clinical and basic scientists: ENT/ORL specialists, audiologists, epidemiologists, psychologists, pharmacologists, psychosomatic medicine specialists, biologists, and neuroscientists. Despite various backgrounds, all of these specialists have dedicated their professional life—at least to some extent—to *better understand the interactions between tinnitus and stress*. But is tinnitus not an auditory problem? Why are so many scientific disciplines taking interest in tinnitus and why stress?

Tinnitus is a phantom sound perceived only by the affected person and can be a symptom of a variety of diseases. A majority of these diseases have a common denominator: they cause hearing loss, their treatment causes hearing damage, or they are associated with overstimulation of the somatosensory system (Shore et al. 2016). The fact that tinnitus is associated with hearing loss has been known for a long time, and it is also known that not all patients with hearing loss necessarily develop tinnitus (Mazurek et al. 2010). The mechanisms of how hearing loss may induce tinnitus are not the topic of this book and are discussed elsewhere, for instance, by Jos Eggermont and Larry Roberts (2004). First looking at Table 1.1 makes one realize that although tinnitus is an auditory symptom, the illnesses associated with tinnitus are distributed over the entire medical field. This, of course, has consequences in *if* and *how* will the patients be treated for their tinnitus symptoms.

A.J. Szczepek, Ph.D. (✉)
Department of Otorhinolaryngology, Head and Neck Surgery,
Charité University Hospital, Berlin, Germany
e-mail: agnes.szczepek@charite.de

B. Mazurek, M.D., Ph.D.
Tinnitus Center, Charité University Hospital, Berlin, Germany

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Table 1.1 Known risk factors for developing tinnitus and conditions associated with tinnitus *partially based on* Baguley et al. (2013)

Medical conditions	
Otological, infectious	Otitis media, labyrinthitis, mastoiditis
Otological, neoplastic	Vestibular schwannoma, meningioma
Otological, labyrinthine	Sensorineural hearing loss, Ménière's disease, vestibular vertigo
Otological, other	Impacted cerumen, otosclerosis, presbycusis, noise exposure
Neurological	Meningitis, migraine, multiple sclerosis, epilepsy
Traumatic	Head or neck injury, loss of consciousness
Orofacial	Temporomandibular joint disorder
Cardiovascular	Hypertension
Rheumatological	Rheumatoid arthritis
Immune mediated	Systemic lupus erythematosus, systemic sclerosis
Genetically mediated	Paget's disease, Alport's syndrome
Infectious diseases mediated	Mumps, Rickettsia, Leishmania
Mitochondrial dysfunction	Nonsyndromic mitochondrial hearing loss, MELAS syndrome
Endocrine and metabolic	Diabetes mellitus, hyperinsulinemia, hypothyroidism, hormonal changes during pregnancy
Psychological	Anxiety, depression, emotional trauma
Ototoxic medications	Analgesics, antibiotics, antineoplastic drugs, corticosteroids, diuretics, immunosuppressive drugs, nonsteroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs, phosphodiesterase 5D inhibitors, methadone, pegylated interferons, inhibitors of viral reverse transcriptase

Tinnitus is a phantom sound perceived only by the affected person and can be a symptom of a variety of diseases and conditions.

Stress is a physiological reaction of the organism to the environmental changes that helps in adaptation to new, unknown circumstances. This reaction is possible because of stress hormones. How, when, and where these hormones are produced and what kind of consequences their presence may have are presented by Ron de Kloet and Agnieszka Szczepek in Chap. 2.

Clinical experience continuously teaches us that **the interface between tinnitus and stress** can change the course of treatment and of convalescence. Patients themselves refer to the emotional or social stress as a major factor influencing the onset and progression of their tinnitus. Further, the already existing tinnitus may act as stressor, thus leading to therapeutic impasse (see Chap. 3 written by Sylvie Hébert, Birgit Mazurek, and Agnieszka Szczepek). Therefore, it is important to recognize

stress and to deal with it and stress-induced conditions that may worsen tinnitus. Similarly, tinnitus-related stress may worsen both—tinnitus itself and comorbid psychological conditions.

The interface between tinnitus and stress can change the course of treatment and of convalescence.

A recent study recognized the **diversity of medical specialists treating tinnitus** (see Fig. 1.1) (Baguley et al. 2013). In practice, this means that in various countries, patients with tinnitus may be seen by practitioners with different medical backgrounds. It is common knowledge that not all health practitioners are by default trained in recognizing and treating the consequences of stress, present in form of depressiveness, generalized anxiety, tinnitus-related distress, and other symptoms. We are fully aware of the fact that the uniform and universal medical treatment of tinnitus all over the world is not possible, at least not yet. However, what is possible would be the additional knowledge sharing—and with this in mind, we wrote this book for you.

Many physicians refer tinnitus patients to specialized centers, but at the same time, the majority of patients report first being told that their condition is "*incurable*," that "*they have to learn how to live with it*," or that "*nothing can be done*" for them. The way in which such declarations are delivered to the patient may have enormous negative psychological consequences and can worsen tinnitus-related distress.

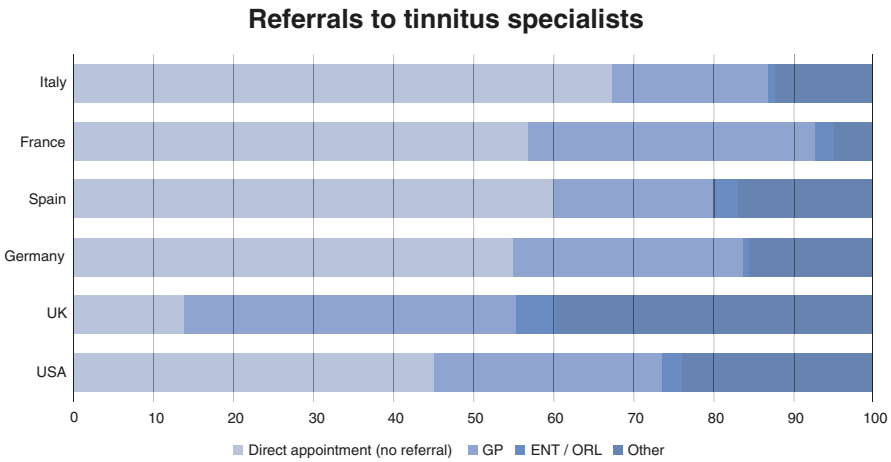

Fig. 1.1 Percentage of medical practitioners referring the patients with tinnitus to specialized individuals or centers depending on a country. *Based on data published in* Baguley et al. (2013)

Telling the patients with tinnitus that their condition is "incurable," that "they have to learn how to live with it," or that "nothing can be done" may have an enormous negative psychological consequences and can worsen tinnitus-related distress.

1.1 Tinnitus and Tinnitus-Related Distress

To apply proper therapy, it is important to differentiate between tinnitus and the tinnitus-related distress. Treatment of tinnitus percept is connected with a treatment of the disease that caused tinnitus, such as for instance treatment of hearing loss with cochlear implants will often result in tinnitus regression (Olze et al. 2011).

Perceiving tinnitus does not necessarily mean being distressed by it (Fig. 1.2). Further, the subjective loudness or pitch of tinnitus must not automatically correlate with the degree of tinnitus-related distress (Bauer et al. 2016). In fact, in several cases of idiopathic tinnitus or tinnitus with known but incurable causes, the main therapeutic objective is to *reduce the distress caused by tinnitus*. By the way, when referring to measures of therapeutic success, one should distinguish what precisely was determined, for instance, tinnitus percept—by evaluating audiometric properties of tinnitus (e.g., tinnitus loudness or tinnitus pitch) or tinnitus-induced distress (e.g., visual analogue scales or one of multiple psychometric questionnaires) (Hall et al. 2016).

Recent discovery of genes and proteins responsible for the regulation of so-called daily or circadian rhythms in the auditory system has dramatically changed our view on how the hearing functions. This discovery explains for instance changing susceptibility of the ear to noise-induced damage depending on the time of the day. Interestingly, the circadian rhythms are highly sensitive to the emotional and

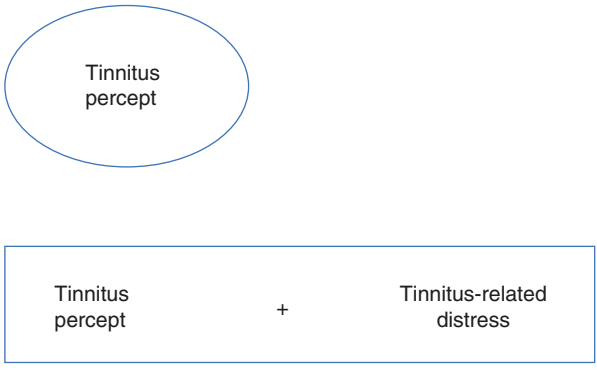

Fig. 1.2 Tinnitus may or may not be accompanied by a tinnitus-related distress

social stress. In Chap. 4, Christopher Cederroth, Vasiliki Basinou, Jung-Sub Park, and Barbara Canlon explain the insides of the internal clock in the ear and its connection with stress.

A bulk of tinnitus research has been done using animal models. Without these experiments we would be far from what we know about tinnitus today. Understanding the experimental set-ups, the ways tinnitus can be induced and measured, and finally the experimental backgrounds used in stress science is essential when translating the basic science results into the clinical situation. In Chap. 5, Jos Eggermont explains how animals help us understanding the paradigm of tinnitus and stress.

The diagnosis of tinnitus-related distress is commonly made based on psychometric instruments (questionnaires). Such instruments are considered as subjective methods. In search of the objective diagnostic means, we present state of the art regarding the use of biomarkers in diagnosis of stress-related conditions as well as in tinnitus (Chap. 6 written by Agnieszka Szczepek and Birgit Mazurek).

Furthermore, we deal with the stress-related psychometric diagnosis (Chap. 7 written by Matthias Rose and Petra Brüggemann), stress-related treatment options (Chap. 8 written by Rilana Cima), and stress-related outcome measurement when treating *tinnitus-related distress* as well as *stress-related comorbid conditions* (Chap. 9 written by Deborah Hall). Although at first these three last chapters may seem redundant—they are not. In Chap. 7, we present and discuss the instruments used to measure stress in general and in context of tinnitus. In Chap. 8, some of the instruments are presented as accompanying various psychological therapy settings. The last Chap. 9 presents and reviews the instruments predominantly used as outcome measurements in clinical trials, which are assessing the effectiveness of drugs and other means of intervention. In addition, as the book is also intended for the electronic version to be read in full or in chapters, we wanted the reader to have access to full information rather than forcing him or her to purchase additional chapters.

In the spring of 2015, Birgit Mazurek and I were contacted by Elisa Geranio from Springer International, who followed our work in the field of tinnitus and stress and suggested writing a book about it. We have met in summer 2015, during the Third Congress of European ORL-HNS in Prague, and while sipping espresso in the exhibition grounds, we talked about this project, discussing the best and the most up-to-date topics for chapters. Over a year has passed, all of our contributors did a great job, and now it is time to finish the last polishing steps and send the book to the publishing house. Our main intention was to help the health practitioners see two, often underestimated aspects of tinnitus, being *the exaggeration of tinnitus symptoms* and *the external stress contributing to the amplification of tinnitus*. Tinnitus is a symptom that clinically requires multiple level competences to be dealt with. Our hope is that the otologists, ENT/ORL specialists, audiologists, and the general practitioners who consult with tinnitus patients and refer them to specialized tinnitus units will benefit from the practical knowledge of stress-related aspects relevant for the treatment of patients with tinnitus.

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Stress and Glucocorticoid Action in the Brain and Ear: Implications for Tinnitus

2

E.R. de Kloet and Agnieszka J. Szczepek

2.1 Introduction

The stress response is nature's tool to facilitate coping and adaptation. However, coping may fail if information is inadequate to predict outcome. Such a lack of control causes feelings of uncertainty and fear, which—if persistent—is damaging to health. The stress response is also activated during adverse conditions such as loud noise, infection, or inflammation that may cause tinnitus.

Tinnitus may be the *consequence* of damage to an auditory system that is insufficiently protected to unwanted stress reactions. Alternatively, tinnitus also is the *cause* of a prolonged state of emotional distress which in itself may aggravate the tinnitus percept (Mazurek et al. 2012). Moreover, lack of control over tinnitus may compromise adequate processing of stressful information and precipitate stress-related pathology. It is therefore of great interest that recent fMRI studies revealed a different processing of emotionally loaded acoustic information in the limbic system of the tinnitus patient (Georgiewa et al. 2016). The studies suggested a functional tinnitus neuronal network that may underlie the cortisol hyporesponsiveness to a severe psychosocial stressor (Hebert and Lupien 2007).

Tinnitus is aggravated by excessive stress reactions.

E.R. de Kloet, Ph.D.
Division of Endocrinology, Department of Internal Medicine,
Leiden University Medical Center, Leiden, The Netherlands

A.J. Szczepek, Ph.D. (✉)
Department of Otorhinolaryngology, Head and Neck Surgery,
Charité University Hospital, Berlin, Germany
e-mail: agnes.szczepek@charite.de

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In this chapter we will focus on cortisol—the principal glucocorticoid hormone of man—and its hypothetical role in generation and/or aggravation of tinnitus. Cortisol is secreted by the adrenal cortex as end product of the hypothalamic-pituitary-adrenal (HPA) axis, which mediates the endocrine stress response. We start with the common concepts of stress, homeostasis/allostasis, and allostatic load. Next, we will discuss the functioning of the HPA axis and the cortisol under basal and stressful conditions. Cortisol action in the brain is mediated by mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), which operate in a complementary manner in processing of stressful information (de Kloet 2014; de Kloet et al. 2005). This implies that also the auditory system is a target of cortisol for better or worse (Kil and Kalinec 2013; Mazurek et al. 2012; Trune and Canlon 2012). Chapter 2 is concluded by asking the question if and how corticosteroids acting through MR and GR expressed in the inner ear, the cochlear neuronal network, and the auditory-limbic system are implicated in tinnitus.

2.2 The Concept Stress, Allostasis, and the Allostatic Load

The term "stress" was coined by the Austrian-Canadian endocrinologist of Hungarian origin—János Hugo Bruno Selye (also known as Hans Selye)—in 1936. Using this term, Selye wanted to describe the "strain or tension" that is building up in the body and brain if the individual is faced with a threat. This state of stress evoked by the stressor is defined as any stimulus that causes on the organismic level a threat to the individuals' psychological and physiological integrity and disrupts cellular homeostasis. The stress response is the array of physiological and behavioral responses aimed to restore homeostasis and integrity. Homeostasis refers to the stability of the "milieu intérieur" (Claude Bernard), e.g., electrolyte concentrations and body temperature that need to be indispensably maintained within narrow limits.

> *Stress is a state of nonspecific tension in living matter, which manifests itself by tangible morphologic changes in various organs and particularly in the endocrine glands which are under anterior pituitary control* (Selye 1936).

The stress concept was initially based on a stimulus-response paradigm. Thus, the experimenter applies a physical stressor (pain, blood loss, ether vapor) and measures the subsequent response. By doing so, Selye highlighted stress as "the syndrome of being sick," which actually captures a state induced by an array of psychological and physical stress reactions. Selye also distinguished three phases upon chronic exposure to a stressor: initial alarm, then resistance, and finally an exhaustion phase, the latter occurring only after several weeks (Selye 1952). This "general adaptation syndrome" had as hallmarks enlarged adrenals, increased vulnerability to infection, and stomach ulcers (both being a consequence of immune resistance being reduced by cortisol) and is considered to be fundamental for pathogenesis of stress-related diseases.

The stress concept developed further with the notion that it is not so much what happens to the individual but rather how the experience is taken or—more importantly—whether coping is successful (Lazarus 2006; McEwen 2007). Coping depends on personality, past experience, controllability (available options), and available information to predict outcome of an action. Self-esteem is important but also social support, sense of safety, and hierarchical position. Accordingly, coping with stress is characterized by a striking difference between individuals. Today's challenge is to identify neuropsychological and biological determinants that could be used for prediction of how given individual will cope in a certain situation.

Since all physical stressors have a psychological component, this has led some researchers to restrict the definition of stress to the ability to cope. Coping depends on the sense of control and predictability of a given situation. Accordingly, stress should be restricted to conditions where an environmental demand exceeds the regulatory and adaptive capacity of an organism, in particular, in case of unpredictability and uncontrollability (Koolhaas et al. 2011). Hence, the most severe stressful condition is no information, no control, and no clue to predict upcoming events and a fearful feeling of uncertainty. This implies that appraisal and anticipation of an either real or imagined situation is in fact the most important determinant of a stressful experience. Appraisal refers to cognitive processes regulated by circuits in the limbic brain (Hermans et al. 2014; Vogel et al. 2016).

The most severe stressful condition includes:

- *No information*
- *No control*
- *No clue to predict upcoming events*

and is characterized by a fearful feeling of uncertainty

To capture this state of readiness in the face of a presumed threat, **the concept of allostasis** was introduced (Sterling and Eyer 1988, 2012). It is not an easy concept primarily because of the variable definitions that are exercised in the literature. McEwen and Wingfield (McEwen and Wingfield 2010) state that allostasis is the "process of achieving stability or homeostasis through physiological and behavioral change," although this viewpoint was also challenged by Day (2005) with the opinion that the stress concept would already sufficiently cover allostasis. In our view, allostasis describes a *labile* equilibrium characterized by structural and functional changes in neuronal networks in anticipation of upcoming events as opposed the homeostatic *stable* equilibrium as in the maintenance of the Na/K balance within narrow limits. The cost of allostasis through energy-consuming adaptations is called **allostatic load** (McEwen and Gianaros 2011).

Seymour Levine, American psychologist and one of the pioneers of stress research, weary of the endless discussion regarding the question "*What is stress?*" turned to use an operational definition:

> Stress is defined as a composite multidimensional construct in which three components interact: (1) the input, when a stimulus, the stressor, is perceived and appraised, (2) the processing of stressful information, and (3) the output, or stress response. The three components interact via complex self-regulating feedback loops with the goal to restore homeostasis through behavioral and physiological adaptations. (Levine 2005)

Allostasis *describes a "labile" equilibrium characterized by variable set points and changes in neuronal network structure and function (comparable with a juggler who keeps a dinner plate in delicate balance on top of a pointer).*

2.3 Mediators of the Stress Response

The principal mediators of the stress response are the HPA axis and the sympathetic nervous system. The latter's workhorses are noradrenaline and adrenaline that evoke centrally a state of arousal, alertness, and vigilance and peripherally the well-known symptoms of the immediate action to deal with imminent danger, i.e., increased heart rate, elevated blood pressure, goose bumps, dry mouth, and suppression of unnecessary reproductive, consummatory, and digestive activities, all in support of Cannon's "fight or flight" reaction (Cannon 1939). In behavioral realm, this immediate coping repertoire was extended with "fright" or "freeze," which is the immobile position the individual assumes in the hope of not to be discovered. The catecholamines make energy substrates available for the subsequent initial defense reactions.

Slower in response is the HPA axis and its adrenal corticosteroid end products. The central conductor of the stress response is located in the parvocellular neurons of the paraventricular nucleus (PVN) in the hypothalamus. The PVN is under control of ascending aminergic neurons originating from the *locus coeruleus* (A6) and the *nucleus tractus solitarii* (A2) that mediate the effect of physical stressors. Psychological stressors are processed in higher brain regions and reach via multiple transsynaptic and inhibitory GABA-ergic network surrounding the PVN (Herman 2013; Herman et al. 2003). The hippocampus has an excitatory input to this network, which implies that stimulation of the hippocampus results in inhibition of the PVN. The amygdala input is inhibitory causing an outcome inhibition of the inhibitory network and thus excitation of the PVN.

The PVN synthetizes besides CRH also vasopressin, which after release during stress in the portal vessels potentiates CRH action on the pituitary level. CRH is responsible for the synthesis of the pro-opiomelanocortin (POMC) precursor of lipotropin (precursor of β-endorphin) and adrenocorticotropin (ACTH), while vasopressin makes intracellular calcium available to enhance in synergy with CRH the

release of ACTH. At the level of the adrenal *zona reticularis*, the synthesis of corticosteroids from cholesterol is initiated causing with some delay the secretion of corticosteroids. The principal corticosteroid of man is cortisol which is secreted in tenfold excess over corticosterone. Rodents lack 11β-hydroxylase and secrete only corticosterone. ACTH also stimulates the growth of the adrenal cortex.

Corticosteroids act back on the body and brain, primarily to contain the initial stress reaction. Presence of corticosteroids suppresses the immune response to infection and the inflammatory reactions to tissue damage. As a result, bacterial and viral infections are not being well controlled by the immune surveillance, and the individuals exposed to chronic stress are more susceptible to infectious diseases. Also in the brain the corticosteroids act back on circuits that were initially involved in processing of stressful information. In principle, the corticosteroids act to contain initial defense (stress) reactions which are essential, but that become damaging if they are overshooting. Marius Tausk, who in the years 1927–1968 acted as a director of the pharmaceutical company Organon, used a metaphor: "*glucocorticoids limit the water damage caused by the fire brigade*" to explain why exogenous glucocorticoids are indicated where the endogenous cortisol is insufficient to contain inflammatory or immune disorders (de Kloet et al. 1998, 2005; Munck et al. 1984; Sapolsky et al. 2000).

Corticosteroid prevents initial stress reactions (e.g., *autonomic, immune, inflammatory, metabolic, neurochemical/physiological*) *from overshooting and becoming damaging themselves.*

Corticosteroids act on immune regulation, the gut microbiome-brain axis, the autonomic nervous system, the renin-angiotensin-aldosterone system (RAAS), and the energy metabolism axis (Dallman 2010). The action of corticosteroids is therefore extremely diverse. For an endocrinologist this may perhaps be not surprising because the task of these hormones is primarily to coordinate and to synchronize these diverse body and brain functions with the goal to promote coping with the stressor. The energy network in the brain largely overlaps with the stress responsive network, as demonstrated by fMRI studies. Corticosteroids are often indicated as glucocorticoids for their activation of gluconeogenesis by breaking down proteins and fatty acids in times of emergency to provide energy substrates. Hence, during episodes of hunger and excessive exercise, corticosteroids are mobilized: the hormones coordinate appetite and food intake with energy disposition and allocation (Dallman and Hellhammer 2011). ACTH also can promote the secretion of aldosterone from the adrenal zona glomerulosa showing how volume depletion and hemorrhage enhance both stress responses (Funder 2015; Jaisser and Farman 2016).

Corticosteroids act on immune regulation, the gut microbiome-brain axis, the autonomic nervous system, the renin-angiotensin-aldosterone system (RAAS), and the energy metabolism axis.

2.4 Pulsatility of the HPA Axis

The HPA axis has two modes of operation: the axis mediates the response to stress and coordinates the circadian activities related to, e.g., feeding, drinking, and sleep-related events. For this purpose the corticosteroids are secreted in pulsatile fashion (Lightman and Conway-Campbell 2010).

Biological rhythms:

CIRCADIAN—rhythm of about 24 hours
DIURNAL—24 hour rhythm pertained to daylight
ULTRADIAN—rhythm with periods shorter than the 24 h circadian cycle
INFRADIAN—rhythm with periods longer than the 24 h circadian cycle

About every hour cortisol and corticosterone are secreted in bursts with largest amplitude around the time physical activity starts. Thus in man the highest secretory pulse is around awakening in the morning: the cortisol awakening response. In rodents which are nighttime animals, corticosterone is highest at the beginning of the dark period. This pattern of corticosteroid pulses shows therefore a characteristic circadian variation with a peak at the beginning and a trough at the end of the activity period. In fact, high corticosteroid concentrations prevent the onset of slow wave sleep (Groch et al. 2013). The networks involved in sleep-wake overlap partly with energy and stress networks (e.g., orexin) and are targets for corticosteroids (Dallman and Hellhammer 2011).

Ultradian rhythmicity regulates tissue responsiveness to stress-induced corticosteroid action.

The hourly ultradian cycles can vary in amplitude, frequency, and organization. For instance, depression is characterized by a larger cortisol amplitude particularly at nighttime, a phenomenon that contributes to the disturbance in sleep hygiene (Groch et al. 2013). Inflammatory disorders display a higher ultradian frequency, and with aging, the pulses diminish in amplitude and become disorganized. In fact, ultradian rhythmicity provides a mechanism to maintain responsiveness of tissues and cells to corticosteroids. Indeed enhanced corticosteroid responsiveness was demonstrated when the effect of pulsatile vs constant exposure to corticosteroids was compared: responsiveness diminished in flattened circulating corticosteroid patterns (Sarabdjitsingh et al. 2010b). Such flattened patterns occur with corticosteroid replacement therapy in case of adrenal insufficiency or during pharmacotherapy with synthetic glucocorticoids (de Kloet 2014).

Stress-induced corticosteroid secretion can occur anytime during the ultradian rhythm of the hormone. If in adrenalectomized animals an hourly pulsatile rhythm

was mimicked with corticosterone infusion, a stressful challenge triggered a much more profound corticosterone secretion at the ascending rather than the descending arm of the pulse (Sarabdjitsingh et al. 2010a). The dynamics of circulating corticosteroid concentrations clearly demonstrate that for the assessment of HPA axis activity *only patterns matter*. Single-point measurements of the hormone in either saliva or blood are useless because of the ultradian variations and stressful influences that often may occur.

2.5 Access of Corticosteroids to Brain Targets

Multidrug resistance P glycoprotein (Pgp or MDR1) is a cell membrane protein that pumps various substances from the cell to the extracellular environment. Because of its activity, Pgp is a barrier to exogenous substances. Synthetic glucocorticoids such as dexamethasone are recognized by Pgp as substrates and are removed from the cells (de Kloet 1997; Meijer et al. 1998). This has been elegantly demonstrated in vitro. That dexamethasone is a substrate for Pgp can also be demonstrated in vivo using Pgp knockout mice. Upon administration of ^{3}H-labeled dexamethasone or ^{3}H prednisone (Karssen et al. 2002) to these mutants, the radioactive steroids were demonstrated to accumulate in the typical target sites: hippocampus, PVN, and biogenic amine neurons. Surprisingly, the ^{3}H-labeled cortisol that is also not retained in wildtype mice with the proper activity of Pgp pump shows profound retention in the Pgp knockouts (Karssen et al. 2001). Hence, corticosterone seems the only steroids that readily penetrate the mouse brain, since also the penetration of aldosterone is hampered. This remarkable dichotomy between cortisol and corticosterone is maintained in people. While in the blood, the ratio cortisol/corticosterone is 10:1, this ratio is decreased to 10:4 in the cerebrospinal fluid (Karssen et al. 2005).

The access of corticosteroids to its brain receptors is regulated by P-glycoprotein transporters in the blood-brain barrier and by an intracellular oxidoreductase.

There is an additional, intracellular mechanism that determines access of corticosterone, cortisol, and aldosterone to the nucleus and finally to the genome. The enzyme 11-β-hydroxysteroid dehydrogenase type 2 (HSD-2) is an oxidase that specifically inactivates cortisol and corticosterone, but not aldosterone. HSD-2 acts as gatekeeper blocking access of the naturally occurring glucocorticoids but allowing binding of bioactive aldosterone to the mineralocorticoid receptors (MR) and the genome (Edwards et al. 1988; Funder et al. 1988). In adult rodent brain, the expression of HSD-2 is discrete and restricted to some periventricular tissues where aldosterone activates circuits involved in salt appetite. Remarkably, also the solitary nucleus

(NTS) near the area postrema expresses abundantly HSD-2. This group of cells has projections innervating the forebrain and provides the limbic-forebrain circuits with an aldosterone-selective mechanism which have been postulated to underlie salt appetite and preference and harbors vital cognitive functions to store spatial information on salt resources (Geerling and Loewy 2009). The HSD-1 isoform is a reductase widely present in the brain and has the capacity (e.g., in the liver) to regenerate bioactive cortisol and corticosterone. Inhibitors to the HSD-1 isoform were developed as a strategy to limit overexposure to corticosteroids (Chapman et al. 2013).

The Fukushima disaster from 2011 has significantly increased the incidence of tinnitus and Ménière syndrome in the local population.

Both HSD proteins have been found in the inner ear: HSD-2 was found in the endolymphatic sac of the inner ear of rodents (Akiyama et al. 2010), whereas HSD-1 was identified in the *stria vascularis* and in the outer and inner auditory hair cells (Terakado et al. 2011). Endolymphatic sac is responsible for the resorption, transport, and recirculation of ions in the entire inner ear, i.e., in the cochlea and in the vestibular system. It is believed that individuals diagnosed with the **Ménière syndrome** have occasionally increased hydraulic pressure within the inner ear endolymphatic system often attributed to the hyperactivity of the endolymphatic sac. This hyperactivity induces a triad of symptoms: **vertigo**, **hearing loss**, **and tinnitus**. Interestingly, patients with Ménière syndrome often report having an attack after being exposed to emotional stress. In the inner ear, upon stress-induced overproduction of cortisol, the decreased activity of HSD-2 or the increased activity of HSD-1 could lead to upregulated infiltration of cortisol, decreased accessibility of aldosterone, and dysregulation of ion dynamics that are responsible for the attacks. Unfortunately, no study addressed this issue in people yet, as only a postmortem study could answer open questions. Recently published systematic review revealed two facts: the first one was confirmation of the association between Meniere syndrome and posttraumatic stress disorder and health anxiety, whereas the second was a need for large, properly designed and conducted epidemiological studies (Kirby and Yardley 2008). Recent study investigating the incidence of otological conditions following the disaster in Fukushima (earthquake and subsequent nuclear accident) in the local Fukushima population demonstrated significant increase in the number of new cases of Ménière syndrome and also of tinnitus coinciding with an increased number of comorbid mental stress-related conditions, such as depression or anxiety (Hasegawa et al. 2015).

2.6 Corticosteroid Receptors

In 1968 Bruce McEwen made a landmark discovery (McEwen et al. 1968, 2015). He discovered that ^{3}H-corticosterone given to adrenalectomized animals was not retained as expected in the hypophysiotropic region in the hypothalamus but in the

hippocampus. In subsequent studies, de Kloet et al. (1975) discovered that the potent synthetic glucocorticoid dexamethasone was not retained by these receptors and also did not compete for ^{3}H-corticosterone or ^{3}H-aldosterone retention, suggesting the presence of two distinct receptor populations for corticosteroids. The pattern of ^{3}H-aldosterone retention appeared to match localization of HSD-2, particularly in NTS (Geerling and Loewy 2009).

In the mid-1980s, the existence of two types of receptors for corticosteroids in the brain was demonstrated. The receptors were cloned and identified as the mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (Evans and Arriza 1989). Around the same time, Reul and de Kloet (1985) demonstrated with binding studies that the rat hippocampus contained two receptor populations that did bind corticosterone with different affinity. The high affinity binding sites were designated type 1 receptors and later MR, the lower affinity sites—type 2 receptors—and later GR. Since in rodents and humans the principal corticosteroid (corticosterone and cortisol, respectively) circulates in a 100–1000-fold excess over aldosterone, these steroids are the predominant MR ligands in vivo. MR is abundantly expressed in limbic brain structures, e.g., hippocampus, lateral septum, and amygdala. GR binds cortisol and corticosterone with a tenfold lower affinity than MR and is widely distributed in neurons and glial cells with highest expression in PVN, limbic structures, and neocortical regions (de Kloet et al. 1998, 2005; de Kloet 1991).

The presence of MR and GR was demonstrated in the inner ear and a very distinct expression pattern of the receptors was shown (Fig. 2.1). *Stria vascularis* contains predominantly MR, which is in agreement with its function, namely, recycling and regulating K+ (and Na+). The spiral ganglion neurons contain predominantly GR, whereas the rest of the cells in the cochlea (auditory hair cells, supporting cells, fibrocytes, interdigital cells, and spiral limbus cells) contains both—MR and GR (Basappa et al. 2012).

The implication of the difference in affinity of the MR and GR for corticosterone and cortisol is differential occupation of these two receptor types during circadian variation and after stress. This differential activation of MR and GR as a function of circulating steroid concentration provided for over 30 years the experimental basis for research on neuronal networks underlying stress coping, behavioral adaptation, and energy metabolism (Dallman 2010; de Kloet 1991, 2014, 2016; de Kloet and Reul 1987; Lupien et al. 2009; McEwen et al. 2015).

Since MR and GR are transcription factors regulating gene expression, they are expected to interact with the genome upon binding their ligand. Using chromatin immunoprecipitation (ChIP) followed by a deep sequencing (ChIP seq), Nicole Datson and Annelies Polman have made a complete inventory of all genomic binding sites for MR and GR in the hippocampal genome (Polman et al. 2013). They observed that 40% of the GR binding sites are within the genes. The experiment involved adrenalectomized animals injected with increasing doses of corticosterone. Also on the genomic level, two populations of genome binding sites for MR and GR were found. Already at a low dose, MR/corticosterone complex associated with DNA and this binding remained relatively constant up to 3 mg of administered corticosterone. GR did bind only at higher doses of corticosterone to DNA binding sites, thus reflecting the differential binding of MR and GR to corticosterone.

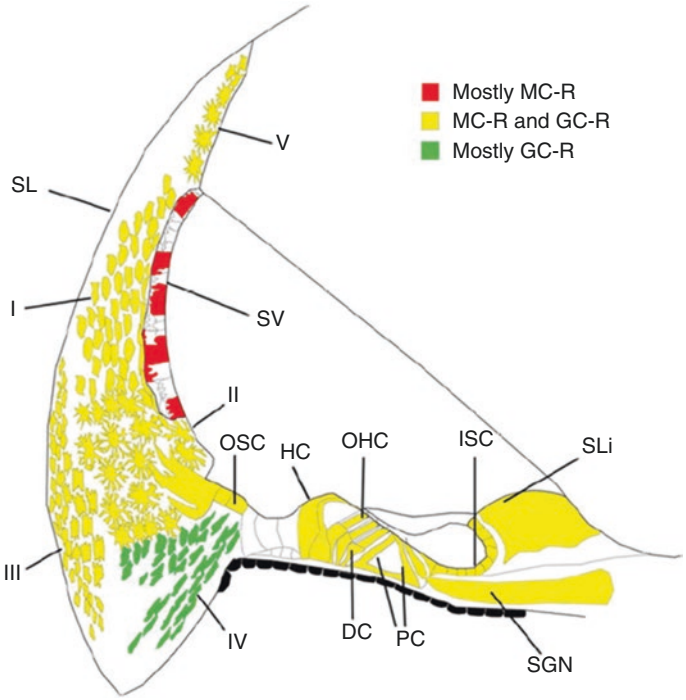

Fig. 2.1 Distribution of MR and GR in the cochlear tissues. *OHC* outer hair cells, *IHC* inner hair cells, *DC* Deiters cells, *IP* inner pillar cells, *OP* outer pillar cells, *HC* Hensen cells, *SV* stria vascularis, *SL* spiral ligament, *SLi* spiral limbus, *ISC* inner sulcus cells, *OSC* outer sulcus cells, *SGN* spiral ganglion neurons, *SP* spiral prominence, *PC* pillar cells (From Kil and Kalinec 2013, Reprinted with permission) (Kil and Kalinec 2013)

Binding of mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) with differential affinity to endogenous corticosteroids enables distinct responses during circadian cycle and after stress.

Moreover, using a neurophysiological approach Marian Joëls and Henk Karst discovered as yet another surprise hidden in corticosteroid receptorology. They demonstrated that pyramidal and dentate gyrus neurons of the hippocampus and neurons of basolateral amygdala harbored an MR variant that responded rapidly to corticosterone, cortisol, and aldosterone (Joels and Baram 2009; Joels and de Kloet 2012; Karst et al. 2005). This membrane MR was deleted in the MR knock animals, and the signal was maintained when the steroids were applied when penetration in the cell was prevented because of coupling of the ligand to bovine serum albumin. Activation of the receptor caused within minutes increased excitatory postsynaptic potentials (EPSP) indicating a rapidly enhanced release of the excitatory transmitter glutamate.

The membrane MR-mediated action depended on an ERK1/2 pathway (Olijslagers et al. 2008). Simultaneous with MR-induced glutamate release, the voltage dependent I(A) K current at the postsynaptic membrane was decreased. Moreover, probably as a result of increased synaptic release of glutamate, the presynaptic mGLU2/3 receptor was downregulated (Nasca et al. 2015). Also GR appeared to entertain a lower affinity GR membrane variant that mediated the release of cannabinoids for transsynaptic inhibitory action on the presynaptic release of glutamate (Di et al. 2003).

2.7 Behavioral and Neuroendocrine Feedback Action of Corticosteroids in the Brain

Corticosteroids secreted by the adrenals after stress exert a negative feedback action to suppress the enhanced HPA axis activity (Fig. 2.2). This phenomenon was demonstrated by a classical endocrine experiment in 1938 by Dwight Ingle (see Raff 2005). He was the first to show that ACTH was needed for adrenal growth and steroid secretion by administering the peptide to hypophysectomized animals. Next, Ingle showed that corticosterone given to the ACTH-treated animal did not affect adrenal weight while it suppressed adrenal weight in the intact animal. Hence, corticosterone exerted in high doses pituitary feedback on ACTH release.

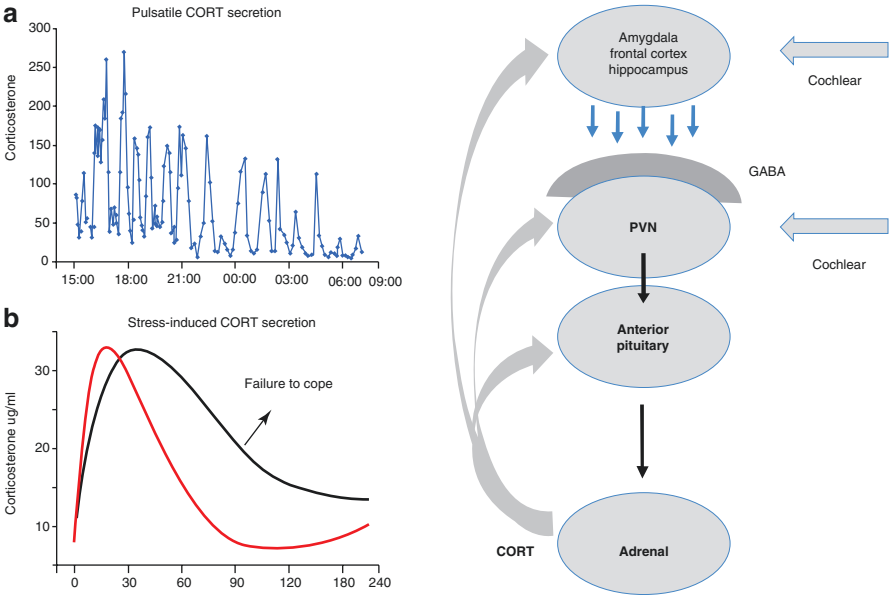

Fig. 2.2 HPA axis: Stress response and ultradian B rhythm. Pulsatile (**a**) and stress-induced CORT (**b**) secretion. The latter figure shows that a prolonged secretion of CORT develops under conditions of failure to cope with stress

Subsequent research demonstrated different levels of corticosteroid feedback operation. The *first level* is on the anterior pituitary level—as noted by Ingle—and mediated by GR expressed in the corticotrophs. This feedback site responds to potent synthetic glucocorticoid such as dexamethasone and very high levels of endogenous cortisol and corticosterone (de Kloet et al. 1974). The onset of suppression occurs with a delay of 30 min, and in case of dexamethasone, the suppression may last several hours, even more than 12 h as used in the dexamethasone suppression test with or without CRH (see Box 2.1). The rise and fall of the dexamethasone suppression test in endocrine psychiatry is wonderfully described in "The riddle of Melancholia" (Shorter and Fink 2010).

Box 2.1

Dexamethasone suppression test (DST): A low dose of dexamethasone is administered at 11.00 pm and plasma cortisol levels are measured the next morning at 9.00 am. In a hyperactive HPA axis—as occurs in depression—cortisol will escape from dexamethasone suppression at that time (Carroll et al. 1976).

Combined dexamethasone-CRH test: dexamethasone is administered at 11.00 pm, but in addition the next afternoon, CRH is administered, and plasma cortisol levels are measured at 15, 30, and 45 min post CRH (Heuser et al. 1994).

The *second* level is at higher brain regions harboring circuits that process stressful information and that communicate transsynaptically with the GABA-ergic network surrounding the PVN. The steroid feedback is complex in these circuits and operates over different time domains depending on the nature and severity of the psychological stressor. The coordinate action exerted by corticosteroids via membrane and genomic MR and GR adds to this complexity (Dallman and Hellhammer 2011; de Kloet 2014).

Figure 2.3 shows the role of MR and GR in processing of stressful information in the limbic brain with the goal to support coping and adaptation. Corticosteroids affect virtually every step from detection and perception of a salient event triggering emotional arousal and appraisal processes until coping, adaptation, and memory storage of the experience to be prepared if a similar encounter occurs in the future. Thus, first corticosteroids affect the detection threshold and perception of auditory information. Lack of steroids was found to enhance detection at the expense of perceiving the significance of the acoustic signal (Henkin and Daly 1968). Next, arousal is triggered (Pfaff et al. 2007) and is necessary for the limbic structures to function optimally in assessment of the valence of a novel experience and selection of an appropriate coping style.

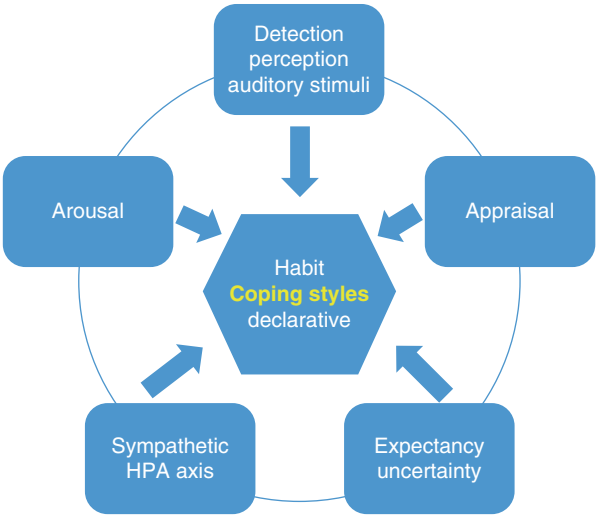

Fig. 2.3 Processing of salient acoustic information

Using a large variety of behavioral tests, Melly Oitzl et al. (Oitzl et al. 2010; Oitzl and de Kloet 1992) have carefully dissected the role of MR and GR during stress coping and adaptation. Thus, corticosteroid appeared to rapidly promote appraisal processes of newly acquired information, retrieval of contextual information, and selection of an appropriate coping style. Since these MR-mediated actions proceed rapidly, they most likely are exerted by the membrane receptor variant regulating excitatory transmission; GR becomes activated only with high amount of corticosteroids induced by stress. GR activation is important for restoring cellular homeostasis and promoting allostatic processes, behavioral adaptation, and memory storage of the experience and coping style. By doing so the input from higher brain regions subsides resulting in attenuation and at last termination of stress-induced HPA axis activity because of adaptation (Box 2.2 and Fig. 2.3).

Box 2.2

- *Limbic genomic MR regulates increases of the excitability of the hippocampus and its afferents to*, e.g., *the mesolimbic dopaminergic reward system.*
- *Limbic membrane MR is involved in encoding and retrieval of information important for appraisal processes and selection of a coping response.*
- *Genomic and membrane GR enhance allostatic processes, facilitate behavioral adaptation, and promote memory storage of the experience.*
- *These actions mediated by MR and GR are complementary in detection, perception, and processing of sensory* (e.g., *auditory*) *information.*

2.8 Role of MR and GR in Coping with Stress

Firstly, MR activation directs coping style. Lars Schwabe et al. (2010a) demonstrated that exposure to a stressful situation switches the coping style. Under resting conditions the rodent uses multiple cues in order to memorize the location of a food resource. If exposed to stress, the animal switches rapidly to a simpler stimulus response. In rodents the pathway activated chronically by a stressor switches from hippocampus toward the dorsal striatum supporting habit-like behavior (Dias-Ferreira et al. 2009). The phenomenon is also observed in humans: with fMRI it was shown that during stress the amygdala-hippocampus pathway rapidly switched to the amygdala-striatum connectivity (Schwabe et al. 2013; Vogel et al. 2015, 2016).

The switch from hippocampus to striatum was observed in males. If the same experiments were performed in females, the opposite results were obtained. Females under resting conditions were rather poor in spatial performance as compared to their male counterparts. Under stress the situation was reversed, females performed better, and these differences were eliminated in the MR forebrain knockout mice (ter Horst et al. 2012). Thus, context and sex determine the outcome of the MR-mediated functions in coping with stress. Anti-mineralocorticoids blocked the switch from hippocampus to striatum in rodents and man (Schwabe et al. 2010b, 2013; Vogel et al. 2015, 2016). Moreover, active vs passive coping style in mouse and rat lines correlates with MR expression in the hippocampus (Cabib and Puglisi-Allegra 2012; Veenema et al. 2003).

Secondly, GR activation promotes adaptation and memory storage. It appeared that GR-mediated effects on memory storage required the presence of noradrenaline (Joels et al. 2012; Roozendaal and McGaugh 2011). For this purpose GR mediates a plethora of activating and suppressive actions in discrete brain regions. Thus, in the CRH neurons of the amygdala GR stimulates the synthesis and release of CRH, while the reverse occurs in the PVN (Zalachoras et al. 2016). In the amygdala, GR promotes and extends MR-mediated glutamatergic excitation (Karst et al. 2010). In the hippocampal pyramidal neurons, MR enhances excitability, which is subsequently suppressed by subsequent stimulation of GR by higher concentrations of corticosteroids (Joels and de Kloet 1989, 1990, 1992). In addition multiple neuropeptide systems (oxytocin, vasopressin) are activated by stress which exert in specific behavioral domains their context-dependent effects on processes modulating the stress response. For instance, oxytocin stimulates bonding and social support, which facilitates coping with a stressful situation (Barrett et al. 2015; Young 2015).

Third, the limbic MR is important for the tone of the HPA axis and sympathetic nervous system. For instance, the higher the hippocampal MR expression, the lower the basal pulsatile and stress-induced HPA axis activation, and thus the average amount of corticosteroids secreted over 24 h is decreased. Under MR antagonists applied intracerebroventricularly enhance basal and stress-induced HPA axis activity (Ratka et al. 1989) and act as an anxiolytic (Korte et al. 1995) and anti-aggressive (Kruk et al. 2013) agent. MR antagonists also decrease the blood pressure response to a stressor (van den Berg et al. 1990). This effect mediated by MR appeared to depend on the condition of 30 min warming the animal which is needed to do a

proper tail sphygmographic measurement of the blood pressure. Using this warming/stress condition of the indirect tail cuff method, the direct telemetric recording revealed that MR antagonist blocked autonomic outflow and, interestingly, now suppressed the stress-induced HPA axis response (de Kloet et al. 2000; Van den Berg et al. 1994).

Collectively, these observations have led to the formulation of the corticosteroid receptor balance hypothesis:

> Upon imbalance in MR: GR-regulated limbic -cortical signaling pathways, the initiation and/or management of the stress response is compromised. At a certain threshold this may lead to a condition of HPA axis dysregulation and impaired behavioral adaptation, which can enhance susceptibility to stress-related neurodegeneration and mental disorders. (de Kloet 2014, 2016; de Kloet et al. 1991, 1998, 2005, 2016; de Kloet and Molendijk 2016; Holsboer 2000)

2.9 MR:GR Balance: Genetics

Genetic variants of MR, GR, and their regulatory proteins such as, e.g., FKBP5, have been identified that appeared associated with HPA axis regulation, emotional expressions, and cognitive performance. Genetic variation may alter control in the promotor and translation region and result in an altered primary structure. The GR variant N363S was found hypersensitive to cortisol and associated with an unhealthy metabolic profile, while E22/23EK is linked to steroid resistance and enhanced risk of depression. The Bcl-1 polymorphism predicts cardiovascular risk and contributes to individual differences in emotional and traumatic memories as well as PTSD symptoms after intensive care treatment (Quax et al. 2013).

In the MR gene, the rs5522 (minor allele frequency 12%) is an A/G SNP located in exon 2, which causes an amino acid change (I180V) in the N-terminal domain of the protein. Roel de Rijk discovered that this G-allele is a loss of function variant as shown by a reduced transactivation capacity in vitro (DeRijk et al. 2006). These G-allele carriers showed increased HPA axis and autonomic reactivity in response to psychological stressors. Moreover, Bogdan reported an association of MR gene variation with depressive symptoms and deficits in reward-motivated learning induced by stress and heightened stress-induced amygdala activity (Bogdan et al. 2010, 2012). Interestingly, the same G-allele is with a high odd ratio considered a risk factor in reverse remodeling in heart failure patients undergoing cardiac resynchronization therapy (De Maria et al. 2012).

Another MR SNP, rs2070951 (C/G), minor allele frequency 49.3%, is located 2 nucleotides before the translation start site. The G-allele produces less MR in vitro and is associated with increased renin and aldosterone and elevated blood pressure (van Leeuwen et al. 2010).

The rs5522 and rs2070951 are in linkage disequilibrium, and if merged, three common haplotypes can be identified. Haplotype (hap) 2 (CA, frequency 35%) is a gain of function variant as was shown from the increased transactivation capacity and increased translation of MR protein in vitro, while hap 4 (GG) is very rare and

produces strongly reduced MR activity as compared to hap 1 (GA, frequency 49%) and hap 3 (CG, frequency 12%) (Hamstra et al. 2015; van Leeuwen et al. 2011).

Carriers of a "gain of function" MR C/A haplotype display dispositional optimism and effective coping styles and are protected from depression.

Hap 2 carriers had lower scores on the Trier Inventory for Chronic Stress (TICS) subscales "excessive demands at work" and "social overload." In females, hap 2 appeared associated with dispositional optimism, optimistic risk decision-making in gambling tests, less rumination, and less feelings of hopelessness. GAIN cohort study ($N = 3600$) has demonstrated that hap 2 carriers are protected from depression (Hamstra et al. 2015; Joels et al. 2008; Klok et al. 2011). Further, this haplotype moderates the effect of childhood maltreatment and depressive symptoms in a population-based cohort ($N = 665$) and an independent clinical cohort from the Netherlands Study of Depression and Anxiety (NESDA, $N = 1639$) (Vinkers et al. 2015).

2.10 MR/GR Balance: Phenotype

Selye showed that a relative excess of mineralocorticoids was pro-inflammatory, while excess of glucocorticoids increased the risk for infection and expressed this view in the *pendulum* hypothesis. The *balance* hypothesis, however, is based on one single corticosteroid hormone which maintains homeostasis via two distinct and co-localized receptor types that carry the pharmacological activity of Selye's two hormones: the MR and GR (de Kloet 1991). As was pointed previously, the MR in the brain, heart, and fat cells binds cortisol and corticosterone rather than aldosterone and does so with a tenfold higher affinity than GR.

Over the past 30 years, the MR/GR balance has been challenged using endocrine, pharmacological, and genetic approaches. The outcome of these challenges was measured on the molecular levels using genomic approaches and on the cellular level with neuroanatomical and electrophysiological techniques, and behavioral and physiological responses were recorded in a great variety of paradigms (de Kloet 2014, de Kloet and Joels 2016; de Kloet and Molendijk 2016; de Kloet et al. 2016; Joels et al. 2012).

Below are some general characteristics of MR/GR imbalance:

Genetically selected rat or mouse lines or strains that display overexpression of MR have a reduced HPA axis tone as expressed by lower basal and stress-induced levels of corticosterone (Harris et al. 2013; Veenema et al. 2003). The male animals have an active coping style if dealing with an inescapable stressor, a high sympathetic tone and reduced 5HT function (Veenema et al. 2003). They show less anxiety in the home environment and improved cognitive performance in

maze learning and fear-motivated tasks. Their behavior once learned perseverates. This phenotype is mimicked in mice with forebrain MR overexpression, particularly in the face of reduced GR. It seems as if limbic overexpression of the MR facilitates during stress the switch from costly time-consuming declarative hippocampal learning and memory processes to a rapid and effective striatal habit performance as coping style. However, these dominant high MR expressing animals become prone to anxiety in novel situations where they have lost control (de Kloet et al. 2016).

Increased MR function in the hippocampus is protective to stress under conditions of high controllability and readily shifts coping from a time- and energy-consuming declarative hippocampal to a more direct striatal habit style.

Exposure to chronic stress decreases the expression of hippocampal MR. Likewise rats or mice exposed to adverse early life conditions have at later life reduced MR. Reduced hippocampal MR expression is observed at senescence and is a characteristic of the depressed patient's hippocampus measured postmortem. Antidepressants increase the synthesis of hippocampal MR. Rats with viral overexpression of MR in the dentate gyrus showed improved short-term memory and were protected against the impairing effect of 3 weeks of corticosterone in a nonspatial object recognition paradigm (Ferguson and Sapolsky 2007). In mutant mice, forebrain MR overexpression restored impaired learning induced by chronic stress but only in a low arousing task. This behavioral change in the MR overexpression mice was paralleled by a normalization of hippocampal dentate gyrus function (Kanatsou et al. 2015).

That chronic stress affects the hippocampus is obvious from the profound neuroanatomical changes: the CA3 pyramidal neurons atrophy and dentate gyrus neurogenesis is reduced (McEwen 2016). Using microarrays it was found that the widely diverse gene patterns were reduced to only a few pathways that regulate chromatin organization, epigenetics, apoptosis, and inflammatory responses in the dentate gyrus. One highly responsive gene network revealed by this procedure is the mammalian target of rapamycin (mTOR) signaling pathway which is critical for different forms of synaptic plasticity and appears associated with depression (Datson et al. 2013; Polman et al. 2012).

2.11 Implications for Tinnitus

Tinnitus is a phantom sound indicating malfunction of the central auditory system. The causes of tinnitus include damage to the inner ear and consequent changes in the auditory system. The damage may, for instance, be due to aging, noise exposure, infections, altered vascular integrity, and inflammatory responses

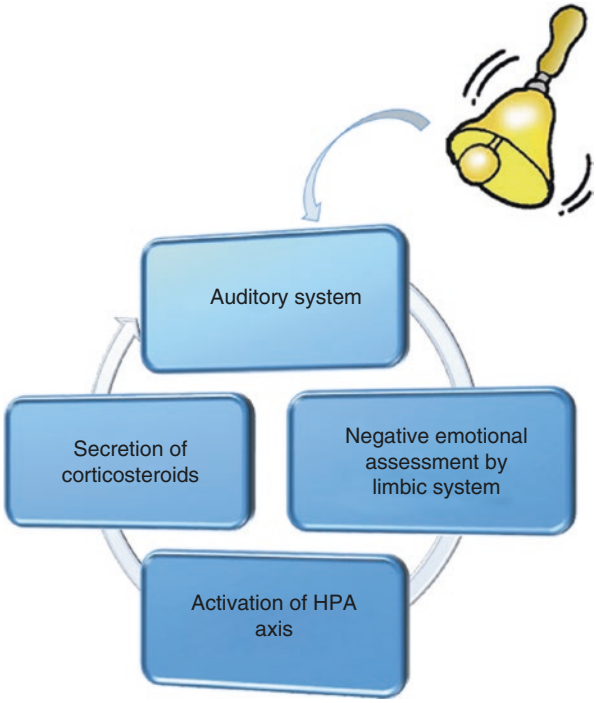

Fig. 2.4 Consequences of connectivity between the auditory and limbic systems

because of hypertension or atherosclerosis and local head or neck injuries (Knipper et al. 2013).

The auditory system comprises the neuronal cochlear circuit connected with the auditory cortex via the olive nucleus and the midbrain geniculate nucleus. This circuit enables arousal via the brainstem-midbrain reticular system and communicates with limbic circuitry (McIntosh and Gonzalez-Lima 1998; Middleton and Tzounopoulos 2012). Each acoustic stimulus received by the ear and passed via the process of auditory transduction into the central auditory pathway undergoes assessment leading to emotional reactions. The majority of acoustic signals are evaluated as neutral but part is appraised with positive or negative emotional weight. This assessment is possible due to the connectivity of auditory brainstem and auditory cortex with limbic circuits in the amygdala, hippocampus, and prefrontal cortex regions (Kraus and Canlon 2012); it is active not only during the awake phase but also during phases of the non-REM sleep (Portas et al. 2000). Thus, the connectivity between the auditory and limbic systems is involved in detecting adversity, danger, and regulation of the HPA axis (Fig. 2.4).

In patients with disturbing tinnitus, the persistent phantom sound is continuously evaluated and classified by the limbic system as adverse and thus negative (Rauschecker et al. 2010). This may in turn lead to a long-term dysregulation of the HPA axis characteristic for a condition of chronic stress (Fig. 2.5). Some of the consequences of the tinnitus-induced chronic stress effects are, for instance, insomnia, as the limbic system signals danger and keeps the victims of tinnitus awake. It

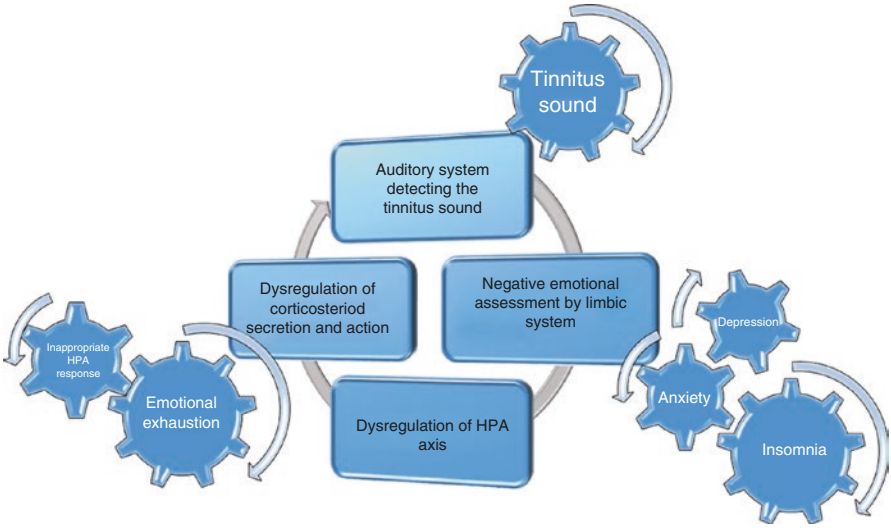

Fig. 2.5 Influence of tinnitus percept on the auditory and limbic systems

would be of interest to accommodate these findings to the current knowledge of the action of corticosteroids, since previously it has been reported that tinnitus patients display hypocortisolism upon exposure to severe psychosocial stressors (Hebert and Lupien 2007). One scenario is therefore that this "hypocortisolism" provides an insufficiently large cortisol signal that is not capable to control the central stress reaction evoked by auditory adversity (see Sect. 3). This would suggest the existence a cortisol sensitive tinnitus connectome or neuronal network underlying an acoustic-induced allostatic load/chronic stress phenotype (McEwen and Wingfield 2010). Recent evidence indeed suggests tinnitus-specific connectivity of a functional limbic neuronal network involved in processing of emotionally loaded and emotionally neutral acoustic information which could be the tinnitus signature of such an altered phenotype (Georgiewa et al. 2016).

Evidence emerges for a corticosteroid-responsive functional neuronal network presenting a tinnitus signature in biological correlates.

Not all of the subjects with tinnitus are disturbed by its sound; however, those who are suffer greatly from tinnitus-related insomnia and concentration problems. In addition, about 50% of patients with tinnitus has additional mental comorbid condition(s) such as depression or anxiety (Pattyn et al. 2016; Zirke et al. 2013), and these are known to be set off or amplified by the emotional stress and MR/GR imbalance (de Kloet et al. 2016).

Tinnitus may cause emotional distress and, finally, stress-related pathology. At the same time, emotional exhaustion or the pathology accompanying posttraumatic stress

disorder was suggested to be predisposing for tinnitus (Fagelson 2007; Hebert et al. 2012; Hinton et al. 2006). The argument is presented by the seminal experiments of Sylvie Hébert et al. (Hebert et al. 2012; Hebert and Lupien 2007; Mazurek et al. 2015). These authors reported a blunted cortisol response to the Trier Social Stress Test and enhanced suppression of the morning rise in cortisol by a low dose of exogenous dexamethasone administered at 11 pm on the previous day (Simoens and Hebert 2012). Collectively, these data reveal an HPA axis phenotype of tinnitus resembling that of fibromyalgia, chronic fatigue syndrome, posttraumatic stress syndrome, and atypical depression, which are all characterized by a relative underexposure to cortisol during stressful conditions (Chrousos and Gold 1992). Such a reduced cortisol secretion maybe the consequence of an overactive limbic MR conveying an enhanced inhibitory tone over the HPA axis. The recently uncovered cytokine signature of tinnitus would fit in a phenotype of an altered functional ratio of MR over GR activity (Betancur et al. 1995; de Kloet et al. 1994) causing prevalence of pro-inflammatory cytokine synthesis (Szczepek et al. 2014).

That cortisol is of relevance for auditory processing is known for a long time. Adrenally deficient patients were shown to have lower detection threshold in the frequencies 500 and 1000 Hz than the healthy controls but have a deficit in speech discrimination (Henkin and Daly 1968). This increased detection and decreased perception cannot be ameliorated by deoxycorticosterone, but the detection threshold was normalized upon ACTH, prednisolone, and fludrocortisone treatment, the latter with either dexamethasone, prednisolone, or cortisone (Henkin and Daly 1968). Corroborating this early clinical finding, recent study demonstrated that although the rats with impaired adrenal function have intact function of the outer hair cells in the inner ear, their distortion produces otoacoustic emissions (DPOAE). These adrenally deficient animals also have significantly elevated auditory brainstem responses (ABR) which are consistent with impaired tone and speech perception in people (Dogan et al. 2015) and indicative of neuronal processing rather than sensory malfunctioning. Further, in support of clinical findings, dexamethasone reversed this impairment auditory information processing. Hence, it seems that enhancing GR function contributes to reinstatement of normal auditory function. Another argument for a positive action of corticosteroids on the auditory system is the therapeutic use of synthetic corticosteroids (prednisone, dexamethasone) to treat inner ear illnesses such as sudden sensorineural hearing loss (SSHL)—a condition that is always accompanied by tinnitus (Hobson et al. 2016; Leung et al. 2016) or idiopathic tinnitus (Barreto et al. 2012; Dodson and Sismanis 2004).

Corticosteroid receptors are expressed in the inner ear and auditory networks in the brain. Several areas of the inner ear are richly endowed with MR and GR (Fig. 2.1) (Kil and Kalinec 2013; Terakado et al. 2011). The current notion is that glucocorticoids prevent the hearing loss via GR because of their anti-inflammatory and immunosuppressive action, while the aldosterone-selective MR is involved in maintenance of ion homeostasis required for optimal hearing (Meltser and Canlon 2011). Since 85% of subjects with tinnitus have some degree of hearing loss (Mazurek et al. 2010), it would be very interesting to examine whether prevention of hearing loss is connected with prevention of tinnitus. Also the cochlear neuronal network expresses differentially in discrete nuclei MR and GR. However, so far no

systematic studies have been reported on the function of these brain receptors in the onset and modulation of tinnitus.

2.12 Corticosteroids-Based Treatment Options

Synthetic corticosteroids are used since decades as systemic or local therapy for tinnitus. Dexamethasone and methylprednisolone are most commonly used, and the administration routes vary from per os, intravenous injection to **intratympanic injections** (see Table 2.1). Recent systematic review scrutinized clinical studies that used the latter method and concluded lack of effectiveness (Lavigne et al. 2016). However, the authors also recognized that the extreme heterogeneity of the clinical protocols and the lack of long-term follow-up undermined their disappointing conclusion.

Lack of successful pharmacological treatment for tinnitus reflects lack of a clear-cut, worldwide accepted classification of tinnitus. Tinnitus is a symptom that can accompany numerous diseases. Curative treatment for tinnitus may depend on its cause. In agreement with this, a case report was published, in which the authors claim that **epidural injection** with triamcinolone acetonide was successfully used to cure the patient from chronic tinnitus (McCormick and Walega 2015). The patient

Table 2.1 Intratympanic steroid injections in tinnitus treatment

References	Patient selection	Dosage	Groups	Results
Choi et al. (2013)	Refractory	Dex 5 mg/mL	15 ITSI 15 Salin	THI 33.3%^{NSS} 40%
Shim et al. (2011)	Idiopathic < 3 months	Dex 5 mg/mL	42 Ala 46 Ala + ITSI 44 Ala + ITSI + PSTG	Cure rate 9.8% 25.8%^{SS} 20.0%^{SS}
Topak et al. (2009)	Refractory	MP 62.5 mg/mL	30 MP 29 Salin	SATLSI 21%^{NSS} 22%
She et al. (2010)	Refractory	MP 0.25 mg/mL Dex 5 mg/mL CBZ 300 mg	35 MP 24 Dex 25 Carb	Control rate 45.7%^{NSS} 29.2%^{NSS} 36.0%
Araujo et al. (2005)	Refractory + severe and disabling	Dex 4 mg/mL	21 ITSI 14 Salin	TVASI 33%^{NSS} 29%

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DEX dexamethasone, *MP* methylprednisolone, *CBZ* carbamazepine, *THI* tinnitus handicap index, *Ala* alazopram, *PSTG* prostaglandin, *ITSI* intratympanic steroids injection, *CC* complete control, *SS* statistically significant, *NSS* not statistically significant, *TQ* tinnitus questionnaire, *SATLSI* self-assessed tinnitus loudness scale improvement, *TVASI* tinnitus visual analog scale improvement

described in that case report had somatic (or somatosensoric) tinnitus. This subtype of tinnitus is characterized by the ability of the patient to modulate the tone or volume of tinnitus by the head and neck movements. Somatic tinnitus is caused due to neuronal convergence of auditory and somatic pathways on the level of dorsal cochlear nucleus and inferior colliculus (Dehmel et al. 2008). McCormick and Walega propose the mechanism for curative action of corticosteroids in that case and attribute it to the afferental modulation of neuronal signals carried by somatic spine roots that converge with auditory pathways. More time and studies with this particular type of tinnitus subtype is needed to prove the general efficacy of synthetic corticosteroids for somatic tinnitus.

Tinnitus is a symptom that can accompany numerous diseases. Curative treatment for tinnitus may depend on its cause.

Taken the data together, after a scholarly discussion of the organization of the HPA axis and the action of its end product cortisol, we concentrated on the precipitation of tinnitus by a great variety of insults. We next discussed the potential role of stress elements in the auditory-limbic connectome with respect to the onset and progression of tinnitus. This refers in particular to the notion that prolonged acoustic adversity evoked by tinnitus would lead to inadequate cortisol containment of stress reactions in the auditory system. As a consequence this chronic stress condition would progressively cause damage to circuits underlying the central processing of auditory information resulting in further aggravation of tinnitus and enhanced vulnerability to mood disorders. The chapter is concluded with a discussion of treatment options to the benefit of the tinnitus patient that are based on corrections of stress-induced changes in the auditory system.

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Declaration of Interest E R. de Kloet is on the scientific advisory Board of Dynacorts Therapeutics and Pharmaseed Ltd. and owns stock of Corcept Therapeutics. The current paper bears no relationship to these interests.

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Stress-Related Psychological Disorders and Tinnitus

3

Sylvie Hébert, Birgit Mazurek, and Agnieszka J. Szczepek

3.1 Introduction

In the previous chapter, we briefly touched upon the subject of tinnitus and comorbid, stress-related disorders. Here, we discuss this topic more in-depth. As a reminder: although tinnitus can be characterized by its psychoacoustic properties (pitch and loudness), which pertain to the auditory domain, the experienced *severity of tinnitus* varies among patients. Tinnitus severity seems to be associated mostly with psychological factors, such as stress. Interestingly, every other patient with chronic persistent tinnitus has an additional, comorbid psychological condition such as anxiety or mood disorder. These conditions often slow down therapeutic progress and sometimes can be a bad prognostic sign. There is a good reason these conditions are discussed in our book—they are related to stress, meaning that they can be caused or worsened by stress and/or that they induce stress. Dealing with psychological disorders is necessary to achieve therapeutic progress when treating tinnitus patients.

S. Hébert, Ph.D. (✉)
School of Speech Pathology and Audiology, Université de Montréal, Montréal, QC, Canada
e-mail: sylvie.hebert@umontreal.ca

B. Mazurek, M.D., Ph.D.
Tinnitus Center, Charité University Hospital, Berlin, Germany

A.J. Szczepek, Ph.D.
Department of Otorhinolaryngology, Head and Neck Surgery, Charité University Hospital, Berlin, Germany

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3.2 Psychological Disorders

Psychological disorders are defined as patterns of behavioral or psychological symptoms that impact multiple areas of life. Psychological disorders comprise a large group of illnesses, but here, we will talk only about some of them that are relevant for tinnitus.

Mental disorders are defined as patterns of behavioral or psychological symptoms that impact multiple areas of life.

A bulk of clinical and scientific evidence supports the hypothesis about the emotional or social stress actively contributing to the development of variety of psychological disorders. Multiple studies in men and animals have demonstrated correlation between stress and depression (Anisman and Merali 2003; Kubera et al. 2011; Slavich et al. 2010) or stress and anxiety disorders (Liu et al. 2012; Swartzman et al. 2017). Intriguingly, many patients with chronic tinnitus tend to be affected by psychological disorders. In case you suspect that your patient might suffer from psychological comorbid disorder, it is always a good idea to refer him or her for a consultation with, e.g., clinical psychologist. Using specialized diagnostic procedures such as for instance the World Health Organization World Mental Health Composite International Diagnostic Interview (CIDI) or disease-specific instruments, the specialists will help to diagnose the psychological disorder with which your patient may be affected. In our experience, at least 50% patients with chronic persistent tinnitus can be diagnosed with one or more psychological condition (Zirke et al. 2013a, b). The conditions commonly diagnosed in patients with tinnitus belong predominantly to the group of affective and anxiety disorders (Fig. 3.1).

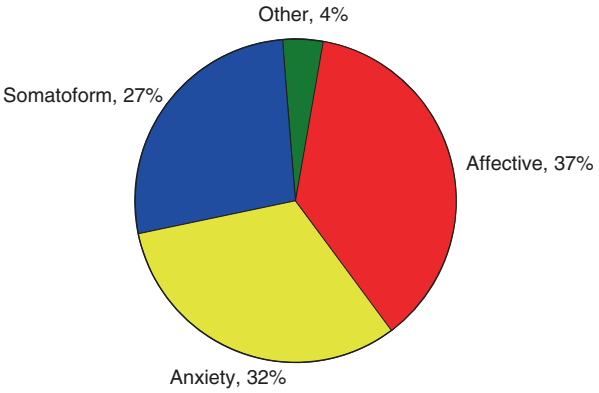

Fig. 3.1 The types of mental disorders found in tinnitus patients (Zirke et al. 2013a). Every other tinnitus patient was diagnosed with one or more mental conditions. Reprinted from Qual Life Res, 22, Zirke N, Seydel C, Arsoy D, Klapp BF, Haupt H, Szczepek AJ, Olze H, Goebel G, Mazurek B: Analysis of mental disorders in tinnitus patients performed with composite international diagnostic interview, 2095–2104, 2013, with permission from Springer

3.3 Affective Disorders

Affective, or mood, disorders are often comorbidities of tinnitus. The International Classification of Diseases (ICD-10, version 2016) classifies affective disorders under mental and behavioral disorders in ICD-10 (Chap. 5). They include disorders in which the fundamental problem is a change in affect. The main types of affective disorders are depression (with or without anxiety) and bipolar disorder. Depression, or major depressive disorder, is characterized by feelings of extreme sadness and hopelessness, reduced energy, and decrease in activity, lasting at least 2 weeks. One hallmark symptom of depression, which distinguishes it from anxiety, is rumination of the past. Depression has been identified for over 20 years as a comorbidity of tinnitus (Halford and Anderson 1991) and continues to be an important research topic nowadays (Langguth et al. 2011; Weidt et al. 2016). Numerous studies have reported significant and rather strong correlations between questionnaires assessing depressive symptoms and those assessing tinnitus distress or handicap (Kehrle et al. 2016; Oishi et al. 2011). One criticism that has been raised about this association is that depression and tinnitus are usually assessed by self-report questionnaires. This method and the fact that some questions overlap in their content might artificially inflate correlations (Ooms et al. 2011). However, it is likely that this overlap may be the direct consequence of the symptomatic similarity of stressful tinnitus and depression and the fact that tinnitus questionnaires were developed to reliably reflect complaints of tinnitus patients (Langguth et al. 2011). In addition, cognitive styles have been reported as different between patients with depression and patients with tinnitus (Andersson et al. 2013), suggesting that tinnitus and depression have some degree of overlap but are not quite the same psychopathology. Nevertheless, there are longitudinal data suggesting that tinnitus-related distress decreases when depressive symptoms decrease (Hebert et al. 2012b).

Longitudinal data suggests that tinnitus-related distress decreases when depressive symptoms decrease.

Yet, evidence regarding the effectiveness of antidepressants on tinnitus (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitor) is conflicting (Baldo et al. 2012; Chang and Wu 2012; Oishi et al. 2010; Robinson et al. 2005). Differences from one study to another in selection criteria (e.g., patient selection, assessment of depression and tinnitus-related distress, presence or absence of clinical depression), treatment administration (e.g., dosage), and study design (e.g., presence of control groups) all contribute to low quality of evidence.

To date, the highest level of evidence for the improvement of mood (i.e., depression and anxiety) and decrease of tinnitus-related distress is the cognitive behavioral therapy (Cima et al. 2012; Maes et al. 2014; Martinez-Devesa et al. 2010), which was originally designed to treat depression and which focuses on the development of personal coping strategies to change unhelpful patterns in cognition, behaviors, and emotional regulation.

To date, the highest level of evidence for the improvement of mood (i.e., *depression and anxiety*) *and decrease of tinnitus-related distress is the cognitive behavioral therapy.*

3.4 Anxiety Disorders

Anxiety disorders are classified under mental and behavioral disorders in ICD-10 (Chap. 5), section "Neurotic, Stress-Related and Somatoform Disorders." They include generalized anxiety disorder, a specific phobia, social anxiety disorder, separation anxiety disorder, agoraphobia, and panic disorder. The ICD-10 defines generalized anxiety disorder as an "anxiety that is generalized and persistent but not restricted to, or even strongly predominating in, any particular environmental circumstances (i.e., it is "free-floating")". The disorder is characterized by several dominant symptoms such as complaints of persistent nervousness, worry, trembling, muscular tension, dizziness, sweating, epigastric discomfort, and fear that an accident or illness will shortly happen for the patients themselves or a relative. Contrary to fear, which provokes a—normal—physiological reaction in response to a real danger, anxiety provokes a similar physiological reaction but without the danger being present. Other types of anxiety are a variation around this definition. High levels of anxiety disorders have been reported in tinnitus patients in many studies (see Sect. 3.6 below), such that anxiety is a comorbidity often found in tinnitus patients.

Anxiety disorder is characterized by several dominant symptoms such as complaints of persistent nervousness, worry, trembling, muscular tension, dizziness, sweating, and epigastric discomfort and is a comorbidity often found in tinnitus patients.

3.5 Type D Personality and Tinnitus

Personality is the combination of characteristics that distinguish an individual from all others. It determines thinking, beliefs, and attitudes and has a significant impact on health and diseases. There are several instruments to assess personality traits, usually validated and structured questionnaires. Many studies have shown that some personality traits are associated with tinnitus severity (Bayar et al. 2002; Collet et al. 1990; House 1981; Langenbach et al. 2005; Tyler et al. 2006; Welch and Dawes 2008). In particular, type D personality has been found prevalent among the tinnitus population (Bartels et al. 2010a, b). Type D personality (where D stands for distressed) describes individuals with a wide range of negative feelings and social inhibition. Type D personality overlaps the neuroticism trait, which involves a broad

range of negative personality characteristics due to distress, anxiety, and behavioral cognitive impairment.

Type D personality describes individuals with a wide range of negative feelings and social inhibition and has been found prevalent among the tinnitus population.

Neuroticism has also been often associated with tinnitus (Adami Dehkordi et al. 2015); therefore, neuroticism and type D personality, in particular, are associated with having tinnitus and might contribute to its perceived severity. On a more positive side, one study involving almost 5000 individuals with tinnitus indicates that tinnitus-related distress is negatively correlated with resilience and that this relationship is mediated by emotional health (Langguth et al. 2007; Wallhausser-Franke et al. 2014). This means that high resilience is associated with better emotional health or less depression, anxiety, and somatic symptom severity, which in turn is associated with a less distressing tinnitus. Working on emotional health has therefore the potential of decreasing tinnitus-related distress.

Working on emotional health has a potential of decreasing tinnitus-related distress.

3.6 Population Studies Reporting Association Between Tinnitus and Stress

Although individual characteristics such as mood and personality contribute to tinnitus distress, other health and life conditions such as hearing and stress are important, too. Population studies with proper response rates focusing on stress and hearing are fairly recent. Even though these studies have all used self-reported measures, they are important because they minimize selection bias compared to clinical studies (Draugalis and Plaza 2009). The Swedish Longitudinal Occupational Survey of Health (hereafter the SLOSH study) (Hasson et al. 2011), which involved nearly 10,000 individuals, assessed hearing problems (including tinnitus) along with work-related stressors, long-term illness, and several other health variables. Hearing problems were classified into the three categories "no hearing problems," "either tinnitus or hearing loss," or "both tinnitus and hearing loss." Unsurprisingly, the prevalence of hearing problems increased with age: in the age group comprising subjects who were 40 years old or younger, 76% reported no hearing problems, 22% reported either tinnitus or hearing loss, and 2% reported both tinnitus and hearing loss. In the age group comprising individuals 60 years old or older, only

58% reported no hearing problems, 30% reported either tinnitus or hearing loss, and 11% reported both tinnitus and hearing loss. Since hearing problems are known to be underreported, especially by older adults (Demeester et al. 2012; Kirk et al. 2012), these figures may underestimate the prevalence of hearing problems. More importantly, however, hearing problems were more prevalent in those who were exposed to work-related stressors (i.e., risk of being moved to another work/job against one's will) or threats (i.e., threats of getting fired) than those who were not. In addition, almost-linear associations were reported across age groups between increased hearing problems and poor self-rated health, worse sleep quality, higher burnout, and greater long-lasting stress, that is, as health, sleep quality, burnout, and long-lasting stress levels got worse, the more hearing problems were reported as well.

In a subsample of the SLOSH study where the focus was more specifically put on tinnitus, hearing loss, uncomfortable loudness levels, and emotional exhaustion (i.e., long-term stress) were significant predictors of tinnitus prevalence (Hebert et al. 2012a). Interestingly, among individuals with tinnitus, emotional exhaustion was highly correlated with tinnitus severity (as assessed by the Tinnitus Handicap Questionnaire) when factoring out hearing loss, whereas hearing loss was not correlated with tinnitus severity when factoring out emotional exhaustion. In other words, the relationship between hearing loss and tinnitus severity was fully explained by long-term stress.

The relationship between hearing loss and tinnitus severity can be explained by a long-term stress.

The influence of stress and noise exposure on the probability of having tinnitus was examined in a parallel study. In a population sample of 12,166 adults aged from 18 to 84 years old (Baigi et al. 2011), the prevalence of tinnitus was 16.6%. Overall stress (i.e., a "yes" answer to the question "Do you feel stressed at present?") was almost as important as noise exposure for the severity of tinnitus, and among those who had tinnitus, increases in stress levels were more important than noise exposure for the transition from mild to severe tinnitus. In other words, current stress self-reported levels were a more determining factor for severe tinnitus than noise exposure. The probability of having tinnitus was twofold when exposed to both noise and stress, with respect to when exposed to either noise or stress.

Some smaller studies corroborated and expanded these findings by focusing on the prevalence of tinnitus among more specific samples of workers exposed to work-related stress. One study conducted in 250 musicians coming from 12 symphony orchestras (Hasson et al. 2009), epidemiological study reported a prevalence of 42% for hearing problems (i.e., a "yes" answer to the question "Do you have any hearing problems?"). Hearing problems (including, but not limited to, tinnitus) were strongly associated with medical symptoms (e.g., headache, muscle pain), stress-related symptoms (e.g., physical or mental fatigue, worry), and work

satisfaction (e.g., frustration at work due to bad conductor). Thus, once again stress—either work related or not—was associated with hearing problems. Similarly, high tinnitus prevalence was found in a study involving 1100 operators (79% women) in call centers of two large communication companies (Lin et al. 2009). Overall prevalence of tinnitus was 40.3% and significantly higher in women (48.3%) compared to men (32.3%). In addition, operators of both genders with higher job stress (i.e., those who responded "always" or "often" to the question "How frequently do you feel stressed at work?") had more than twice the risk of various health complaints, including tinnitus, compared to low-stress operators. Although none of the two above studies assessed the influence of environmental noise on hearing or tinnitus, one can assume that both symphony orchestra musicians and call operators work in noisy environments and that the very high prevalence rates of tinnitus might reflect a combined effect of noise exposure and stress.

Finally, a recent study conducted in 1632 employees of a large pharmaceutical company investigated more precisely the impact of work-related stress on tinnitus, controlling for many factors including noise exposure. Work stress was conceptualized in terms of organizational justice, which is perceived fairness at the workplace (Stattrop et al. 2013). Overall organizational justice was inversely related to tinnitus, that is, the lower the perceived justice, the more frequent the tinnitus was reported. Although this association was independent of demographics, socioeconomic status, job characteristics—including potential noise exposure—and health behaviors, it was partly explained by individual differences in depressive symptoms and, more particularly, in burnout symptoms. In other words, burnout, which pertains exclusively to the work context, is the underlying mechanism by which the lack of fairness at work is associated with tinnitus prevalence.

In sum, if the role of noise exposure as a risk factor for tinnitus prevalence has been known for a long time (Mazurek et al. 2010), data is now accumulating about psychological factors such as chronic and work stress as even more important factors than noise exposure for tinnitus prevalence and severity.

The lower the perceived justice at the workplace, the more frequent the reports of tinnitus.

3.7 Does Tinnitus Cause Stress or Does Stress Cause Tinnitus?

The direction of the relationship between tinnitus severity and stress cannot be determined from these studies, i.e., whether severe tinnitus causes stress or whether stress can trigger severe tinnitus (Figs. 3.2 and 3.3). Although the traditional view has been that tinnitus causes stress and that a main therapeutic objective is to reduce the stress caused by tinnitus (Stattrop et al. 2013), other models suggest that the other possibility is equally plausible (Rauschecker et al. 2010).

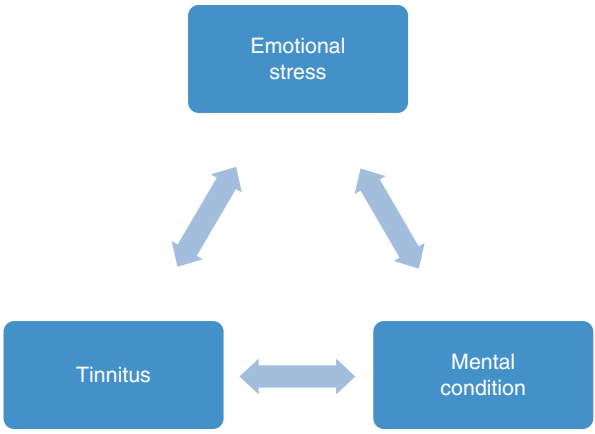

Fig. 3.2 The vicious circle of tinnitus and stress

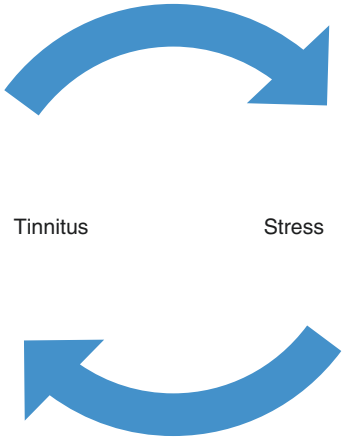

Fig. 3.3 Stress can induce or worsen the course of mental disorders, such as depression or anxiety. Tinnitus as stressor may contribute to overall stress load. At the same time, tinnitus may get worsened by other stressors

Let us consider the first possibility, that is, that severe tinnitus causes stress: The sound is perceived as an alarm signal that creates an emotional stress, which activates the hypothalamic-pituitary-adrenal (HPA) axis (see Chap. 2) and sympathetic nervous system (SNS) (Mazurek et al. 2015). At first, basal cortisol levels may increase and because of the chronic stress could be followed by an enhanced sensitivity to negative feedback, eventually resulting in a blunted acute stress response and HPA axis exhaustion (see (Mazurek et al. 2015) for a more detailed description of the model). Indeed, clinical studies using the stress hormone cortisol as an objective measure of stress have shown that tinnitus is associated with significant HPA axis dysregulation as found in other stress-related diseases (Hebert and Lupien 2007; Hebert et al. 2004; Simoens and Hebert 2012). Although compatible with the hypothesis, these studies are not longitudinal, and therefore the causality of the relationship cannot be ascertained.

A different model proposed a relationship in the opposite direction between emotional factors and tinnitus (Rauschecker et al. 2010). This model assumes the

widely accepted idea that the initial tinnitus signal results from peripheral deafferentation and subsequent lesion-induced cortical plasticity. According to this model, limbic and auditory brain areas interact at the thalamic level. The tinnitus signal can be tuned out by feedback connections from limbic regions, which block the tinnitus signal at the thalamic level from reaching auditory cortex (compensated tinnitus). If the limbic regions are dysfunctional, for instance, by way of chronic stress, sleep deprivation, or depression, this noise-cancellation mechanism breaks down, resulting in chronic tinnitus. The model is interesting because it explains that hearing loss can occur without tinnitus. However, the model does not make predictions about the severity of tinnitus: tinnitus is either present or absent.

A further interesting model, although not proposed for tinnitus specifically, is the one of O'Donovan and colleagues (O'Donovan et al. 2013). According to this model, and coming back to individual traits, anxious individuals have an exaggerated neurobiological sensitivity to threat that may lead to sustained threat perception. This threat perception, expressed by cognitive biases in threat-related information processing, is accompanied by prolonged activation of threat-related and threat-responsive biological systems such as the HPA axis, autonomic nervous system (ANS), and inflammatory response. This pattern of responding can over time produce chronic inflammation through structural and functional brain changes, dysregulation of the HPA axis and ANS, and accelerated cellular aging. Thus, individuals with chronically high levels of anxiety are at increased risk for several aging diseases such as cardiovascular, autoimmune, and neurodegenerative disorders. If applying the model to tinnitus, it is possible that in anxious individuals who are in a chronic state of cognitive-behavioral avoidance of perceived threats, i.e., constantly scanning their environment for possible threats, will perceive tinnitus as a major threat to their health when it happens and judge it as very disturbing (see Fig. 3.4). This vulnerability will activate or renew—because it has been already activated through past experiences of environment or personal events—threat-related and threat-responsive biological systems such as the HPA axis, autonomic nervous system (ANS), and inflammatory response. In other words, it is likely that anxious individuals have already shown signs of advanced deleterious bodily responses, well before tinnitus appears, such as a dysregulated stress response, and thus tinnitus will only keep this maladaptive physiological response going. Therefore, it is not surprising that a high percentage of tinnitus patients have a lifetime history of depression and anxiety and that only a small percentage report that they had tinnitus prior to their disorder (Zöger et al. 2001). Also not surprising is the fact that emotional exhaustion, which supposedly takes time to develop, is a more important factor compared to hearing loss for tinnitus severity (Hebert et al. 2012a).

In support of this model, a recent retrospective study (Yuksel and Karatas 2016) examined several blood platelet indices related to inflammatory events in 100 patients with tinnitus and 100 sex- and age-matched controls. One targeted index was mean platelet volume (MPV), which is inversely correlated with disease activity of several inflammatory diseases. The results showed that MPV levels were significantly lower in patients with subjective tinnitus than the control group. Platelet distribution width and platelet count levels were also significantly higher than control group, supporting that subjective tinnitus appears to be characterized by

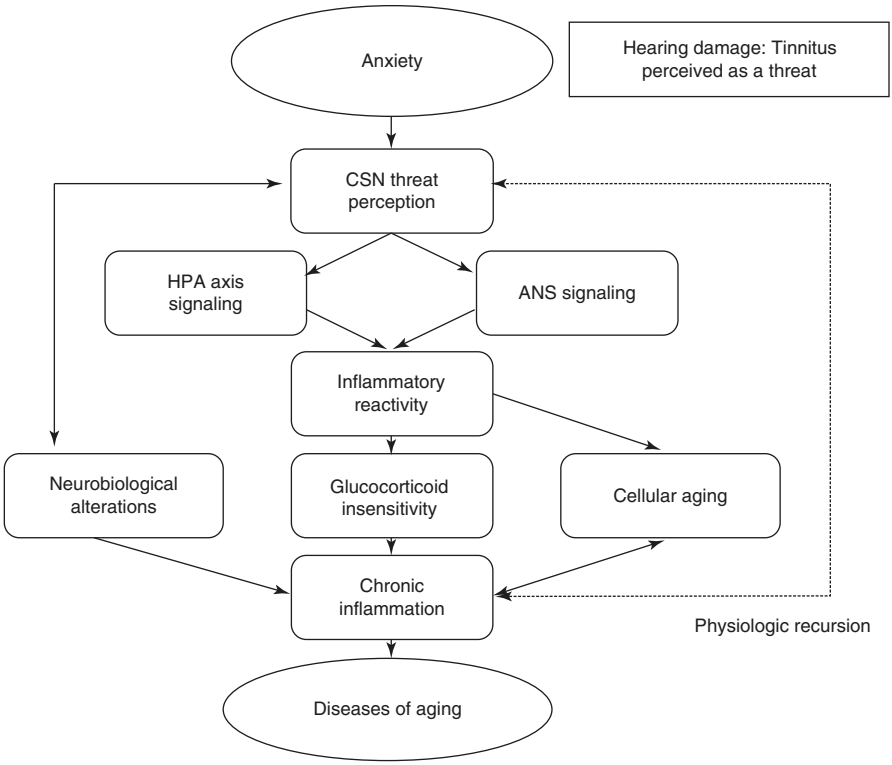

Fig. 3.4 Exaggerated neurobiological sensitivity to threat as a vulnerability factor for severe tinnitus and harmful bodily consequences in anxious individuals. Reprinted from Neurosci Biobehav Rev., 37, O'Donovan A, Slavich GM, Epel ES, Neylan TC: Exaggerated neurobiological sensitivity to threat as a mechanism linking anxiety with increased risk for diseases of aging, 96–108, 2013, with permission from Elsevier (O'Donovan et al. 2013)

autoimmune and/or inflammatory events. The model is also supported indirectly by studies that have reported high levels of anxiety in individuals with tinnitus. For instance, individuals with tinnitus have increased acoustic startle (Fournier and Hebert 2013), which is linked to anxiety. Studies in clinical tinnitus patients—some examining consecutive patients—have found prevalence of anxiety disorders as high as between 45 and 60% (Ooms et al. 2012; Zirke et al. 2013a, b; Zöger et al. 2006). A recent meta-analysis examining 117 articles found a prevalence of 45% of anxiety disorders in a lifetime in populations with tinnitus (Pattyn et al. 2016). A population study involving nearly 15,000 adults found a prevalence of 20.4% for anxiety disorder in individuals with frequent tinnitus (experiencing tinnitus almost always or at least once a day) compared to 3.1% in the general population (Shargorodsky et al. 2010). In individuals with any tinnitus, the prevalence was 49.7% compared to 20.3% in those without tinnitus. Interestingly, individuals with any or frequent tinnitus had more cardiovascular risk factors, hypertension, diabetes, and dyslipidemia than their non-tinnitus counterparts. In addition, severe

tinnitus is associated with a faster processing of fear and anger images and with a slower processing of positive images, suggesting cognitive biases in threat-related information processing compatible with anxious patients (Ooms et al. 2013). Similarly, individuals with tinnitus process emotional sounds more rapidly than neutral sounds compared to controls without tinnitus (Carpenter-Thompson et al. 2014).

Evidence supporting the anxiety hypothesis comes also indirectly from adults without tinnitus. Trait anxiety increases the effects of stress in the illusory perception of sounds in noise: Anxious individuals become more liberal in their criteria to decide whether or not there is a signal in noise (Hoskin et al. 2014). A similar effect is found with transcranial magnetic stimulation (TMS), which increases cortical excitability. When TMS is applied to auditory associative areas, false auditory perceptions (voice in noise) are induced (Hoskin et al. 2014).

Above and beyond these models, it is possible that dysregulation of the HPA axis can promote the development of severe tinnitus via genetic and epigenetic mechanisms (see Chap. 2).

3.8 Proposing Treatments: Enrolment Issues

Clearly, more high-quality clinical trials will lead to better treatment options for tinnitus. For clinicians who would like to endeavor to do so, however, it is useful to know that enrolment of tinnitus patients in studies where treatment is offered may be difficult. For instance, a recent study (Bauer et al. 2016) investigating the effectiveness of Tinnitus Retraining Therapy (a therapy combining sound therapy and counselling (Jastreboff 2007, 2015)), 21% of study participants who had responded to advertisement had subsequently declined participation because they did not want to wear hearing aids—provided for free—or to travel to obtain treatment and participate in follow-ups. Enrolment rates in this particular multicenter clinical study varied between 3.5 and 11.9% depending on sites and overall totalled 6.3% over a 17-month recruitment period. Another study (Piccirillo et al. 2007) that investigated pharmacological treatment reported that of 1028 patients recruited, 259 came to screening, and 135 eventually participated, which represents only a rate of 13%. Given the great distress and severity of symptoms reported by this population, these low rates of enrolment are surprising. Although studies do not systematically report their enrolment rates, qualitative studies may be useful to get more information about this situation.

3.9 Treatment of Comorbid Psychological Disorders in Patients with Tinnitus

In tinnitus patients with comorbid psychological disorders, the success of tinnitus therapy depends largely on its personalized design. In Chaps. 7–9, the stress-related psychometric diagnostic and outcome measure instruments as well as the

stress-related psychological therapy methods are presented. Essential for good treatment are the proper diagnosis and proper therapeutic elements.

Given that tinnitus severity and more severe depression are among the most significant predictors of both health-care costs and societal costs of tinnitus (Maes et al. 2013), it is imperative to refer tinnitus patients—especially those with severe comorbidities—to useful resources. Fortunately, many specialized tinnitus units offer this multimodal, interdisciplinary, and individualized approach for treating patients. However, many audiological centers, family physicians, or ENT/ORL specialists are still unaware of the fact that serious comorbidities may prevent patients from improving their condition. In particular, although it is essential to encourage patients to improve their hearing through services from hearing specialists, it is also essential to refer those patients with psychological disorders to appropriate specialists to improve their psychological well-being.

Psychological comorbidities may prevent tinnitus patients from improving their condition.

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Circadian Influences on the Auditory System

4

Christopher R. Cederroth, Vasiliki Basinou, Jung-Sub Park, and Barbara Canlon

4.1 Introduction

In this chapter, we will deal with circadian rhythms and their influence on hearing and tinnitus. Circadian rhythms control bodily functions such as sleep, inflammation, metabolism, renal function, hormone secretion, as well as auditory functions. Animal studies have revealed that the auditory system has an inbuilt clock machinery that regulates sensitivity to noise throughout the day. Due to the detrimental consequences of disrupted circadian rhythms on human health (e.g., jet lag, shift workers), it is important to understand how the clock system regulates auditory function with the aim of providing new avenues for the development of targeted therapies.

4.2 Circadian Rhythms

4.2.1 What Are They

Circadian rhythms ("circa *diem*" meaning "approximately a day") are among the most conserved systems of biological function, already emerging in light-sensitive bacteria and evolving into complex internal timing systems in mammals. Sensing periodic changes has allowed almost all organisms (from cyanobacterias, fungi, green plants, metazoans, to mammals) to adapt their behavior and optimize their physiological functions to changes in the external environment (Paranjpe and Sharma 2005). The synchronization of the rhythmic entrainment by regular daily events, such as light/dark cycles, temperature, or humidity variations, facilitates the

C.R. Cederroth (✉) • V. Basinou • J.-S. Park • B. Canlon
Experimental Audiology Group, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden
e-mail: christopher.cederroth@ki.se

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anticipation of these predictable changes, maximizing ecological fitness—meaning the ability to adapt to a given environment.

Circadian rhythms enable synchronization of the rhythmic entrainment by regular daily events, such as light/dark cycles, temperature, or humidity variations.

These external and rhythmic environmental cues (inputs) are called *zeitgebers* (German for "time-giver"). In the same way that metronomes help musicians internalizing the sense of tempo, these *zeitgebers* influence biological clocks to facilitate the internal representation of time and anticipate predictable consequences of rhythmic events. The most important *zeitgebers*, in addition to the light-dark cycle and temperature mentioned above, are also found food consumption and social interactions (Davidson and Menaker 2003; Lowrey and Takahashi 2004).

In mammals, most physiological processes are subjected to temporal regulations (Dibner et al. 2010). These include cerebral activity (sleep and wake cycles), feeding behavior, metabolism and energy homeostasis, immune responses, heart rate, blood pressure, renal activity, hormonal and cytokine secretion, detoxification, and, recently, auditory functions (Meltser et al. 2014). In anticipation of a resting period, the temperature of the body falls, glucocorticoids decrease, anabolism increases, and melatonin is secreted. Reversely, in preparation of the high demands of daily activities, the opposite phenomenon occurs. In modern societies, disruptions of the alignment of body functions with the environmental cycle are seen in shift and night works, reductions in sleep time and sleep deprivation, travel, and jet lags. The understanding of the consequences of circadian arrhythmia and their mechanisms has emerged from studies of mutant animal models with altered rhythms.

In modern societies, disruptions of the alignment of body functions with the environmental cycle is seen in shift and night works, reductions in sleep time and sleep deprivation, travel, and jet lags.

4.2.2 Organization of the Circadian System

Three levels of organization characterize the circadian system (Fig. 4.1): (1) inputs by which the environment communicates information to the internal master clock located in the brain, namely, the suprachiasmatic nucleus (SCN); (2) factors that contribute to brain-dependent outputs such as sleep onset, sleep-wake cycles, and other CNS-dependent behavioral changes; and (3) peripheral outputs that are the physiological consequences of the coordinated hormonal, metabolic, immune, thermoregulatory, and autonomic nervous functions. Most organs and, hence, most cells, have their own biological clocks. These cellular and organ clocks have their

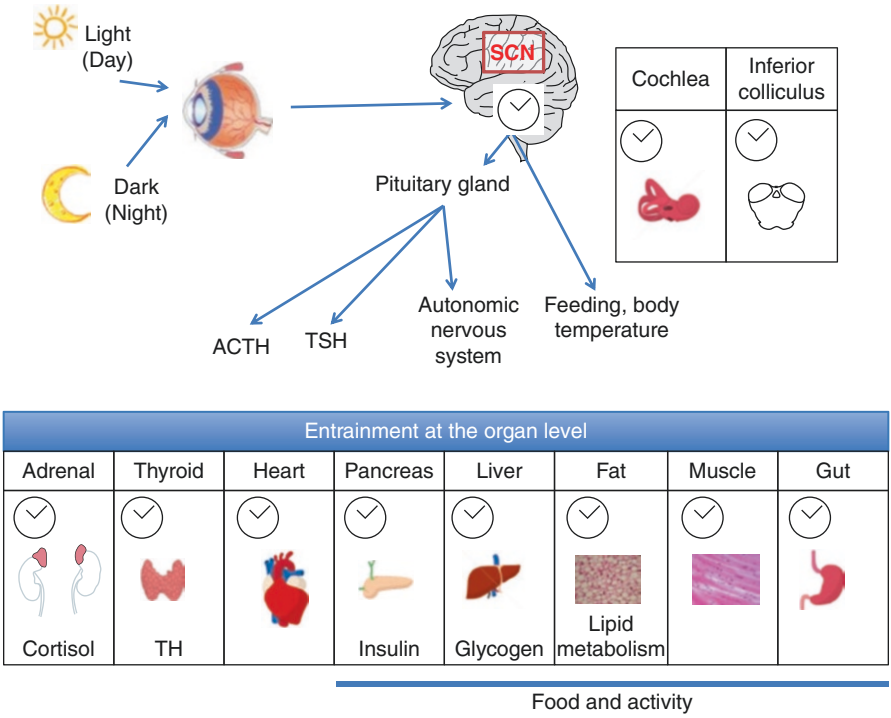

Fig. 4.1 Peripheral clocks and regulation of circadian physiology. The suprachiasmatic nucleus (SCN) is the major pacemaker of the circadian system that receives photic information directly from the retina and synchronizes peripheral oscillators found in other brain areas and peripheral tissues (entrainment). This is mediated by autonomic innervation, humoral signals, hormones, and the regulation of body temperature and feeding. Modified from Hickie et al., BMC Medicine, 2013, 11:79 with permission from BMC journals

own phase with respect to their own physiological duties. This is where the master clock aligns cellular and organ clocks to the external 24 h light-dark cycle in order to form a coherent pattern of behavioral and physiological rhythms.

Prior to describing the recent identification of clock systems in the auditory pathway, we will review general aspects of the structure and function of the mammalian circadian system.

4.3 Molecular Biology of Circadian Rhythms

4.3.1 Core Clock Genes

As evolution has progressed into more and more complex organisms, the biological clocks have incorporated more subtle mechanisms of regulation to incorporate the timing cues of a variety of *zeitgebers* and produce a variety of biological functions.

A major advance in the circadian field was the concept that biological rhythms are generated at the level of molecules that constitute autoregulatory feedback loops that self-regulate their transcription within a 24 h period. This process, which ballpark is conserved across various phylae, involves a series of activators that promote the transcription of repressors, which protein products translocate back in the nucleus to inhibit the transcription of the initial activators. The subsequent decrease of activator mRNA transcription reduces the level of inhibitory protein production, releasing the transcriptional machinery from its molecular breaks, thereby reinitiating the cycle.

In mammals, the circadian machinery has evolved into a complex cellular process to incorporate a large number of cues. The molecular clock can be paralleled to the machinery of normal clocks, with core large clocks regulating the rhythms of the smaller clocks. The molecular clock machinery is based on two interlocked autoregulatory transcriptional/translational feedback loops (TTFL) (Albrecht 2002; Kondratov et al. 2007; Lowrey and Takahashi 2004). In the center of the feedback loops, two basic helix-loop-helix (bHLH) transcription factors, CLOCK and BMAL1, dimerize and bind to E-box elements at the promoter regions of negative-feedback genes called *Period* (*mPer1* and *mPer2* in the mouse) and *Cryptochrome* (*mCry1* and *mCry2*) to trigger their transcription. The CRY and PER protein products dimerize and form large corepressor complexes. As their concentration increases, they bind to CLOCK/BMAL1 complexes thereby interfering with its transcriptional regulation. The attenuation of their own transcription leads to a decrease in CRY and PER proteins. With a short life cycle, the decrease in PER-CRY complexes no longer interferes with CLOCK-BMAL1 heterodimers, and a new cycle of PER and CRY generation can follow (Fig. 4.2a).

An additional "interlocking" loop consists of ROR (RORα, RORβ, and RORγ) and REV-ERβ (REV-ERβα and REV-ERβ) proteins that are activated by the CLOCK/BMAL1 dimers. The resulting activated proteins recognize RORE response elements (RREs) within the promoter region of *Bmal1* and *Clock* genes to regulate their transcription. RORs activate *Bmal* and *Clock* transcription, whereas REV-ERβs recruit the corepressor NCoR1 to inhibit gene transcription (Fig. 4.2b). Overall, the rhythmic regulation of *Bmal1* transcription is thus typically in anti-phase with that of *mPer*, *mCry*, and *mREV-ERβ* mRNAs.

Disruption of both *mPer* genes, or both *mCry* genes, causes immediate behavioral arrhythmicity when the double knockout animals are placed in constant darkness (meaning in the absence of light entrainment), showing the essential role of PER and CRY in the maintenance of a functional clock (van der Horst et al. 1999; Zheng et al. 2001). Single mutants show continued clock oscillations indicating that there is partial compensation among family members.

Outside the core clock elements are found the clock-controlled genes, which output function is to control diverse physiological functions (Fig. 4.2c). The mechanism of regulation of clock-controlled genes resembles a lot to that of the core clock as suggested by the identification of main regulatory motifs of rhythmically expressed clock-controlled genes: E-boxes, D-boxes, and cAMP-responsive

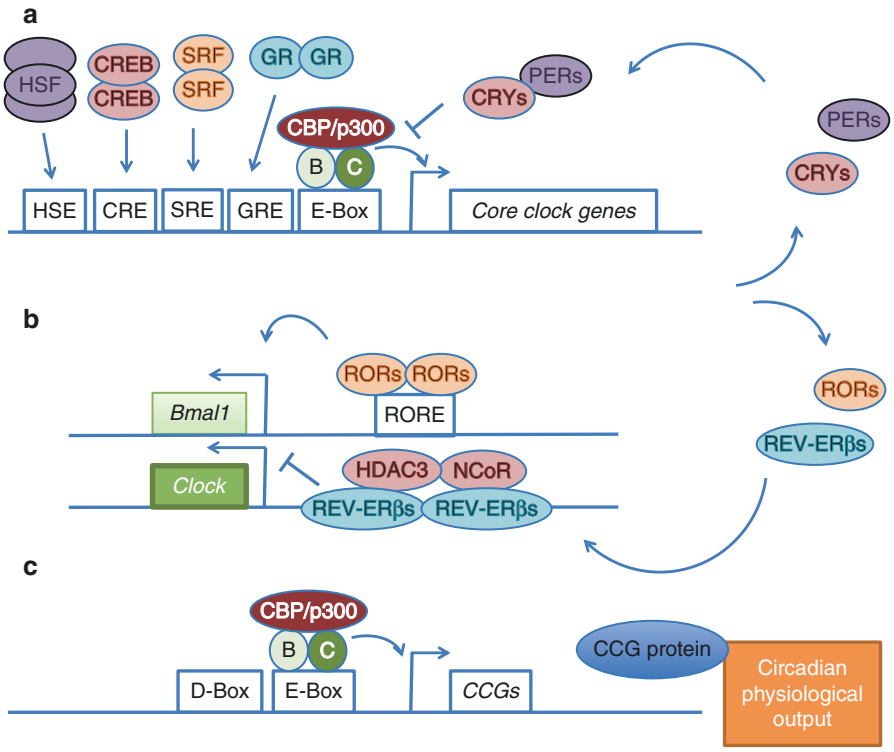

Fig. 4.2 The molecular clock machinery. (**a**) *Core loop*: a complex of CBP/p300, CLOCK (C), and BMAL1 (B) binds to E-box on the promoter of *Per* and *Cry* genes (*Per1*, *Per2*, *Cry1*, and *Cry2*) to induce their transcription. Accumulation of PER/CRY complexes inhibit CLOCK and BMAL1 complexes, thereby repressing their own transcription. The progressive decline of PER and CRY proteins allows CLOCK and BMAL1 to initiate a new cycle of gene expression. *Per1* and *Per2* transcription can be additionally modulated by additional tran: heat shock factor (HSF) binding to heat shock elements (HSEs), cAMP-responsive element (CRE)-binding protein (CREB), and glucocorticoid receptor (GR) binding to glucocorticoid-responsive elements (GRE). (**b**) *Interlocking loop*: CLOCK and BMAL1 also trigger the expression of the orphan nuclear receptor genes *Ror* (*Rorα*, *Rorβ*, and *Rorγ*) and *Rev-Erβ* (*Rev-Erβα* and *Rev-Erβ*). The transcription of *Bmal1* and *Clock* is regulated through competition between REV-ERβ repressors and ROR activators, acting on retinoid-related orphan receptor response elements (RORE). (**c**) *Regulation of clock-controlled genes (CCGs):* CLOCK and BMAL1 can regulate the transcription of CCGs by binding to E-box elements on their promoter area. These genes then are translated into CCG protein products and regulate physiological processes in a temporal way. Modified from Basinou et al., Hearing Research, 2016, in press with permission from Elsevier

element (CREs) (Bozek et al. 2009, 2010; Korencic et al. 2014). For example in the liver, transcription factors of the bZIP family (DPB, TEF, and HLF) bind to D-boxes in the promoter area of the aldosterone receptor (*CAR*) gene, which in turn regulates the rhythms of detoxification via ALAS1 and cytochrome P450 expression (Gachon et al. 2006).

The accurate coordination of these transcriptional/translational feedback loops requires the tight control of posttranscriptional and posttranslational loops to generate a 24 h periodicity. Accumulating evidence shows that the activation and the stability of the core clock proteins is regulated by phosphorylation/dephosphorylation, SUMOylation, ubiquitination, acetylation/deacetylation, and polyADP-ribosylation (Dibner et al. 2010; Mehra et al. 2009). Even, it has been found that circadian rhythms of some specific metabolic functions such as peroxiredoxins in the absence of transcription (Edgar et al. 2012; O'Neill et al. 2011). At a broader scale, hormones, temperature, neurotransmitters, and second messengers (Dibner and Schibler 2015) also interfere with the expression of core clock genes such as *Period*, which allows resetting the phase of the core clock rhythms according to systemic cues.

At a broader scale, hormones, temperature, neurotransmitters, and second messengers also interfere with the expression of core clock genes.

It is interesting to note that near 10–20% of mRNA transcripts display circadian patterns of expression depending on the organ (Akhtar et al. 2002; Hughes et al. 2009; Panda et al. 2002; Storch et al. 2002; Ueda et al. 2002) but that 50% of rhythmic liver proteins are encoded by nonrhythmic mRNA transcripts (Mauvoisin et al. 2015), emphasizing the importance of translational and posttranslational modifications for the control of clock output pathways.

4.3.2 From Molecules to Physiology

A number of signals regulate the core clock and interfere with the rhythms of clock-controlled genes. This allows the cellular systems to respond in a timely manner to environmental changes with specific physiological outputs. As a consequence, cellular clocks appear ubiquitously present throughout the mammalian body (Yoo et al. 2004). Within a tissue, an ensemble of cellular clocks—although not all in synchrony—generate a coherent rhythmic physiological function. For all tissues to perform their functions on time, a master clock is needed to harmonize body rhythms. Located in the hypothalamus around the third ventricle, near 2000 neurons in rodents form the suprachiasmatic nucleus (SCN) that orchestrate the circadian system. The SCN was named the master clock after lesion and grafting studies demonstrated it is necessary and sufficient for the generation of body rhythms (Moore and Eichler 1972; Ralph et al. 1990; Stephan and Zucker 1972).

For all tissues to perform their functions on time, a master clock is needed to harmonize body rhythms.

Interactions between these neurons through chemical coupling and gap junctions facilitate their synchronization (Davidson and Menaker 2003), making the rhythms of the SCN robust enough to act as a pacemaker of all body rhythms. The SCN is entrained by light captured by the retina (Fig. 4.1), where intrinsically photoreceptive retinal ganglion cells (ipRGCs), which express melanopsin, project photic signals to the SCN via retinohypothalamic fibers (Hannibal and Fahrenkrug 2002; Hattar et al. 2002). This was evidenced in elegant genetic studies in mice, whereby the loss of these few hundred cells still allowed normal vision but not the synchronization of body rhythms to light input (Guler et al. 2008). Specific neurons (VIP) from the SCN transpose the electric signals to the cellular clock, through the activation of Ca^{2+}-dependent kinase/CREB signaling cascades that initiate the cycles of molecular rhythms by triggering *Per* gene expression (Dibner et al. 2010). Neuronal interactions spread the rhythmic information across the SCN, which robust and synchronized output signals orchestrate central (e.g., olfactory bulbs and hippocampus) and peripheral tissues (e.g., liver, muscle, and adrenal glands) (Guilding and Piggins 2007; Richards and Gumz 2012).

The communication between the SCN and the other clocks occurs through autonomic innervation and to a second degree through the regulation of systemic cues such as body temperature, hormonal signaling, and feeding (Mohawk et al. 2012) (Fig. 4.1). In return, peripheral clocks provide feedback to the SCN regarding the internal status of the body by means of hormones and metabolites. A continuous and effective communication between external and internal signals allows to produce a coherent rhythmic physiological output.

Whereas the SCN is mainly entrained by light, peripheral clocks are regulated by signals either directly or indirectly controlled by the SCN. The SCN can directly influence peripheral rhythms thanks to the secretion of key factors such as prokineticin 2 (PK2) that can directly regulate locomotor activity rhythms (Cheng et al. 2002) and VIP that regulates core clock gene expression down to the liver and adrenal glands (Loh et al. 2011). Autonomic innervation plays an important role in the indirect communication between the SCN and peripheral clocks. For instance, the SCN projects efferent toward the paraventricular nucleus to control glucose homeostasis in the liver or glucocorticoid secretion by the adrenal glands (Ishida et al. 2005; Kalsbeek et al. 2004). Glucocorticoids (GCs) are of particular interest since they are powerful synchronizers of circadian rhythms. Glucocorticoid receptors are ubiquitously expressed nuclear receptors that recognize glucocorticoid response elements (GRE) present in the promoter and enhancer regions of core clock genes and clock-controlled genes. The glucocorticoid synthetic agent dexamethasone (DEX) is a well-known drug to synchronize circadian rhythms in culture.

Clocks from the heart, kidney, pancreas, lung, and thyroid glands are also controlled by autonomic nervous connections.

Rest and activity cycles drive feeding and body temperature rhythms that are additional zeitgebers. For instance, feeding cycles are important zeitgebers in the liver, the pancreas, the heart, and the kidneys (Dibner et al. 2010), possibly through glucose-sensing pathways and sirtuin signaling (Gachon et al. 2004a). Changes in

body temperature (1–4 °C) can reset peripheral clocks via heat shock factor 1 (HSF1), which also regulates core clock gene expression through the binding to heat shock response elements (Reinke et al. 2008). However, it is thought that the robust rhythms from the SCN make it resistant to feeding and temperature changes (Abraham et al. 2010). Imposed feeding schedules in mice during resting phase can completely invert the circadian rhythms of peripheral tissues, while the SCN remains unaffected. These experiments also show that feeding cues can dominate hormonal signals (Abraham et al. 2010). Once normal feeding schemes are provided, the phase of the tissues resets in 2–3 days showing that the SCN can rapidly take over its role as a master clock. The importance of the SCN in synchronizing peripheral rhythms has been evidenced in lesion experiments where, in absence of the SCN, peripheral tissues became desynchronized with time (Yoo et al. 2004). It is now very well established that the SCN acts as a conductor of an orchestra, whereby peripheral tissues respond to the director's instructions to provide a consistent physiological response.

4.3.2.1 The SCN and the Adrenal Glands: Teamwork for Body Synchrony?

If it can be concluded that almost any tissue harbors a circadian machinery, it remains that each organ harbors its own set of molecular elements to coordinate its physiological functions. In a study of Panda and others, the overlap between circadian transcripts in the SCN and the liver (among 650 oscillating transcripts) was compared, and only 28 transcripts were found common to the two tissues (Panda et al. 2002). Few of these 28 genes were core clock genes showing that the control of most circadian genes is highly tissue-specific, each peripheral clock being responsible for a specific output program dependent on the physiological functions.

The control of most circadian genes is highly tissue-specific. Each organ needs to tightly coordinate different functions at different times.

Each organ also needs to tightly coordinate different functions at different times. For instance, the liver is capable of regulating at appropriate times of the day gluconeogenesis and glycolysis, two chemically antagonistic processes. The temporal control of tissue- and time-specific physiological functions is done through the expression of clock-controlled genes that harbor various *cis*-regulatory elements to allow their on or off transcriptional states thereby generating a broad range of time-regulated cyclic activity within the same tissue.

An illustration of how clock-controlled genes are regulated by different *zeitgebers* has been shown in adrenalectomized mice, deprived of circulating glucocorticoids. Near 2/3 of rhythmic liver transcripts lost their rhythmicity in absence of adrenal glands, none of which were core clock genes (Oishi et al. 2005). These glucocorticoid-controlled genes were in a large part encoding liver enzymes (such as glucokinase, HMG-CoA reductase, and glucose-6-phosphatase). This proportion

was replicated in a pharmacological study, in which DEX resynchronized 57% of liver genes from SCN-lesioned animals (Reddy et al. 2007) likely through a mechanism involving GR and CRY interactions (Lamia et al. 2011). Possibly, the SCN controls core clock rhythms, and secondary entrainment cures such as GCs orchestrate the rhythmicity of genes that regulate physiological functions in a given organ.

As such, the adrenal gland emerges as an important relay station downstream of the SCN to synchronize peripheral clock rhythms. Its endocrine functions are regulated in a circadian fashion (e.g., GCs show a rhythmic secretion pattern). The control of GC circadian secretion by the SCN is known from a long time and evidenced by SCN ablations (Moore and Eichler 1972; Stephan and Zucker 1972). In contrast, the pulsatile (or ultradian—see Chap. 2) pattern of GC secretion is independent of the SCN (Waite et al. 2012). The broad range of actions of GCs, from the regulation of stress or immune responses, as well as cognitive functions, suggests that the circadian actions of GCs might serve as key influencers of physiological rhythms. GCs exert their action via the glucocorticoid receptor (GR), expressed throughout the body including the cochlea (Meltser et al. 2014) and the brain—with the exception of the SCN (Balsalobre et al. 2000). GCs also activate the mineralocorticoid receptor (MR). The circadian secretion of GCs is a complex involvement of autonomic innervation controlled by the SCN, the hypothalamic-pituitary-adrenal (HPA) axis, and local adrenocortical clocks.

4.3.2.2 Physiological Functions Controlled by Circadian Rhythms and Their Dysregulation

Transcript analyses using qRT-PCR showed the circadian expression of core clock genes in the heart, lung, liver, stomach, spleen, and kidney (Yamamoto et al. 2004). Using transgenic rats driving luciferase expression under the control of Per1 promoter (*Per1-luc*), tissue explant cultures showed oscillations in the SCN, skeletal muscle, liver, lung, pineal, adrenal, and thyroid glands (Yamazaki et al. 2000, 2009). Another rodent model in which the luciferase-coding sequence was knocked-in the Per2 mouse locus (PER2::LUC) allowed to identify rhythmic oscillations in additional organs such as the cornea, the pituitary, and the retrochiasmatic area (RCA) (Yoo et al. 2004). How circadian cycles of luciferase expression are captured is illustrated in Fig. 4.3. As a consequence, numerous physiological functions manifest daily oscillations including detoxification processes by the liver, the kidney, and the small intestine (Gachon et al. 2006); carbohydrate and lipid metabolism by the liver, muscle, and adipose tissue (Lamia et al. 2008; Le Martelot et al. 2009); renal flow and urine production, blood pressure; and the rate of heart beats (Gachon et al. 2004a). Understanding of the physiological outputs from molecular clocks in each organ derives mainly from functional studies using mice lacking *Bmal1*, either systemically or in a tissue-specific manner, or mice lacking *Per1* and/or *Per2*. For instance, mice lacking *Bmal1* display a complete loss of circadian behavior, metabolic abnormalities, and subsequent reduced life span (Kondratov et al. 2006). *Bmal1* or *Clock* mutants develop diabetes due to reduced insulin secretion by the pancreatic islets (Marcheva et al. 2010), a process specific to β-cells that regulates insulin secretion in a circadian manner (Perelis et al. 2015).

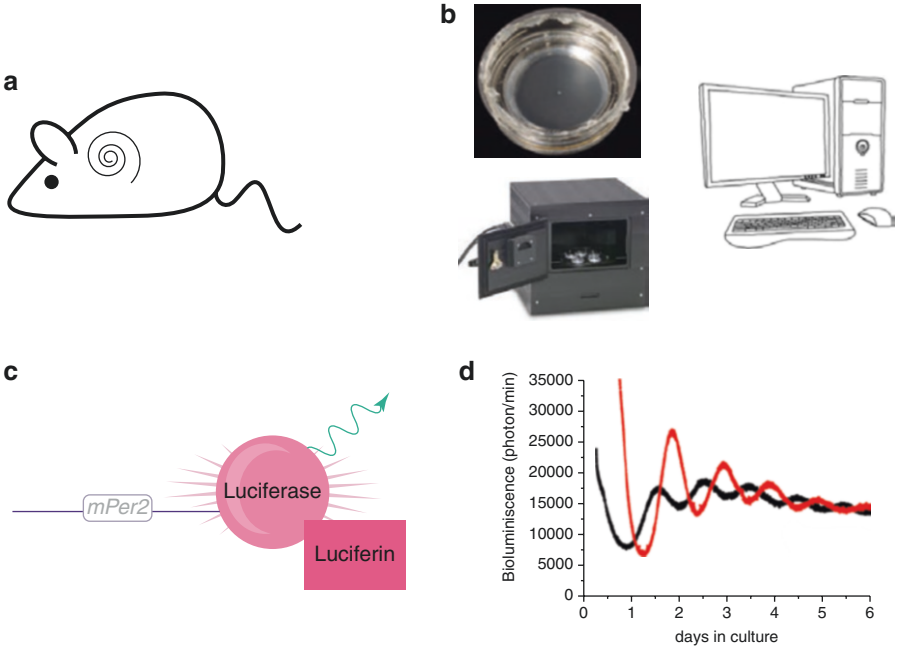

Fig. 4.3 Measures of circadian PER2::LUC oscillations in explant cultures. (**a**) The experimental system to analyze circadian gene expression in explants consists of isolating organs from mice expressing a luciferase fused to Period 2. (**b**) Organ explants are placed on membranes, and real-time bioluminescent imaging of PER2::LUC organs is collected using photomultiplier tubes which is highly sensitive and has low noise. Representative bioluminescence record of circadian PER2::LUC expression in cultured organs is then collected (**c**) and analyzed (**d**) for amplitude, period, and phase

Altered eating regimes, sleep and wake cycles, as well as medications can potentially alter the synchronicity of different organs and their harmonization at the body level leading to abnormal physiological functions.

Altered eating regimes, sleep and wake cycles, as well as medications can potentially alter the synchronicity of different organs and their harmonization at the body level leading to abnormal physiological functions. Shift workers suffer from the chronic desynchronization of their body with the regular environmental cues and of the SCN and peripheral clocks leading to increased prevalence of symptoms of the metabolic syndrome (Evans and Davidson 2013). Despite the fact that the SCN rapidly synchronizes its rhythms to light cues (e.g., in long-distance travelers changing time zones), their organs require more time to readjust their rhythms (jet lag). Underlying the human relevance, polymorphisms in *hPER2 and hCRY2* associate with blood glucose levels. Those in *hCLOCK* are linked with obesity and *hBMAL1* with hypertension and type 2 diabetes (Dibner and Schibler 2015).

4.3.3 Auditory System and Circadian Rhythms

Whether the auditory system harbors a molecular clock was unknown until recently. Several evidences pointed toward such circadian regulation. Firstly, noise can act as a *zeitgeber* to regulate body rhythms (Menaker and Eskin 1966; Reebs 1989). Secondly, outer hair cell function—measured by means of distortion products of otoacoustic emissions—appears to fluctuate throughout the day (Cacace et al. 1996; Haggerty et al. 1993). Thirdly, aminoglycoside-mediated ototoxicity is more damaging at night than during the day (Yonovitz and Fisch 1991). The later could however involve several mechanisms: different rates of liver detoxification around the clock could alter systemic bioavailability; the function of the cochlear blood barrier could fluctuate throughout the day making it more permeable to ototoxic drugs in the night than in the day; finally, the cochlear response to ototoxic insults could be weaker during the night due to varying metabolic rates throughout the day. Our laboratory revealed in an initial study that the cochlea possesses a robust molecular clock that responds differentially to day or night noise stimulation (Meltser et al. 2014). In a second work, we provided evidence that the inferior colliculus (IC), a midbrain relay of the auditory pathway, also has a molecular clock (Park et al. 2016). Here, we describe the findings of these two studies.

4.3.3.1 The Day-Night Susceptibility to Auditory Trauma

The fact that sensitivity to noise also varies at different times of the day was unknown until recently. Awake mice (non-anesthetized) exposed to a noise trauma (6–12 kHz, 1 h, 100 dB SPL) during the night (9 PM) displayed permanent shifts in hearing thresholds measured by auditory brainstem responses (ABRs) 2 weeks after noise trauma, whereas those exposed during daytime (9 AM) recovered to normal hearing thresholds (Meltser et al. 2014). Interestingly, ABRs measured 24 h post-trauma revealed equivalent shifts in hearing thresholds (15–30 dB, from 8 to 24 kHz) in day or night exposed animals. Although distortion products of otoacoustic emissions (DPOAEs) were not performed in this study, cochleograms revealed that no hair cell loss had occurred in both day and night noise groups. These findings suggest that immediate synaptic uncoupling, mainly caused by glutamate excitotoxicity after noise exposure, is similar during the day or during the night. Although levels of glutamate in the cochlea were not measured after day or night noise exposure, no differences were found in the wave I amplitude of the ABR 24 h post-trauma suggesting that animals were exposed to similar levels of sound in this paradigm (unpublished observations). This notion is important since nocturnal animals are more active during the night, whereas they are sleepy during daytime, and the resulting differences in hearing thresholds after day or night noise exposure could be due to varying levels of sound reaching the ear simply because of different behavioral patterns. This potential bias appeared to be negligible since fine and gross locomotor activity (measured by infrared beam breakage) showed no difference during day or night noise exposure (Park et al. 2016).

The sensitivity to noise varies at different times of the day.

4.3.3.2 Involvement of Neurotrophic Signaling in the Differential Sensitivity to Noise Trauma Throughout the Day

A potential mechanism to explain the day and night differences in response to noise trauma included neurotrophic signaling in the cochlea (Meltser et al. 2014). Neurotrophins are important regulators of synaptogenesis and synaptic plasticity in the cochlea. Two important neutrophins, namely, neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BDNF), play an important role during cochlear development and in adult auditory recovery. Mice lacking NT-3 or BDNF, or their respective ligand-specific receptors of tropomyosin receptor kinase (TrkC or TrkB), lack a portion of the auditory neurons (Fritzsch et al. 2004). TrkC appears more important to auditory neuron development since its genetic ablation leads to the loss of 51–66% of auditory neurons, whereas loss of TrkB function causes a loss of only 15–20% of auditory neurons (from the high-frequency region). Their role appear inverted in the vestibular system where TrkB −/− mice show a loss of 56–85% of vestibular neurons whereas TrkC −/− only have 16–29% loss (Fritzsch et al. 2004). The similitude between the neurotrophin mutants and the receptor mutants provides strong evidence of their important contribution for the innervation in the inner ear.

The study from Meltser et al. revealed that the response of *Bdnf* transcription differed after day or night noise exposure. During the day, noise caused a 32-fold increase in *Bdnf* mRNA transcript levels, whereas no increase was after night noise. These findings indicate that the incapability of the cochlea to trigger a BDNF-dependent protective response after night noise could underlie the increased vulnerability to night noise exposure. Treatment before night noise exposure with dihydroxyflavone (DHF), a selective agonist of TrkB (Jang et al. 2010), restored the recovery of hearing thresholds to a level comparable to day noise exposure (in absence of drug treatment). Interestingly, night noise exposure caused a twofold reduction of the synaptic ribbons 2 weeks after noise exposure and DHF pretreatment protected synaptic ribbons (Meltser et al. 2014). These findings provide an evidence of the involvement of neurotrophins in the circadian recovery to noise trauma.

These results are somewhat conflicting with genetic studies that evaluated the contribution of NT-3 and BDNF to noise injury. In elegant genetic gain and loss of function studies, mice overexpressing Ntf3 or Bdnf via a tamoxifen-inducible Cre system (*Ntf3*^{STOP}*:Plp1/CreER*^{T} or *Bdnf*^{STOP}*:Plp1/CreER*^{T}) showed different responses to noise trauma, whereby only mice overexpressing *Ntf3* showed accelerated recovery—not those overexpressing *Bdnf* (Wan et al. 2014). A potential explanation for the differences between Meltser et al. and Wan et al. is that DHF treatment (that mimics Bdnf actions on TrkB) was acute (single injection) and performed at night, whereas the genetic model of Ntf3 overexpression is comparable to a constitutively active (chronic) TrkC system. The role of Ntf3 in the differential responses to day or night noise exposure remains to be investigated.

4.3.3.3 Molecular Biology of Cochlear Circadian Rhythm

The differential response to day or night noise trauma led to the hypothesis that the cochlea could harbor a clock machinery. Using a mouse reporter in which the

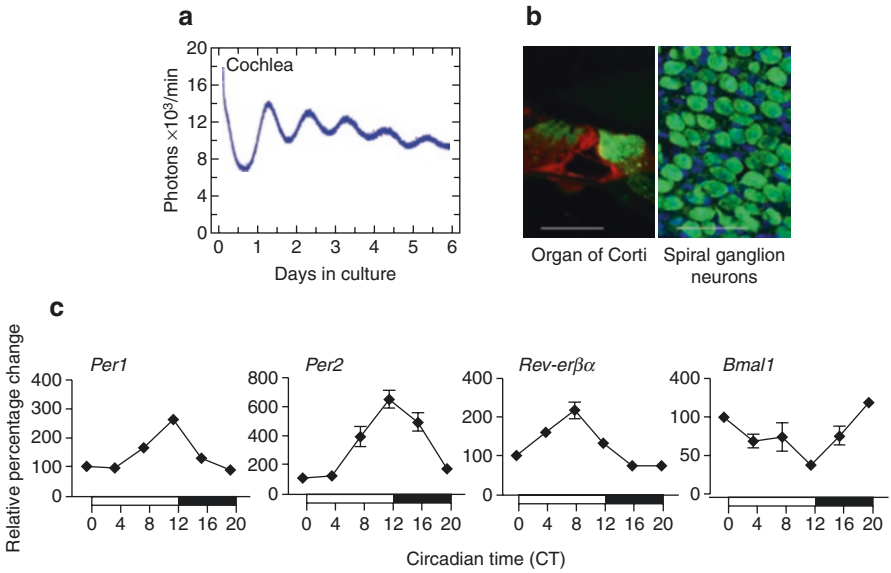

Fig. 4.4 Circadian oscillations in the cochlea: representative bioluminescence records of circadian PER2::LUC expression in cultured adult cochleae explants (**a**). (**b**) Immunostaining of PER2 in a cochlea of intact adult CBA/CaJ mouse shows the localization of the protein in inner and outer hair and supporting cells of the organ of Corti and in the spiral ganglion neurons of the cochlea. Scale bar: 50 mm. (**c**) Temporal expression of *Per1*, *Per2*, *Rev-Erβα*, and *Bmal1* mRNAs in the cochlea assessed by q-RTPCR. The *vertical axis* shows normalized mean values ± SEM (n = 3–4). The *horizontal axis* shows the sampling circadian time (CT) across 24 h at which the animals were sacrificed and samples collected. The *shaded area* illustrates the dark phase of the day from CT 12 to CT 0. All conditions were plotted as relative percentage change using CT 0 as baseline value. Basinou et al (2017)

luciferase gene was fused in frame with the endogenous *Period 2* gene (PER2::LUC) (Yoo et al. 2004), real-time bioluminescence from cochlear explants could be monitored as a readout of PER2 expression. PER2::LUC rhythms from the cochlea ex vivo appeared as ample as those from the liver (Fig. 4.4a), and after fading out, these rhythms could be kicked off with dexamethasone treatment, a known synchronizing agent (Meltser et al. 2014). PER2 protein expression originated from hair cells and spiral ganglion neurons (Fig. 4.4b).

The expression of core clock genes was further evidenced by qRT-PCR, thanks to improvements in a method of cochlear RNA extraction, yielding high quantities of RNA of a quality suitable for such molecular analyses (Vikhe Patil et al. 2015). Subsequently, the circadian expression of *Per1, Per2, Bmal1,* and *Rev-Erβα* was revealed, demonstrating that the cochlea harbors key components of the core clock machinery (Fig. 4.4c). Presence of additional circadian genes was revealed using a more sensitive methodology, namely, the NanoString nCounter (Cederroth and Canlon, unpublished observations).

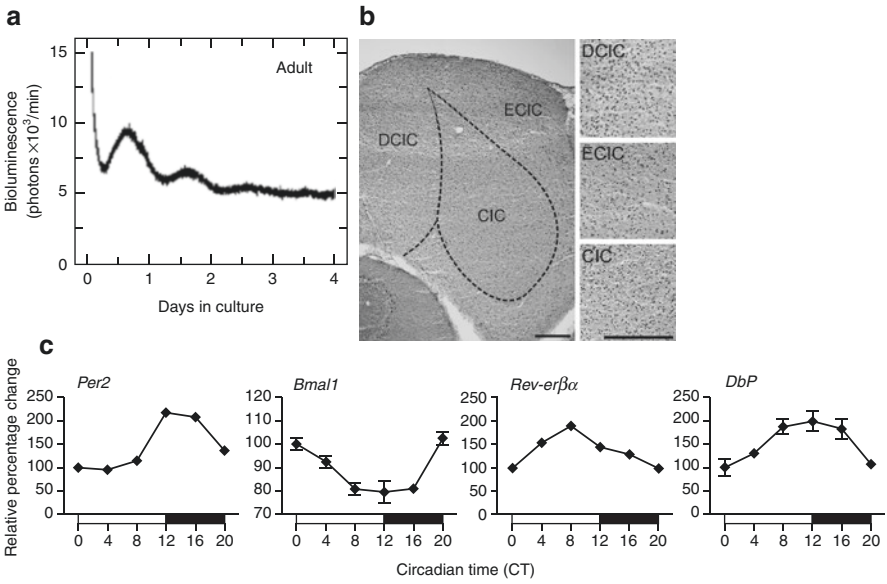

Fig. 4.5 Circadian oscillations in the IC. (**a**) Representative recordings of bioluminescence from whole IC at different ages (P4, P16, and adult) maintained in culture for 4 days. (**b**) Representative coronal section from the caudal part of the IC from a control animal sampled at ZT 11 showing PER2 immunoreactivity throughout the IC. The corresponding anteroposterior stereotaxic coordinate relative to the bregma is indicated in mm. The subdivisions of the different regions of the IC are outlined with the *dashed lines*. The *boxes* in each subdivision indicate the region of interest (DCIC, ECIC, and CIC) and are magnified in the inserts to the right. The *asterisk* and *daggers* indicate the aqueduct and cerebellum, respectively. Scale bars indicate 200 μm. (**c**) Temporal expression of clock mRNAs in the IC assessed with the NanoString nCounter. The *vertical axis* shows normalized mean values ± SEM (n = 3–4). The *horizontal axis* shows the sampling circadian time (CT) across 24 h at which the animals were sacrificed and samples collected. The *shaded area* illustrates the dark phase of the day from CT 12 to CT 0. All conditions were plotted as relative percentage change using CT 0 as baseline value. Modified from Park et al., J. Neuroscience, 2016, in press with permission from the Society of Neuroscience

The cochlea harbors key components of the core clock machinery.

Interestingly, noise exposure at night affected to a greater extent than day noise exposure the amplitude of *Per1, Per2, Bmal1,* and *Rev-Erβα* mRNA expression, a finding further validated via the monitoring of PER2::LUC rhythms in vitro. In addition, activation of TrkB with DHF modulated PER2::LUC oscillations to a greater extend in the day than in the night (Meltser et al. 2014). How these changes in cochlear rhythms are coupled to the physiological responses to noise trauma is a challenging area of research, but overall these findings illustrate the complex and interdependent links between noise, neurotrophins, and circadian rhythms in the cochlea.

4.3.3.4 Circadian Rhythms in the Inferior Colliculus

Recent experimental work from our laboratory revealed that the IC, an important relay of the auditory pathway involved in tinnitus, also possesses a molecular clock (Park et al. 2016). PER2::LUC rhythms in vitro were also captured in whole mount or sectioned IC (Fig. 4.5a). Immunohistochemistry revealed that PER2 is homogeneously expressed throughout the IC according to the different subdivisions, namely, the central nucleus of the IC (CIC), dorsal cortex of the IC (DIC), and external cortex of the IC (ECIC) along the rostro-caudal axis (Fig. 4.5b). NanoString nCounter arrays revealed circadian mRNA transcript profiles for *Per1, Per2,* and *Bmal1*, among others, and the clock-dependent genes *Dbp* (Fig. 4.5c). Curiously, the analysis of PER2::LUC rhythms indicates that the IC in the postnatal stage showed more robust circadian oscillations than the adult stage. In postnatal day 4 (P4) ICs, 100% of cultured IC oscillated, and in adult ones (P50), this dropped to 30%. To explain this phenomenon, multiple factors were investigated such as the experimenter, the gender of the animals, whole mount vs sections, the thickness of the sections, and their orientations (coronal, sagittal, horizontal), but none explained this decline in successful oscillations. A potential explanation is that aging influences the synchronicity of the oscillations, which suggests that a greater proportion of ICs might fail to show oscillations in adult stage, or that as an animal ages, components of the expression of core clock machinery could decrease until affecting the whole machinery.

Some scientists might argue that an oscillatory clock machinery might be detectable in any organ or tissue. However, as much as the clock machinery has been shown to be very important in the context of metabolic function such as hepatic glucose clearance and insulin secretion by the β-cells of the pancreas, that much it has been less obvious in the CNS. A landmark study investigated 27 areas of the brain and found that only 50% of these showed evidence of PER1 rhythmicity (Abe et al. 2002) indicating that the presence of the clock machinery cannot be expected everywhere. Similarly, results showing rhythms in reproductive organs have been conflicting (Dibner et al. 2010). Importantly, the physiological relevance of the clock system will only be revealed with functional studies using genetic mutants.

The presence of clock machinery cannot be expected everywhere.

In this regard, this information is still lacking for the cochlea and the IC. Nonetheless, the work of Park and colleagues revealed that clock genes in the IC also respond to noise, although in a partially inverted manner when compared to the cochlea. In the cochlea, night noise exposure affects the clock genes to a greater extent compared to day noise exposure. In contrast, day noise exposure alters clock genes in the IC more than the night noise exposure. These findings suggest that the response of the IC to noise is uncoupled to that of the cochlea. Supporting this idea, the induction of *Bdnf* transcription in the IC is similar between day and night noises, whereas in the cochlea, only day noise exposure triggers a *Bdnf* transcriptional response. Thus, the circadian relationship to noise sensitivity appears independent between the cochlea and the IC.

4.3.3.5 Central Influence of Cochlear and IC Rhythms: Predictive Models

The factors (*zeitgebers*) that synchronize cochlear or IC rhythms—if any—are still unknown. Several models can be proposed to predict the relationship between the cochlea, the IC, and the master clock (Fig. 4.6). It is possible that the cochlea or the IC function is fully dependent from SCN cues (directed control of auditory rhythms). However, the entrainment (the alignment of a circadian system's period and phase to the period and phase of an external rhythm) might not originate from the SCN but rather from other cues unrelated to SCN signals (e.g., feeding regimes), thus being completely independent from the master clock. Finally, a combination of the two models making the auditory system sensitive to some SCN-dependent or SCN-independent cues is what appears to be most plausible.

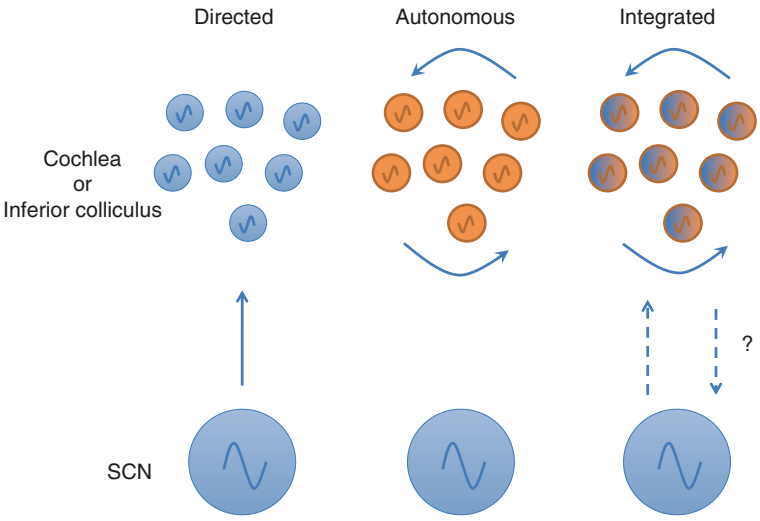

Fig. 4.6 Potential model of the circadian regulation of the auditory pathway. The SCN acts as the master clock that interacts with peripheral organs to synchronize their rhythms either directly or through the autonomic nervous system, feeding, or body temperature. Whether the SCN regulates the oscillations in the auditory circuit or whether cells from the cochlea or the IC are completely autonomous remains to be determined. A plausible mechanism is an integrated system whereby the cochlea and the IC have some control over their rhythms, coordinated by either direct or indirect inputs from the SCN. *Blue circles* represent SCN-driven oscillators, and *orange circles* represent autonomous oscillators. *Solid arrows* represent direct input, whereas *dashed arrows* represent an influence over the oscillators. Whether the cochlea or the IC communicates back to the SCN is unknown and illustrated with a question mark (?). Modified from Gerstner et al., Nature Reviews Neuroscience, 2010, 11:577 with permission from the Nature Publishing Group

4.3.4 Auditory Pathologies and Disrupted Circadian Rhythms

Whether there is a relationship between circadian rhythms and tinnitus remains unknown. The IC has been implicated in auditory pathologies such as tinnitus, hyperacusis, and seizures. In rats, direct stimulation of the IC increases the susceptibility to audiogenic seizures (Faingold et al. 1992).

Audiogenic seizures are convulsions induced by extended exposure to high-frequency sound, particularly in small mammals.

When generated at night, audiogenic seizures induced by sound stimulation cause greater convulsions and death in comparison to day stimulation (Halberg et al. 1958). These two studies connect the inferior colliculus with the circadian vulnerability to audiogenic seizures. Interestingly, mice lacking the clock-controlled genes encoding three PAR bZip (proline and acidic amino-acid-rich basic leucine zipper) proteins (*Tef*, *Hlf*, and *Dbp*) also develop spontaneous seizures and are more vulnerable to audiogenic seizures (Gachon et al. 2004b). Curiously, *Tef* and *Hlf* do not show circadian expression in the IC (Park et al. 2016), which might indicate that the source of audiogenic seizures in this triple mutant might not stem from the IC but rather in the cochlea, where these transcription factors were found highly circadian (Cederroth and Canlon, unpublished observations). It is also possible that other parts of the auditory pathway show strong circadian rhythms; however, this requires further investigation.

Assuming that disruption of circadian rhythms in the cochlea could not only be related to central auditory pathologies such as seizures but also to tinnitus and hyperacusis, then important CNS-related phenotypes should be expected in mutants in which the clock machinery has been specifically knocked out from the cochlea. Unfortunately, to the best of our knowledge, there is no genetic tool to allow cochlea-specific deletion of clock-related gene function without affecting other central auditory and non-auditory areas or other peripheral organs involved in circadian rhythms. Thus, testing this hypothesis will remain a challenging task. Nonetheless, studies have found in animal models of noise-induced tinnitus that the development of tinnitus correlates with a greater number of missing synaptic ribbons in inner hair cells, leading to decreased wave I amplitude of the ABR (Ruttiger et al. 2013). The permanent damage occurring after night noise trauma suggests greater loss of ribbons than after day noise trauma, although this remains to be ascertained. DPOAE measures should also clarify whether outer hair cell dysfunction contributes to the permanent threshold shifts happening after night noise exposure. The relevance of these findings to humans was evidenced in a study from Schaette et al. in which tinnitus subjects displayed lower wave I amplitude of click ABRs than control subjects (Schaette and McAlpine 2011). Further research is required to reveal the importance of cochlear rhythms in the generation of auditory pathologies.

In the animal models of noise-induced tinnitus, the development of tinnitus correlated with a greater number of missing synaptic ribbons in inner hair cells, leading to a decreased amplitude of the ABR wave I.

Importantly, no information is available on whether disruption of circadian rhythms causes auditory dysfunctions or tinnitus in humans. Epidemiological studies on shift workers, flight crews, and others will need to investigate whether the timing of noise exposure combined with the working schedule are associated with hearing deficits or tinnitus.

4.3.4.1 Psychological Consequences of Disrupted Circadian Rhythms and the Potential Role in Tinnitus

While the causal relationship between stress, depression, and anxiety in tinnitus is still unclear, there is an evident association of these emotional factors with tinnitus (see Chap. 3). Since these psychological states are controlled by circadian rhythms, it is tempting to speculate that disruptions in daily rhythms may increase the vulnerability to develop tinnitus in association with a psychological burden or increase the severity of an already established tinnitus symptom.

Disruptions in daily rhythms may possibly increase the vulnerability to develop tinnitus in association with a psychological burden.

Animal studies support the notion that the disruption of the clock system causes depression and anxiety. Mice harboring a point mutation in the *Clock* gene are hyperactive over the light-dark cycle and display reduced depression-like behavior and increased reward value (Dzirasa et al. 2010; McClung et al. 2005; Roybal et al. 2007). Dopamine release is increased in *Clock* mutants, and sensitivity to dopamine receptor agonist is increased (Spencer et al. 2012). Mice lacking *Per1* and *Per2* display increased anxiety (Spencer et al. 2013). In people with major depressive disorder, the amplitude and rhythm of melatonin secretion is altered. It has been proposed that neuropsychiatric disorders are the result of desynchrony between key behavioral and physiological events, as it is the case for major depression (e.g., different sleep-wake cycles, cognition, mood, hormonal, immune, metabolic, and thermoregulatory) (Germain and Kupfer 2008). This is why many studies do not assess absolute changes in serum levels of key hormones but rather investigate the deviations from normal circadian patterns.

Psychosocial stress at different times of the day can alter the molecular clock.

Reversely, psychosocial stress at different times of the day can alter the molecular clock. Repeated social defeat at night but not in the day blunts activity rhythms and flattens glucocorticoid rhythms (Bartlang et al. 2012). At the molecular level, this phenomenon was associated with increased amplitude of PER2::LUC rhythms in the SCN after night social defeat and in the adrenal gland after day social defeat (Bartlang et al. 2014). Since the SCN does not express GR (Balsalobre et al. 2000), it is thought that either indirect feedback from circulating glucocorticoids acting on other brain areas expressing GRs could occur or that glucocorticoid action on the raphe nucleus could reach the SCN via serotonergic projections (Kiessling et al. 2010; Malek et al. 2007). Another paradigm using chronic stress but being unpredictable causes a decrease in PER2 protein expression in the SCN (Jiang et al. 2011). Thus, different stressors act differently on the molecular clock and its alterations, whatever the direction (either suppressed or increased rhythmicity) could lead to changes in physiological functions such as the amplitude of glucocorticoid secretion. The presence of GR receptors in the cochlea (see Chap. 2) and the known effects of stress on the auditory system (Meltser and Canlon 2011; Tahera et al. 2006) suggests that tinnitus generation by stress (*stress inducing tinnitus*) may occur at the level of the cochlea. On the other hand, the exacerbation of tinnitus severity by stress (*stress increasing tinnitus*) may occur through the known involvement of the limbic system in tinnitus (see Chap. 3) (Elgoyhen et al. 2015).

4.4 Clinical Implications of Circadian Influences for Tinnitus Therapy

Although auditory chronobiology is an extremely new discipline of research, it draws the attention to the important association of diurnal rhythms with hearing. The key discovery of the increased vulnerability of the rodent auditory system to noise at night in comparison to daytime helps to better understand the increased incidence of hearing loss in communities exposed to 24 h of noise pollution (aircraft, train, or highway noise) (Basner et al. 2014, 2015).

Understanding the pathological basis of tinnitus (such as night noise-induced hearing loss) is one issue in which the circadian rhythms may be very helpful. Another issue is the use of this new knowledge for therapeutic purposes. The physiological rhythmicity of cells, tissues, and organs keeps our bodies in the state of homeostasis and health. Disrupting this rhythm can have pathological consequences, and it remains to be determined whether it can be corrected. Daily routines (also known as social rhythm) such as going to work or school or exercise influence the sleep patterns, and correlations have been found between people with daily routines and healthy sleep (Moss et al. 2015).

To recover from disturbed routines, a special treatment has been developed, namely, social rhythm therapy (Haynes et al. 2016a). Social rhythm therapy is an evidence-based psychotherapy and has been used for various mood conditions,

such as bipolar disorder, post-traumatic stress disorder, insomnia, and depression (Haynes 2015; Haynes et al. 2016a, b). However, the effectiveness of social rhythm therapy has not been studied, to our knowledge, in individuals with tinnitus. Nevertheless, it could be an attractive therapeutic avenue for patients with tinnitus, since near 50% of them have at least one comorbid psychological disorder (see Chap. 6). The question remains whether reinstating daily routines would restore diurnal rhythms and have a positive influence on tinnitus or on hearing abilities in general.

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Animal Models of Stress and Tinnitus

5

Jos J. Eggermont

5.1 Stress

"Stress" can be divided into different levels as "good stress," "tolerable stress," and "toxic stress." *Good stress* is "characterized by moderate, short-lived increases in heart rate, blood pressure, and stress hormone levels." *Tolerable stress* "refers to a physiological state that could potentially disrupt brain architecture, e.g., through cortisol-induced disruption of neural circuits or neuronal death in the hippocampus." *Toxic stress* "refers to strong, frequent, and/or prolonged activation of the body's stress-response systems. The defining characteristic of toxic stress is that it disrupts brain architecture, and affects other organ systems" (Shonkoff et al. 2009).

A stressful situation activates three major systems in the brain that regulate bodily functions. The first of these systems is the *voluntary nervous system*, which activates the motor system to, e.g., allow behavioral response to auditory information. The second is the *autonomic nervous system*, which responds to emergencies. The third system is the *neuroendocrine system*, which maintains the body's internal functioning and consists of a set of cells secreting amine- and peptide-based hormones/transmitters (Toni 2004). These "stress hormones" are transported through the bloodstream and stimulate the release of other hormones. Major stress hormones are adrenaline and cortisol. When the body is exposed to stressors, adrenaline is quickly released into the bloodstream to put the body into a general state of arousal and enable it to cope with a challenge. The adrenal glands secrete glucocorticoids, i.e., hormones that affect glucose metabolism. In humans, the main glucocorticoid is cortisol, whereas in common animal models such as rodents, it is corticosterone.

J.J. Eggermont, Ph.D., F.R.S.C.
Department of Physiology, Pharmacology, and Psychology, University of Calgary, Calgary, AB, Canada
e-mail: eggermon@ucalgary.ca

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Glucocorticoids help to mediate the stress response, and some of its slower actions counteract the primary response to stress and help reestablish homeostasis (Brain facts 2015).

5.2 Hypothalamic-Pituitary-Adrenal Axis and the Auditory System

The hypothalamic-pituitary-adrenal (HPA) axis is part of the neuroendocrine system and is the major stress-response system of the body (Fig. 5.1). In response to stress, the hypothalamus releases corticotropin-releasing factor (CRF), which travels via blood circulation to the pituitary, where it binds to its receptor and produces adrenocorticotropic hormone (ACTH). ACTH is then secreted into the systemic blood circulation and travels to the adrenal cortex, where it binds to the melanocortin receptor 2 (MCR2) to stimulate the production and release of glucocorticoids (Toni 2004; Mazurek et al. 2012). HPA-induced glucocorticoids affect their target tissue trough the glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs). GRs are nearly expressed everywhere in the body; however, expression of MR receptors is restricted to selected tissues including the brain and pituitary gland (providing feedback; Fig. 5.1), the eye, kidney, and the inner ear. Mice demonstrate the highest expression level of *MR* mRNA in the inner ear, as compared to other tissues. MRs regulate the ionic and water transports resulting in the reabsorption of sodium and an excretion of potassium (Basappa et al. 2012; Mazurek et al. 2012).

The HPA axis involves adaptation to increased demands and maintains homeostasis after stressful challenges, but it also supports normal physiology and homeostasis (Canlon et al. 2007). The overall function of the HPA axis is controlled by several negative feedback loops (Fig. 5.1). A dysfunctional HPA axis is associated with manifestations of psychosomatic and psychiatric disorders. Hyperactivity of the HPA axis is often found in major depression and is associated with increased susceptibility to infection and cardiovascular problems (McEwen 2007). The glucocorticoid receptors, affecting the main targets of the HPA axis, are important regulators for protecting against noise trauma (Canlon et al. 2007).

5.3 Recognizing Stress in Animals

Stress does not occur unless the animal perceives a threat (Carstens and Moberg 2000). Because most stressors are brief, the changes in biological function required to cope with the stressor are minimal and of little consequence to the animal's well-being (Carstens and Moberg 2000). These brief stressors include stressors

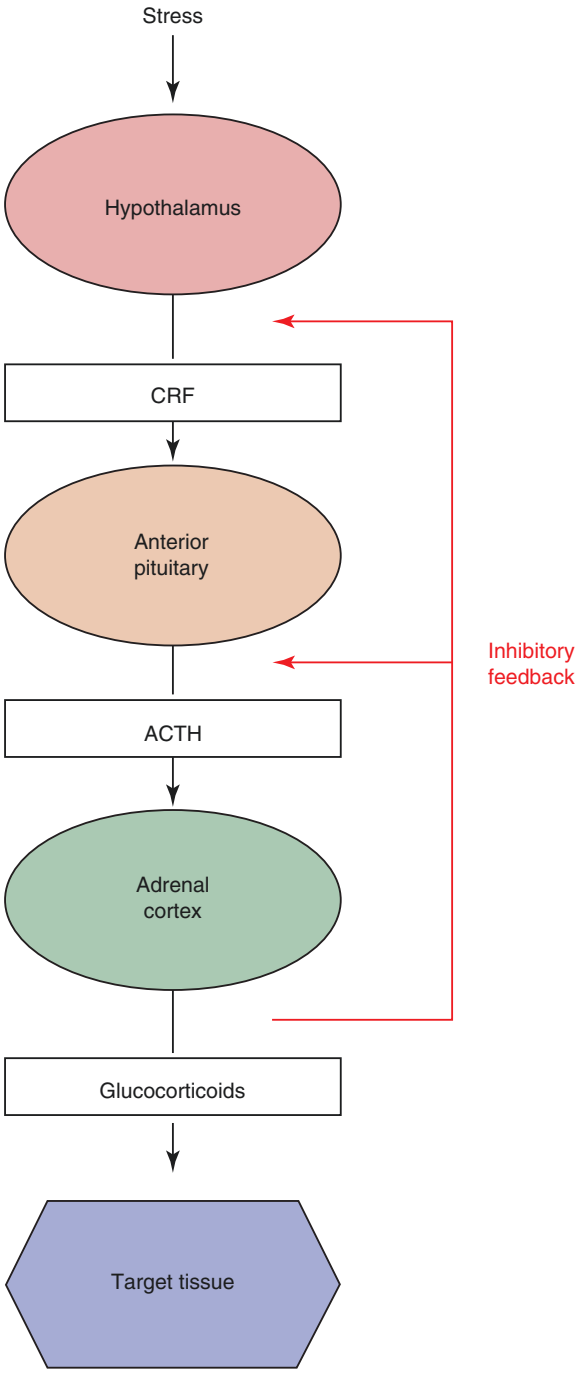

Fig. 5.1 Simplified representation of the classic hypothalamic–pituitary–adrenal (HPA) axis. *ACTH* adrenocorticotropic hormone, *CRF* corticotropin-releasing factor. Redrawn and simplified from Basappa et al. (2012)

associated with the experimental manipulation and handling of the animal (Carstens and Moberg 2000). According to Bali and Jaggi (2015), stress in animals may be assessed (1) at the behavioral level reflected in social interaction, (2) at the biochemical level by measuring plasma corticosterone and ACTH, and (3) at the physiological level by measuring food intake and body weight. Carstens and Moberg (2000) pointed out that the stressor responses of the HPA axis provide an example of the difficulty encountered in measuring stress: "Measuring the secretion of the glucocorticosteroids—cortisol (primates) and corticosterone (rodents)—has been the most popular tool for evaluating stress, and frequently increases in circulating glucocorticosteroids have been used as proof of stress. It is evident that numerous stressors do elicit an increase in circulating steroids but not all stressors elicit an HPA response" (Carstens and Moberg 2000).

5.4 Causing Stress in Animals

The well-described stress models used in research include immobilization, restraint, electric foot shock, and social isolation (Bali and Jaggi 2015). We will first describe restraint stress and foot-shock stress, as they are most used in auditory research. However, we should also realize that noise exposure in itself is a stressor associated with increase in plasma norepinephrine levels in awake animals (Muchnik et al. 1998).

5.4.1 Restraint Stress

Restraint stress is a form of immobilization stress in which animals are not allowed to move for a specified period of time. Restraint stress is induced by placing the test animal in a plastic tube or wire-mesh container. This does allow limb movement but limits the range of overall movement. Based on neural and endocrine responses, restraint stress appears to be less intense than immobilization. Restraint stress is a commonly employed model for the induction of acute as well as chronic stress in rodents (Bali and Jaggi 2015).

5.4.2 Electric Foot Shock-Induced Stress

The electric foot shock paradigm mainly comprises acute or chronic exposures of foot shocks with variable intensity and duration on an electrified grid floor in an electric foot shock apparatus. Electric foot shocks are an integral part of classical conditioning tests used to assess the presence of tinnitus in animals (Sect. 5.8). It is generally not appreciated that foot shocks cause acute stress and may affect the very thing the procedure aims to measure. As Bali and Jaggi (2015) noted: "Electric foot shock stressor includes both physical as well as emotional components and it is used as direct (physical stress) and indirect stressor (psychological stress). It has been mainly used with varying degree to produce mild as well severe stress of both acute and chronic in nature."

5.4.3 Noise-Induced Stress

Chronic noise-induced activation of the HPA axis might cause a variety of problems because of abnormally high levels of circulating stress hormones. The auditory system connects via the amygdala and other circuits to the HPA axis and can thereby cause the release of stress-related hormones (Fig. 5.2). Henkin and Knigge (1963) suggested that noise-induced corticosterone elevations persist for up to ~12 h after

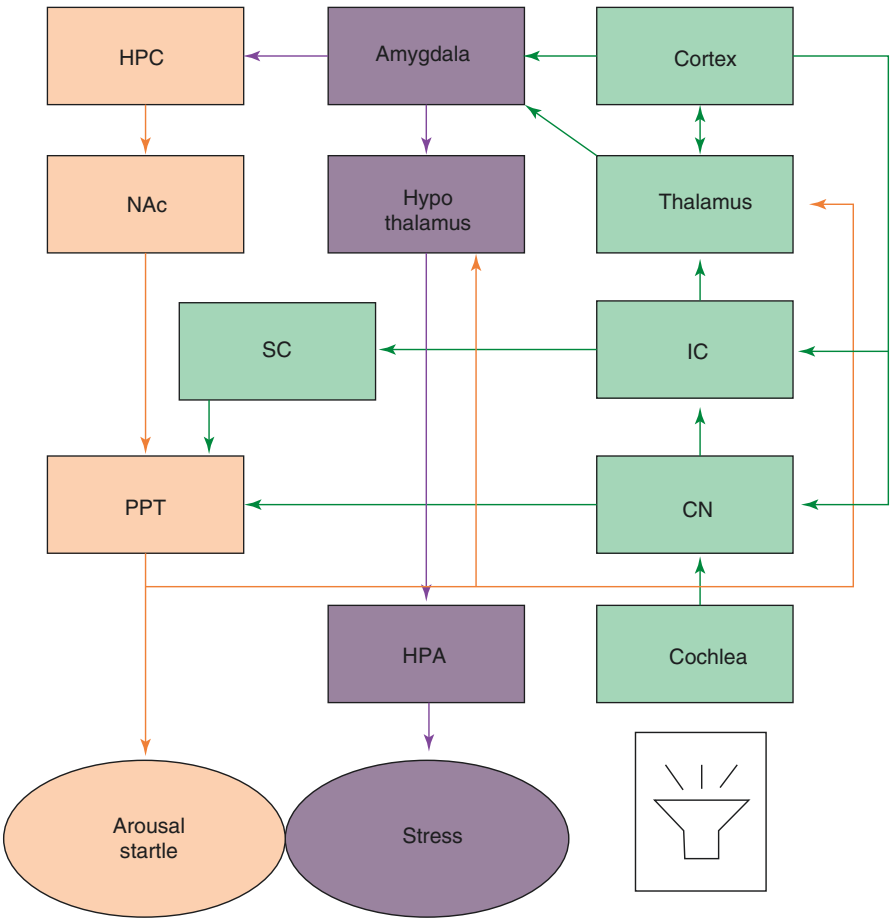

Fig. 5.2 Schematic of the various interconnections between the auditory system and the structures involved in noise-induced arousal, startle, and stress. The *green boxes* and *lines* represent the auditory system. The *purple boxes* and *lines* the HPA stress system. The *orange boxes* and *lines* represent the arousal and startle system. *CN* cochlear nucleus, *IC* inferior colliculus, *SC* superior colliculus, *HPC* hippocampus, *NAc* nucleus acumbens, *PPT* pedunculopontine tegmental nucleus, *HPA* hypothalamic-pituitary-adrenal axis. Modified from Eggermont (2013a)

stress induction. Noise-induced stress can affect arousal and startle responses, the latter being more and more used in the gap-startle test for tinnitus in animals. We will expand on this in Sect. 5.8.

The mechanism of noise-induced stress on the cochlea briefly can be described as (Eggermont 2013a): noise exposure activates neuroendocrine cells containing corticotropin-releasing hormone (CRH) in the hypothalamic paraventricular nucleus, which stimulates the release of ACTH in the pituitary gland (Fig. 5.1). ACTH release and the resulting secretion of corticosterone (in rodents) in the adrenal gland increase with noise intensity. The increased levels of ACTH as well as corticosterone remained elevated for the duration of noise presentation along with behavioral stress response. As we have seen, corticosterone in turn activates glucocorticoid receptors in target structures such as the inner ear (Kraus and Canlon 2012).

5.5 Stress and the Cochlea

5.5.1 The HPA Axis Signaling System

The effects of noise stress on the cochlea are well studied (Horner 2003). After exposing rats daily to 85 dB SPL white noise for 4 h on 3 consecutive days, Rarey et al. (1995) detected a significant decrease in glucocorticoid receptor protein levels in the organ of Corti, but not in the spiral ligament, together with a significant increase in serum corticosterone levels compared to nonexposed controls. Curtis and Rarey (1995) then used immobilization stress. They observed a significant quadratic trend of GR levels in spiral ligament tissues of rats restrained from 6 h daily. GR levels were elevated by day 2, and by day 21 GR levels had returned to near normal values. There was also a statistically significant decrease in the organ of Corti's GR levels when the daily restraint stress was applied for up to 7 days, but was again no longer observed after 21 days.

There are several reports demonstrating that acute stress can protect the auditory system. Noise-induced temporary threshold shifts after noise exposure (120 dB, 20 min) were less in stressed guinea pigs than in unstressed controls (Muchnik et al., 1998). Wang and Liberman (2002) showed that two 12-h epochs of mild physical restraint significantly reduced permanent threshold shifts from a subsequent acoustic overexposure, as long as the treatment-trauma interval was short ($\leq$2 h). The period of protection coincided with the period of elevated corticosterone levels. Thus, cochlear protective effects of sound conditioning may be mediated by stress pathways through the activation of glucocorticoid receptors in the inner ear (Canlon et al. 2007; Meltser and Canlon 2011). Kraus and Canlon (2012) summarized this as: "while there are positive correlations between stress and hearing problems, a large body of studies provides evidence that acute stress can enhance hearing or mediate protection against noise-induced hearing loss."

Mazurek et al. (2010) examined the effect of stress on the auditory system of Wistar rats. Stress was induced by a combination of handling the animals, moving the animals to a new cage and a different room, exposed them to unpleasant sound and vibration, and restrain them. The unstressed control animals were kept in their home cage. Mazurek et al. (2010) found that such induced 24-h stress decreased auditory brainstem response (ABR) thresholds and increased ABR amplitude and strength of distortion product otoacoustic emissions (DPOAEs). The increased ABR and DPOAE amplitudes were most pronounced between 3 and 6 h post-stress, and 1 week later returned to control levels. Corticosterone and tumor necrosis factor alpha concentrations were systemically elevated in stressed animals between 3 and 6 h post-stress, pointing to the activation of the HPA axis. Expression of the HPA-axis-associated *GR* and hypoxia-inducible factor 1 alpha (*Hif1a*) genes was modulated in some auditory tissues. In the inferior colliculus (IC), Mazurek et al. (2010) found an upregulation of *GR* mRNA 3 h post-stress and continuous upregulation of *Hif1a* up to 24 h post-stress. In the spiral ganglion, there were no differences in gene expression between stressed and control animals. In the organ of Corti, no changes in the expression of *GR* mRNA were found; however, the expression of *Hif1a* was significantly downregulated 1 week after stress induction. In addition, the expression of *prestin* in the OHCs was significantly upregulated 6 h post-stress. Mazurek et al. (2010) concluded "that 24-h stress induces transient hypersensitivity of the auditory system and modulates gene expression in a tissue-specific manner." Knipper et al. (2013) reported an influence of stress on the IHC synapse in rodents. Two days after stress induction, the number of release sites (ribbons) at IHC synapses was increased in animals that exhibited high corticosterone levels (Singer et al. 2013).

5.5.2 The Local Cochlear CRF-Signaling System

Vetter and colleagues (Basappa et al. 2012) recently discovered "a novel cochlear signaling system that is molecularly equivalent to the classic hypothalamic–pituitary–adrenal (HPA) axis." This cochlear signaling system balances auditory sensitivity and susceptibility to noise-induced hearing loss and protects against metabolic insults from exposures to ototoxic drugs (Basappa et al. 2012). This local HPA system appears independent of the systemic HPA signaling to the cochlea. It consists of locally produced CRF, a CRF1-receptor, and ACTH (Fig. 5.3). Deletion of the CRF1-receptor gene resulted in auditory impairment of knockout animals (Graham and Vetter 2011). As we have seen, systemic HPA activation also influences hearing via delivery of systemic glucocorticoids through the circulation (Basappa et al. 2012).

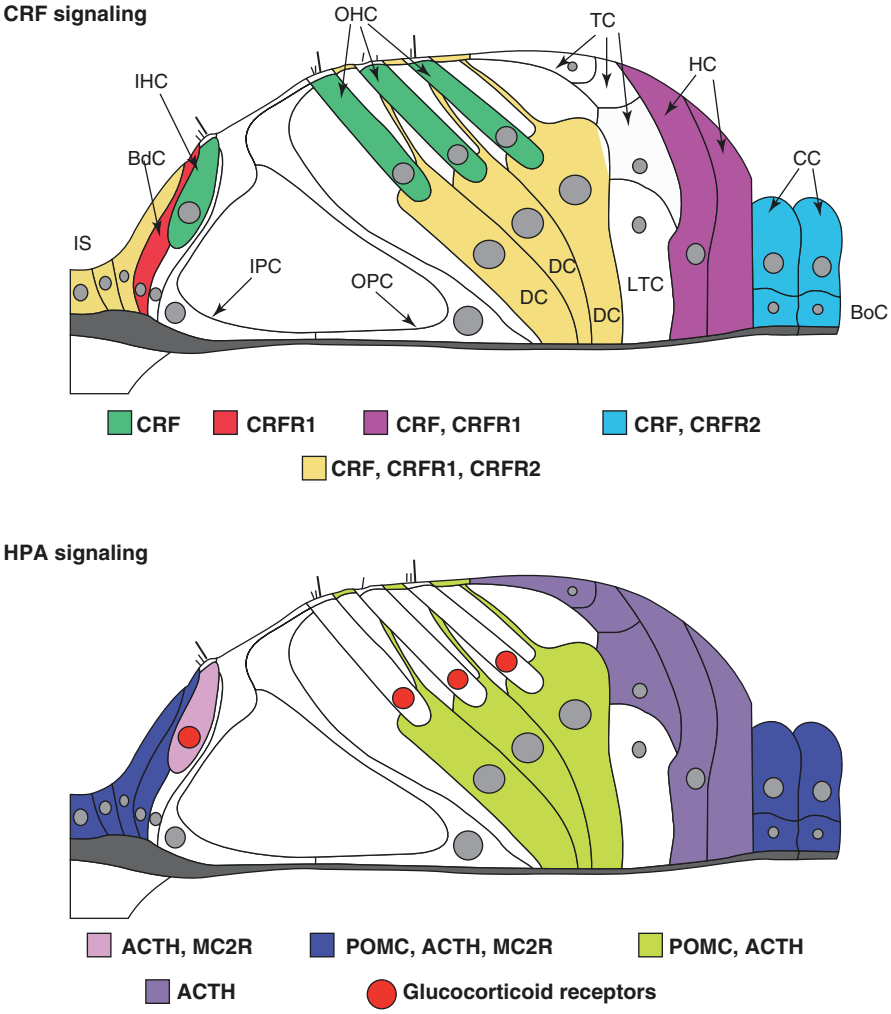

Fig. 5.3 The cochlea CRF signaling system (*top*) expresses an HPA-equivalent signaling system (*bottom*). *ACTH* adrenocorticothropin, *CRF* corticotropin-releasing factor, *CRF1* and *CRF2* are CRF-receptors, *MC2R* mineralcorticoid receptor, *POMC* pro-opiomelanocortin. From Basappa et al. (2012)

5.6 Stress and the Central Nervous System

Mazurek et al. (2015) emphasized that stress causes changes in neuroplasticity. Auditory neural plasticity may be defined as the dynamic changes that occur in the structural and functional characteristics of auditory neurons in response to changes in, or in the significance of, the sound they receive (Irvine 2010). Synaptic plasticity affecting the glutamate postsynaptic system and especially the AMPA and NMDA

receptors appears to be regulated by stress (Hubert et al. 2014; Timmermans et al. 2013). A stressful acoustic stimulus, such as noise, causes amygdala-mediated release of stress hormones via the HPA-axis, which may have negative effects on the central nervous system (Fig. 5.2). The hippocampus can affect auditory processing by being able to mediate novelty detection. Noise exposure affects hippocampal neurogenesis and LTP in a manner that affects structural plasticity, learning, and memory (Kraus and Canlon 2012). High stress levels at the time of a moderate auditory trauma led to a "tinnitus-specific" central responsiveness, including more severe IHC ribbon loss, reduction of ABR amplitudes, and the decline of Arc/Arg3.1 expression levels in the hippocampal CA1 or auditory cortex (Singer et al. 2013). In contrast, moderate stress levels at the time of trauma could prevent such a tinnitus-specific central response and restore adaptive central responses (Knipper et al. 2013).

Nava et al. (2017) studied the time course of acute stress by foot shock on dendritic remodeling within the prelimbic (PL) region of the rodent prefrontal cortex (PFC). They analyzed dendritic length and spine density at 1 day, 7 days, and 14 days after inducing stress. At day 1, they found increased small-spine density and dendritic retraction, together with significant atrophy of apical dendrites. After 7 and 14 days recovery, complete normalization of spine density was observed. Nava et al. (2017) concluded that acute stressors may induce rapid and sustained changes of PL neurons. These changes in the PFC could affect the protective gating effect that was hypothesized to prevent tinnitus (Leaver et al. 2011; next section).

5.7 Stress and Tinnitus

Tinnitus is strongly associated with emotional stress, anxiety, and depression (Langguth 2011; Mazurek et al. 2012). Like external environmental noise, the internally generated noise of tinnitus may cause emotional distress resulting in mood disorders like depression. In turn, stress or depression may contribute to the development of tinnitus (Halford and Anderson 1991; Robinson et al. 2007; Canlon et al. 2013). Reciprocal interactions of auditory areas and areas processing emotion seem essential for tinnitus generation (Rauschecker et al. 2010; Langguth et al. 2011; Fig. 5.4). The phantom sound may be caused by disinhibition, increased spontaneous firing rates, increased neural synchronization, and tonotopic reorganization in the central auditory system (Eggermont and Roberts 2004; Roberts et al. 2010). Furthermore, since the auditory and limbic systems are interconnected, tinnitus can affect emotional as well as cognitive properties of the limbic system. In turn, the limbic system may play a role for tinnitus generation or stabilization.

Canlon et al. (2013) described findings in a cross-sectional study on the association of hyperacusis and stress on tinnitus, assessed by the tinnitus handicap questionnaire (THQ; Kuk et al. 1990) score. They found that the only significant predictors of mean THQ score for the left ear were hyperacusis and stress and only stress for the right ear. Canlon et al. (2013) suggested that stress seems an important predictor of tinnitus severity.

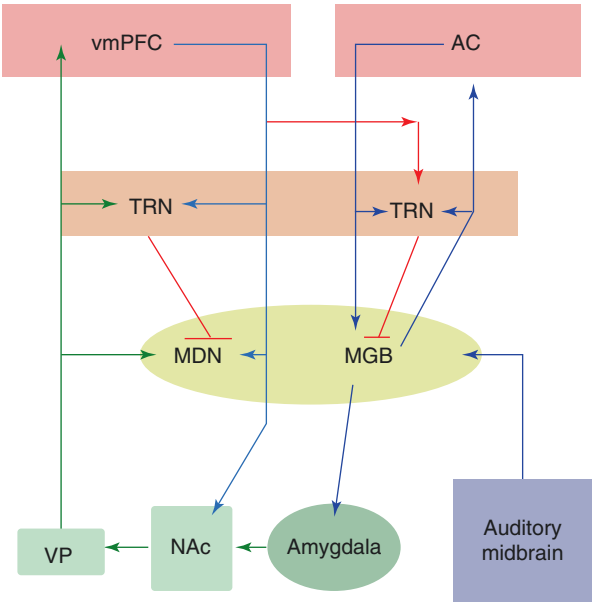

Fig. 5.4 Schematic of putative auditory-limbic interactions in tinnitus. Sensory input originates from the auditory midbrain (*purple*) and enters both auditory and limbic circuits via the medial geniculate body (MGB; *yellow*). Under normal circumstances, the limbic system may identify a sensory signal as perceptually irrelevant and inhibit the unwanted signal at the MGB via projections from the ventromedial prefrontal cortex (vmPFC; *pink*) to the auditory thalamic reticular nucleus (TRN) via the *red* pathway. In chronic tinnitus, inefficient vmPFC output via the *red* pathway prevents inhibition of the tinnitus signal at the level of the MGB, resulting in a constant perceptual presence of the tinnitus signal. Cortical structures are indicated in *pink*, the thalamus is indicated in *yellow*, the thalamic reticular nucleus in *orange*, the basal ganglia in *light green*, and the amygdala in *dark green*. *MDN* medial dorsal nucleus, *VP* ventral pallidum, *AC* auditory cortex, *NAc* nucleus accumbens. Based on Leaver et al. (2011)

5.7.1 Stress Causing Tinnitus

Hu et al. (2010) used a mild-chronic stress model of depression in Sprague-Dawley rat and evaluated the effects with positron emission tomography (PET) imaging technique. They used both physical stressors (e.g., sleep deprivation, water deprivation, and heat stress) and psychosocial stressors (e.g., crowding, loud sound). After 4 weeks of random mixed stressing, brain PET analysis showed activation of left auditory cortex and deactivation of left inferior colliculus. No changes were detectable in the visual pathway. Changes in the auditory system correlated significantly with the depressive symptoms of experimental animals (Hu et al. 2010). Although this does not directly relates to tinnitus, the comorbidity with depressive symptoms and increased metabolic activation in auditory cortex is suggestive.

Another link to tinnitus may be found in the stress-induced increase in central opioid-dynorphin activity that potentiates the HPA-axis. Opioid peptides are found within and released from neural systems that regulate the body's overall biologic

response to physical/emotional stress. Emotional or physical stress induces potent analgesic effects, and the biologic response to stress is likely to involve multiple opioid systems (Sahley et al. 2013). Naturally occurring opioid dynorphins are also released from lateral efferent olivocochlear axons into the synaptic region beneath the cochlear IHCs during stressful episodes (Sahley and Nodar 2001). This results in altered neural excitability and/or distribution of spontaneous firing rates in type I auditory nerve fibers with low SFRs and high thresholds. Incidentally, the same subset of type I nerve fibers is affected by TTS, via the damaged ribbon synapses (Kujawa and Liberman 2009). Sahley et al. (2013) wondered if a lateral efferent olivocochlear-activated release of endogenous dynorphins may generate increased SFRs in ANFs (in the same way as induced by salicylate; Ruel et al. 2008) that could be processed by the central auditory system as either an acute subjective tinnitus. This so far remains in the domain of speculation.

5.7.2 Tinnitus Causing Stress

Recent reviews by Kraus and Canlon (2012) and Wallhäusser-Franke et al. (2012) connected nonauditory effects of noise and tinnitus respectively to the activity in the limbic system. The sensation of sound and noise, or the absence of sound, not only induces structural or functional changes in the central auditory system but can also affect limbic regions such as the amygdala and hippocampus (Fig. 5.5). The amygdala is particularly sensitive to meaningful sound, such as animal vocalizations or speech, crying, or music. As we have seen, the amygdala plays a central role in auditory fear conditioning, regulation of the acoustic startle response, and can modulate auditory cortex plasticity. A stressful acoustic stimulus, such as noise, causes amygdala-mediated release of stress hormones via the HPA-axis, which may have negative effects on health, as well as on the central nervous system. In contrast, short-term exposure to stress hormones elicits positive effects such as hearing protection. Noise exposure affects hippocampal neurogenesis and LTP in a manner that affects structural plasticity, learning, and memory. Tinnitus, typically induced by NIHL, is associated with emotional stress, depression, and anatomical changes of the hippocampus (Goble et al. 2009). In turn, the limbic system may play a role in the generation as well as the suppression of tinnitus indicating that the limbic system may be an essential target for tinnitus treatment (Eggermont 2013a).

Hyperarousal also plays a role in Jastreboff's (1990) neurophysiological tinnitus model. Besides altered activation in auditory brain regions, there is evidence that tinnitus is associated with increased activity in regions associated with emotion processing and the control of autonomic bodily functions such as the prefrontal cortex and the amygdala (Fig. 5.4; Leaver et al. 2011). This is thought to be a feature that is common to many disorders that are associated with unexplained functional somatic symptoms and that show high comorbidities with depressivity and anxiety such as tinnitus or sleep disorders (De Ridder et al. 2011).

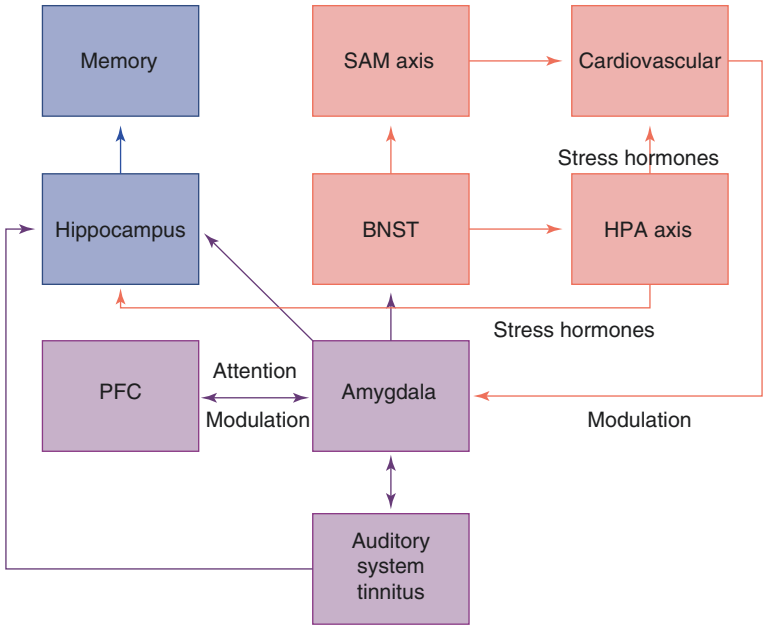

Fig. 5.5 Effects of tinnitus on limbic structures. Tinnitus, just as environmental noise, activates the amygdala, which in turn initiates stress hormone (corticosteroids such as glucocorticoids and, in animals, corticosterone) release through the limbic HPA-axis. Stress hormones as well as neuronal activity in the amygdala or auditory system affect the hippocampus by reducing neuronal activity, modifying synaptic plasticity, memory properties, and inducing long-term changes such as altered cell morphology and decrease of neurogenesis. *BNST* bed nucleus of stria terminalis, *HPA* hypothalamic-pituitary-adrenal, *PFC* prefrontal cortex, *SAM* sympathetic-adrenal-medullary. From Eggermont (2013a)

5.8 Recognizing Tinnitus in Animals?

In my discussion of what we might actually measure in animal models of tinnitus (Eggermont 2013b), I wrote "The search for neural substrates of tinnitus requires animal models that show behavioral evidence of tinnitus under conditions similar to those that cause tinnitus in humans. Humans can tell us if they have tinnitus and can describe how loud it is, what it sounds like and whether they are bothered by it. They don't experience it during sleep and can affect its perception by directing attention away from it (Searchfield et al. 2007); in other words tinnitus is a conscious percept (De Ridder et al. 2011)." The main question is: do animals experience tinnitus in similar ways, including cognitive and emotional aspects, and can it be demonstrated? In some behavioral test protocols, an animal is trained to respond differently to silence than to a presented sound with properties preferably similar to the expected tinnitus. Then the animal receives a tinnitus-inducing drug such as salicylate or is exposed to noise. The animal is subsequently assessed on its behavioral responses to continuous silence and external sound, the dominant idea being that tinnitus abolishes the notion of silence, i.e., the absence of an external sound.

5.8.1 Using Classical Conditioning

The classical behavioral techniques are based on conditioned response suppression (Estes and Skinner 1941; Fig. 5.6). Jastreboff et al. (1988a, b) introduced these tests into tinnitus research. They deprived rats of water and had them continuously engaged in licking behavior during each experimental session. A constant 24-h background noise functioned as a safe-to-drink signal. The conditioned stimulus consisted of a temporary interruption of the background noise, which was paired with a mild foot shock during the training (*note the stressor!*). The occurrence of silence thus slowly produced a decreased number of licks. Using this procedure, Jastreboff et al. showed that rats given salicylate after the training were less likely than control animals to stop drinking when the noise was turned off. The interpretation is that the treated animals still hear a sound when no external sound is present, i.e., they have tinnitus. Heffner and Harrington (2002) modified this procedure for use in hamsters. Bauer and Brozoski (2001) trained rats to press a lever in the presence of a 60 dB SPL broadband noise to obtain food, but they had to stop pressing the lever during silent intervals to avoid a foot shock (*note the stressor!*). After noise exposure, the animals were then tested by a procedure where four intervals containing a tone without shocks were presented, followed by four silent intervals where a shock was administered if the animal did

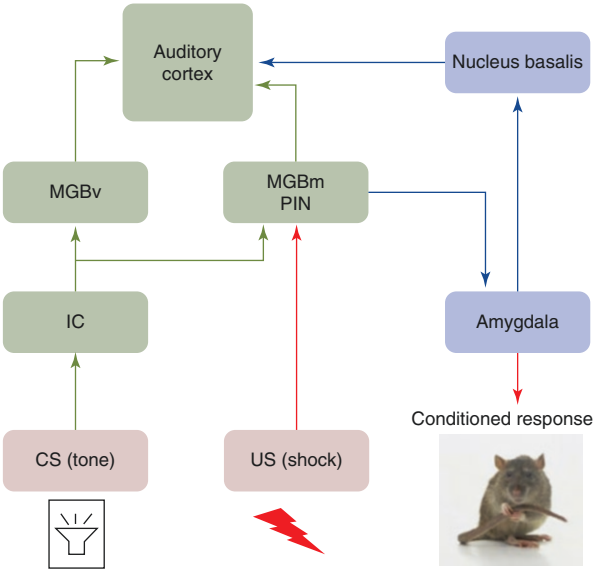

Fig. 5.6 Neural circuit for fear conditioning. The crucial point here is that the auditory cortex is not involved in generating the activity that leads to the conditioned response. This crucial role is reserved for the medial part of the medial geniculate body (MGBm)—posterior intralaminar nucleus (PIN) complex—making this behavioral response dominated by subcortical activity. *CS* conditioned stimulus, *IC* inferior colliculus, *MGBm* medial part of the medial geniculate body, *MGBv* ventral part of the medial geniculate body, *PIN* posterior intralaminar nucleus, *US* unconditioned stimulus. From Eggermont (2013b)

not stop lever pressing. The tone was varied in frequency and intensity with the expectation that animals with tinnitus would respond differently to the tones matching the tinnitus pitch than the control animals. This modification would allow an estimate of "tinnitus pitch."

Another approach used a shock avoidance (*note the stressor!*) conditioning procedure in which rats learned to climb a pole during the presentation of a sound to avoid a foot shock. Animals could remain on the cage floor during quiet intervals when the shocks were turned off (Guitton et al. 2003). Following salicylate treatment, rats climbed the pole (false positive) during quiet, which was interpreted as evidence of tinnitus. A schedule-induced polydipsia avoidance conditioning procedure (Lobarinas et al. 2004) also associated shock avoidance (*note the stressor!*) behavior with the presence of sound. Animals suppressed licking during sound trials. High doses of salicylate suppressed licks-in-quiet; this was interpreted as evidence of tinnitus.

Rüttiger et al. (2003) introduced a (putatively stress-free) positive reinforcement technique in which responses made in the presence of sound were reinforced with a fluid reward, but not during quiet. Salicylates induced a high false response rate in quiet; the false alarm rate was equivalent to the access rate evoked by a 30 dB SPL broadband noise.

5.8.2 Using the Gap-Startle Response

Turner et al. (2006) introduced a completely different and potentially powerful method for tinnitus screening in rats using a modified pre-pulse inhibition of the acoustic startle reflex (Fig. 5.7). This method does not require training but can be made more sensitive by fear conditioning (*note the stressor!*) on the pre-pulse. The presence of a gap in a continuous acoustic background functioned as the pre-pulse and induced an inhibition or reduction of a very loud noise-burst-induced startle reflex (*a putative stressor!*). The authors hypothesized that if the background acoustic signal was qualitatively similar to the rat's tinnitus, poorer detection of a silent gap in this background would be expected, and the startle reflex would not be inhibited.

Animal models of tinnitus require an unambiguous behavioral correlate of the presence of tinnitus. Various conditioned response methods and gap-startle reflex methods as described above are in use, and the outcomes generally correspond with putative electrophysiological substrates of tinnitus. However, for salicylate-induced tinnitus, there is clear discordance between the behavioral and electrophysiological test results. As a result, it is not clear if the various tests reflect tinnitus, hyperacusis, or may be just hearing loss (Eggermont 2013b).

Salloum et al. (2016) may have provided a solution to distinguish the effects of tinnitus and hyperacusis on the gap-startle. They hypothesized that hyperacusis-like enhancements of the acoustic startle response could lead to an apparent reduction of gap suppression, resembling that caused by tinnitus, by altering responses to the startle stimulus or the background noise. Salloum et al. (2016) demonstrated that

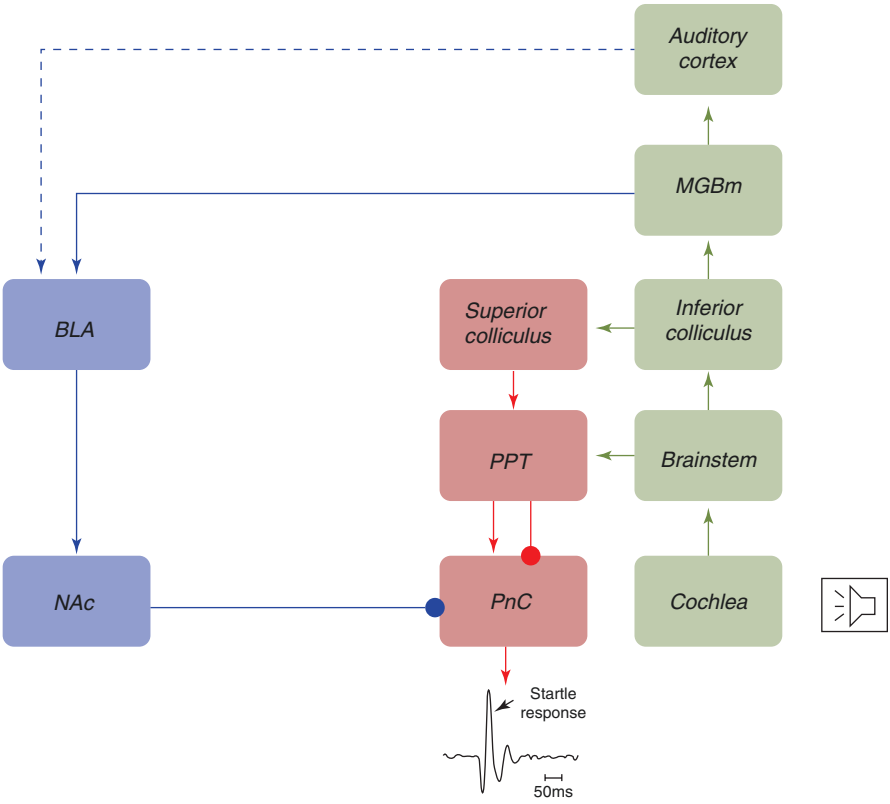

Fig. 5.7 Simplified pre-pulse startle response circuit. The auditory pathway is indicated with *olive-colored boxes* and *connections*. The startle circuit is indicated by *pink boxes* and *red connections*. The pre-pulse inhibition modulating circuit includes the path through the superior colliculus but could in addition be affected by the pathway and structures indicated in *blue*. This latter pathway inhibits the PnC and is potentially affected by auditory cortex and more directly by the MGB via the amygdala (BLA). The *arrowheads* indicate excitatory connections, and *round-dotted endings* indicate inhibitory connections. *BLA* basolateral amygdala, *MGBm* medial part of the medial geniculate body, *NAc* nucleus accumbens, *PnC* nucleus reticularis pontis caudalis, *PPT* pedunculopontine tegmental nucleus. From Eggermont (2013b)

besides hearing loss, also changes in sensitivity to background noise or to startle stimuli are potential confounds that, when present, can underlie changes in gap detection irrespective of tinnitus.

Could the behavioral techniques to assess tinnitus induce stress and consequently induce or exaggerate tinnitus? Looking back at the standard methods used to induce stress, handling, foot shock, noise exposure, and moving to a different cage, i.e., from cage to startle box, it should not be surprising if it did. If not all animals are similarly sensitive to these types of stress, this idea could explain why typically only ~$^1/_3$ to ½ of the animals in the gap-startle test show a "tinnitus" response. This should be investigated.

5.9 Summary

Stress induced in and auditory research context is characterized by moderate, short-lived increases in heart rate, blood pressure, and stress hormone levels. The well-described stress models used in auditory research include immobilization, restraint, and electric foot shocks. Handling is also a common source of stress in laboratory animals. Noise exposure is also a stressor associated with increase in plasma norepinephrine levels in awake animals. Stress induced by noise can protect the auditory system. The cochlea is affected by the glucocorticoids systemically released by the HPA system, but also by a local corticotropin-releasing factor signaling system. Stress may cause tinnitus, but tinnitus may in turn cause or acerbate stress.

No stress occurs unless the animal perceives a threat. Stress in animals may be assessed (1) at the behavioral level reflected in social interaction, (2) at the biochemical level by measuring plasma corticosterone and ACTH, and (3) at the physiological level by measuring food intake and body weight. Tinnitus in animals has been assessed by conditioned response suppression or by the gap-startle reflex. Both methods use stressors, i.e., foot shock and loud noise. I suggest that these may interfere with the outcome of these tests.

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Stress-Related Blood Biomarkers

6

Agnieszka J. Szczepek and Birgit Mazurek

6.1 Introduction

In medicine, the term *biomarker* refers to biological correlate of disease. Biomarker can be used to either objectively assess the predisposition of an individual for developing certain disease, to diagnose given condition, to assess its stage, or to measure its progress and response to treatment. Biomarkers are quantifiable substances that can be found in blood, serum, urine, or in the tissue. National Cancer Institute defines biomarker as "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease."

> *The term "biomarker" is used in a broad sense to include almost any measurement reflecting an interaction between a biological system and an environmental agent, which may be chemical, physical or biological.*
> *World Health Organization 1993* (WHO 1993)

The most prominent and perhaps historically longest use of biomarkers is that in oncology (Hughes 2007). In the sixties of last century, oncologists identified so-called Philadelphia chromosome, which characterizes leukemic cancer cells. Philadelphia chromosome is derived from the reciprocal translocation of chromosome 9 and 22 resulting in creation of a fused gene—BCR-ABL responsible for uncontrolled cell division and inhibition of DNA repair (Nowell 2007). Monitoring

A.J. Szczepek, Ph.D. (✉)
Department of Otorhinolaryngology, Head and Neck Surgery, Charité University Hospital, Berlin, Germany
e-mail: agnes.szczepek@charite.de

B. Mazurek, M.D., Ph.D.
Tinnitus Center, Charité University Hospital, Berlin, Germany

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the numbers of cells carrying the Philadelphia chromosome pioneered the concept of biomarkers in the prognostic scoring systems for leukemia.

Currently, biomarkers are used not only in oncology but in all medical disciplines. For instance, the quantity and quality of antibodies against pathogens is one of the most common biomarkers enabling diagnosis of infectious diseases. By now, not only the infectious diseases but almost all conditions have own, specific biomarker(s); the tendency of the biomarker discovery increases and heads toward personalized medicine.

Biomarker can be used to either:

1. *Objectively assess the predisposition of an individual for developing certain disease*
2. *To diagnose given condition*
3. *To assess its stage*
4. *To measure its progress and response to treatment*

Some medical disciplines use the measurable biological activities of selected organs as biomarkers. A good example will be here the use of electroencephalography (EEG) as well as diffusion tensor imaging (DTI), 18F–fluorodeoxyglucose-positron emission tomography (PET FDG), magnetic resonance spectroscopy (MRS) or functional magnetic resonance imaging (fMRI) for the diagnosis and monitoring of various neurodegenerative conditions (Potter 2015).

In this chapter, *we will strictly focus on the biomarkers that can be measured in the blood* and in addition, on these *associated with the emotional stress.*

The lack of subjective biological biomarker-based tests available for identification and monitoring of tinnitus-related distress is one of the difficulties in controlling the treatment response. The common use of psychometric instruments that probe the changes in patients' tinnitus-related distress, the quality of life, perceived stress, and the depressive and other symptoms may with time present a burden for patients, who slowly become tired of filling endless questionnaires. In addition, psychometric questionnaires belong to the group of subjective measurements. Still, the diagnosis and monitoring of tinnitus continue to be driven by these instruments.

Discovery and use of biomarkers for monitoring tinnitus-related distress emerges as an important, objective element of diagnosis and therapy.

Discovery of biomarkers which could serve as clinical tools for monitoring tinnitus-related distress emerges as an important, *objective* element of diagnosis and therapy. In the recent years, steps have been made toward the biomarker detection for tinnitus-related distress; however, there are no standard clinical protocols established.

This chapter gives an overview of blood biomarkers used for in the diagnosis and monitoring of stress-related conditions, in context of their possible application in tinnitus clinical research and in the future, as a part of clinical SOP.

6.2 Neuroendocrine Biomarkers of Stress

Although stress was shown to associate with changes in neuroendocrine biomarkers, each psychological condition has its signature pattern regarding the baseline, diurnal, or challenge-related concentration of neuroendocrine biomarkers. We hypothesize that such patterns could also be found in patients with tinnitus. We also think that some of the biomarkers may reflect the *stress induced by the duration of tinnitus*; some other could reflect the *comorbid mental symptoms* that are commonly diagnosed in tinnitus patients whereas another set could be specific for the *tinnitus-induced distress*. Current attempts of many researchers to determine and to classify sub-phenotypes of tinnitus (http://journal.frontiersin.org/researchtopic/4725/towards-an-understanding-of-tinnitus-heterogeneity) should facilitate the search for tinnitus-specific biomarkers.

6.2.1 Cortisol

Cortisol is a steroid hormone released in response to stress and low glucose concentration. The details about the production and release of cortisol can be found in Chap. 2. For decades, biologists, endocrinologists, and psychologists have been using the concentration of free cortisol as a stress marker; however, one needs to be careful when interpreting the results. Cortisol concentration is often used as a biomarker of the HPA axis and the measurements can be done in blood, urine, saliva, and hair (Gaudl et al. 2016). The assessment can either be done by taking multiple samples during the day for the evaluation of *cortisol diurnal secretion* or by challenging the HPA system with experimental stress or medicaments (e.g., dexamethasone) for the *assessment of HPA functionality*. One of the critical tests that measure responses to stress in laboratory settings is Trier social stress test (TSST) (Kirschbaum et al. 1993). During this test, persons are subjected to highly standardized components of public speaking, mental arithmetic, and anticipation. Cortisol production that is measured before, during, and after the experimental stress in the blood or in saliva reflects the immediate impact of stress on HPA axis (Kirschbaum et al. 1999). The stress-dependent cortisol release pattern may be affected by various factors such as, for instance, age or gender. Importantly, also the stress-related conditions—for instance, anxiety or dissociative disorders—associate with specific changes in TSST cortisol release pattern (Simeon et al. 2007; Villada et al. 2016).

The TSST was also performed in tinnitus patients to reveal that the post stress cortisol peak is reduced, and it occurs later (Fig. 6.1) than in the control subjects (Hebert and Lupien 2007). Interestingly, blunted cortisol responses noted by TSST participants were noted in subjects with anxiety disorders (Petrowski et al. 2013);

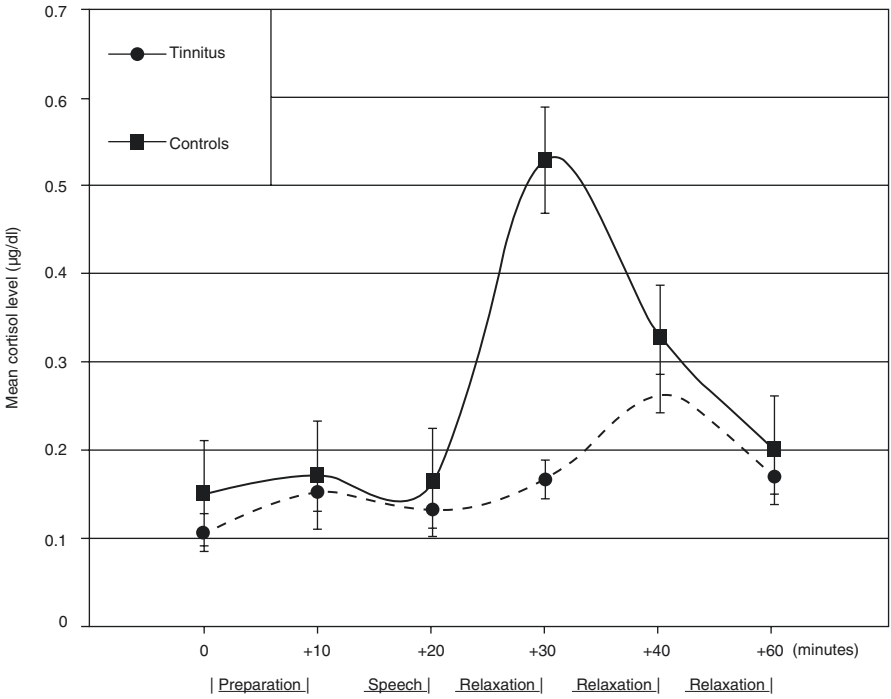

Fig. 6.1 Blunted response of tinnitus patients to experimental stress. *Reprinted with permission from* (Hebert and Lupien 2007)

chronic, inflammatory disorders (Buske-Kirschbaum et al. 2010; Buske-Kirschbaum et al. 2003) or with the disease- and treatment-related fatigue (Bower et al. 2005). Larger sample and more studies with well-defined inclusion and exclusion criteria are needed to determine if the profile of post-TSST cortisol secretion is specific for tinnitus-related distress and if it correlates with the prognosis.

In tinnitus patients, the post-TSST cortisol peak is reduced, and it occurs later than in the control subjects.

Interestingly, after a challenge with 0.5 mg of dexamethasone, tinnitus patients experienced deeper and longer-lasting suppression of cortisol production than the control subjects, suggesting increased glucocorticoid sensitivity and augmented HPA axis feedback (Simoens and Hebert 2012). Measurement of cortisol responses seems to be a promising step toward development of reliable set of tinnitus biomarkers.

6.2.2 Catecholamines: Dopamine, Epinephrine (Adrenaline), and Norepinephrine

Catecholamines are monoamines derived from tyrosine with a catechol side chain. Catecholamines comprise epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine. Adrenaline and noradrenaline are synthesized in response to sympathoadrenal medullary axis activation.

Two studies investigated the systemic concentrations and various correlations between blood/urine catecholamines and tinnitus-related distress; however, no conclusive correlations have been shown between the catecholamine concentrations and psychometric scores (Kim et al. 2014; Savastano et al. 2007). It is possible that the future classification of tinnitus subtypes, which will take under account all the comorbid conditions, may facilitate the use of catecholamines as tinnitus biomarkers.

6.3 Immune Biomarkers of Stress

To understand the biological basis of the immune biomarkers of stress, we have to turn back into the past. Until evolutionarily recent times (about 200 years ago), people's life expectancy was rather short and was on average 30 years (Finch 2012). The developments in medicine and technology occurring in the past two centuries, contributed to the enormous extension of human life expectancy by roughly two-and-a half-fold. While today, the life expectancy is restricted by neurodegenerative, cancer, and heart diseases, in the past, the main life expectancy-restricting factors were infectious diseases.

The evolutionary process positively selected individuals that upon being wounded (which was connected with emotional stress, imminent infection, and a consequent danger of serious illness and death), quickly responded with an inflammatory reaction. Also the *sickness behavior* was evolutionarily driven, ensuring that the infected individual kept away from the group to not to spread the infection further, and was vigilant regarding possible sources of infection (Miller and Raison 2016). The *sickness behavior* is also a feature of depression whereas *vigilant behavior* characterizes anxiety disorders.

Also until recent times, commensal microorganisms and parasites, such as helminths, kept the "background" systemic inflammatory reaction under control, by activating regulatory T cells, inducing production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) or transforming growth factor beta (TGF-beta) (Finlay et al. 2014). What it meant for people was that they would have low "spontaneous" or "background" inflammation.

In the past, being wounded belonged to the major and most common emotional stressors. Stress not only affects the neuroendocrine system but also immediately activates the white blood cells to produce proinflammatory interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF alpha). In addition, stress activates special proteases (caspase-1) to cleave the inactive form of already produced proinflammatory

interleukin-1 beta (IL-1 beta) into its active form. As a result, when a person is wounded, strong inflammatory reaction supported by emotional stress is mounted in an attempt to eliminate the dangerous pathogen.

Our contemporary, highly hygienic living condition, prevent the modern people from the contact with commensal organisms. As a result, the inflammatory background, for which our ancestors were positively selected, can no longer be mitigated. This is believed to be the cause for ever increasing incidence of allergies, autoimmune reactions, and other proinflammatory conditions.

The *pathogen-host defense hypothesis of depression* is a novel notion in the field that explains the origin of depressive symptoms as well as the even increasing incidence of depression in the industrialized world. According to this hypothesis, individuals with the increased inflammatory background (i.e., producing proinflammatory cytokines or C-reactive protein) will react to it with the *sickness behavior* that includes social withdrawal (as in depression) and increased vigilance (as in anxiety) (Fig. 6.2). Of note—depressive and anxiety symptoms are very often diagnosed in patients with tinnitus—see Chap. 3 (Zirke et al. 2013a, b).

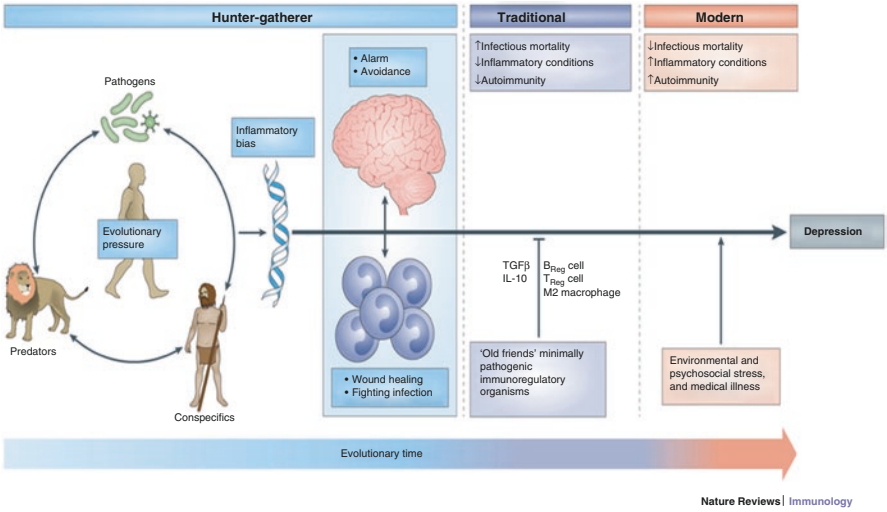

Fig. 6.2 The evolutionary theory of inflammation and depression. Early evolutionary pressures derived from human interactions with pathogens, predators and human conspecifics (such as rivals) resulted in an inflammatory bias that included an integrated suite of immunological and behavioral responses that conserved energy for fighting infection and healing wounds, while maintaining vigilance against attack. This inflammatory bias is believed to have been held in check during much of human evolution by exposure to minimally pathogenic, tolerogenic organisms in traditional (that is, rural) environments that engendered immunological responses characterized by the production of the anti-inflammatory cytokines. In modern times, sanitized urban environments of more developed societies are rife with psychological challenges but generally lacking in the types of infectious challenges that were primary sources of morbidity and mortality across most of human evolution. In the absence of traditional immunological checks and balances, the psychological challenges of the modern world instigate ancestral immunological and behavioral repertoires that represent a decided liability, such as high rates of various inflammation-related disorders including depression. *Reprinted with permission from* (Miller and Raison 2016)

Pathogen-host Defense Hypothesis of Depression
Our ancestors were evolutionarily selected by exposure to pathogens because of proinflammatory immune response and specific behavior induced by this response (social isolation and vigilance).

Interleukin-1 beta (IL-1 beta), Interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF alpha) belong to a group of cytokines commonly associated with the process of inflammation (so-called proinflammatory cytokines).

6.3.1 Cytokines

Cytokines are peptides used for communication between the cells and comprise interferons, lymphokines (e.g., interleukins), chemokines, and tumor necrosis factors. Cytokines are released from the producing cells and act on cells with an appropriate receptor by inducing signal transduction, which is cytokine-, receptor- and cell type-specific. First reports about cytokines date form the late fifties in the last century and regard interferons produced in response to viral infection. In the eighties, the cytokine discovery picked up enormously whereas presently, the field comprises several hundreds of molecules (for more detail, see Horst Ibelgaufts' cytokine encyclopedia "COPE" under http://www.cells-talk.com).

For decades, cytokines were considered to be strictly connected with the immune system; however, presently we know that also the nonimmune cells are also capable to synthesize, release, and react to cytokines. A very important issue regarding cytokines in the field of biomarkers is to realize that *the local production, and release of cytokines by specific tissues, e.g., the brain or the lymph node* (local changes), *must not necessarily change the levels of cytokines in blood* (systemic changes). Short-term and long-term stresses act differently on the immune system and consequently on the release of cytokines.

Earlier, cytokines were considered to be strictly connected with the immune system; however, by now we know that nonimmune cells are also capable to synthesize, release and react to cytokines.

6.3.1.1 Interleukin-1 Beta

Interleukin-1 beta (IL-1 beta) is a small peptide (17.5 kDa) produced in an inactive form and activated by cleavage with caspase 1. IL-1 beta was cloned and characterized in 1984 by the group of Charles A. Dinarello (Dinarello 1994). Dinarello was scientifically captivated by the pyrogenic (inducing fever) properties of interleukin-1 beta—a clear link between the immune and neuronal systems (Dinarello 1999). IL-1 beta has another important property—it is a major mediator of fatigue in

various unrelated diseases (Roerink et al. 2017). In addition, increased concentrations of IL-1 beta in blood in individuals who were exposed to acute experimental stress were observed. The increases could be seen already 30 min after the stressor application (Brydon et al. 2005). The source of stress-induced blood IL-1 beta was identified as peripheral blood mononuclear cells.

Interestingly, in the subjects with post-traumatic stress disorder (PTSD), spontaneous production of IL-1 beta by peripheral blood mononuclear cells was greater than in control subjects (Gola et al. 2013). Moreover, patients with major depression have lower concentrations of IL-1 beta in blood than the non-depressed subjects (Hernandez et al. 2013). The influence of IL-1 beta on the anxiety behavior was evidenced by using animal knock-out or knock-down models, which demonstrated that reducing the ability of cells to react to IL-1 beta, correlates with abolishment of anxiety behavior (Murray et al. 2013; Wohleb et al. 2014).

In 2014, our group used several psychometric instruments to assess the tinnitus-related distress in 30 patients with chronic tinnitus and correlated the scores with the concentrations of selected cytokines in serum (Szczepek et al. 2014). We found significant positive correlation between the scores of visual analogue scale testing the awareness of tinnitus and IL-1 beta concentration (see Fig. 6.3).

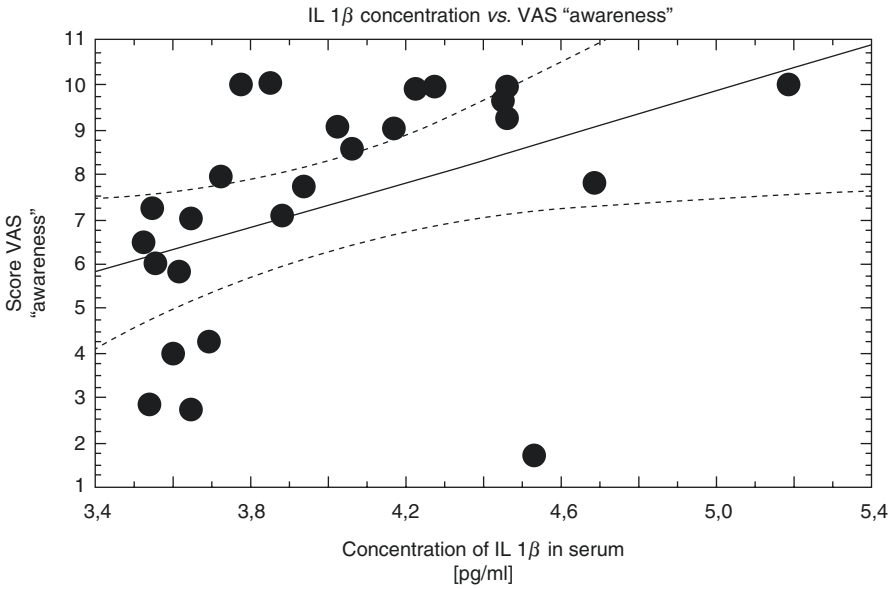

Fig. 6.3 Correlation between the concentration of circulating IL-1 beta and psychometric scores. Shown are the *regression lines* indicating significant correlations between the concentration of circulating IL-1 beta and the scores representing three VAS scale "awareness" of the patients with chronic tinnitus. *Dotted lines* represent 95% confidence interval (CI). Shown are the *regression lines* indicating significant correlations between the concentration of circulating tumor necrosis factor α and the scores of VAS "loudness," total PSQ, and PSQ subscales "tension" and "joy." *Dotted lines* represent 95% confidence interval (CI). *Reprinted with permission from* (Szczepek et al. 2014)

Unfortunately, we did not measure anxiety symptoms in the patients studied. This was so far the only attempt to use this cytokine as a possible biomarker. The time and more experiments will demonstrate the usefulness of determining the blood concentration of IL-1 beta for tinnitus diagnostics and monitoring.

We found significant positive correlation between the scores of visual analogue scale testing the awareness of tinnitus and IL-1 beta concentration ($r = 0.466$, $p < 0.05$).

6.3.1.2 Interleukin-6

Interleukin-6 (IL-6) is a 24 kDa peptide cloned in 1986 (Hirano 2014) that can be produced by ample types of cells and that induces various responses in numerous cells and tissues. Acting via IL-6 receptor complex and JAK-STAT signal transduction pathway as well as other routes (Hirano 1998) IL-6 mediates several effects such as antibody production by B cells, T- and B-cell activation, growth and differentiation of diverse cells, growth of some tumors and also fever by acting on specific neurons in the brain. In the recent years, the key role of IL-6 in many noninfectious but inflammatory diseases as well as in cancer started to be recognized (Ho et al. 2015). In addition, the anti-IL-6 or anti-IL-6 receptor strategies have been developed. At the same time, presence and the concentration of IL-6 in blood began to be used as a biomarker for many illnesses such as multiple myeloma (Kyle 1995), colorectal carcinoma (Xu et al. 2016), rheumatoid arthritis (da Mota et al. 2009), and many other.

Important for the tinnitus research was the discovery of positive correlation between the presence of IL-6 in blood and the psychosocial stress. For instance, psychologically traumatized women were found to have an increased blood concentration of IL-6. The concentration went down after successful stress reduction therapy (Gallegos et al. 2015). Moreover, both types of stress, acute and chronic, were associated with overproduction of IL-6 in blood.

The normal baseline production of IL-6 undergoes circadian regulation (*see* Chap. 4 *for circadian regulation*) (Vgontzas et al. 2005). Physiologically increased levels of IL-6 at the end of the day mediate sleepiness, whereas the modulation of the systemic IL-6 concentration induces disturbances in sleep pattern. Reversely, disturbances in sleep pattern are accompanied by abnormal diurnal secretion of IL-6. Interestingly, the IL-6-dependent sleepiness can be modulated by cortisol, producing deep sleep when cortisol level is low (healthy pattern) or shallow sleep and the feeling of tiredness (*sickness behavior*) when cortisol is elevated (Vgontzas et al. 2005).

The fact, that the elevated concentrations of circulating IL-6 were found in persons with depression, made the IL-6 *the* recent target molecule in major depression clinical research (Hodes et al. 2016). The already existing biologics developed against IL-6 (e.g., siltuximab) or against IL-6 receptor (e.g., tocilizumab) are being

presently used in the clinical trials with patients suffering with major depression (Hodes et al. 2016). These biologics have to our best knowledge not yet been tried in patients with tinnitus.

What do we know about IL-6 in patients with tinnitus? In an early prospective study with a "before-after" design, we determined the concentration of IL-6 at three time points in serum of tinnitus patients who decided to do relaxation training, another group that was not doing the relaxation and in subjects without tinnitus (Weber et al. 2002). We found that the relaxation exercises corresponded with an improvement of stress management and with lowering the concentrations of circulating IL-6. Our next attempt to use the IL-6 as a biomarker was a recent pilot study, where we used validated psychometric instruments to assess tinnitus-related distress (Szczepek et al. 2014). Unfortunately, the detected levels of IL-6 were below the detectability thresholds of ELISA and, therefore, could not be used for further analyses. More studies with larger sample and more sensitive detection methods are necessary to confirm or reject the usefulness of IL-6 as a biomarker in tinnitus.

Performing relaxation exercises corresponded with an improvement of stress management and with lowering the concentrations of circulating IL-6 in the blood of tinnitus patients.

6.3.1.3 Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNF alpha) is another small, 17 kDa cytokine that can be produced and secreted by many cell types. It was cloned and described by a group of Bharat B. Aggarwal in 1984 (Aggarwal et al. 1984). Similarly to IL-1 beta and IL-6, TNF alpha is a pyrogenic cytokine, and it also induces the *sickness behavior*. Three types of TNF alpha receptor have been characterized to date—they all bind TNF alpha but mediate various functions (see Fig. 6.4), from the cell survival and tissue regeneration to the cell death (Kalliolias and Ivashkiv 2016). Experimental animal models enabled detailed understanding of molecular mechanisms linking the presence of TNF alpha with depressive symptoms (Fig. 6.5) with a key finding being that chronic mild stress induces production of proinflammatory cytokines such as TNF alpha, and this in turn contributes to the development of depression (Kubera et al. 2011).

Intriguing case report about possible causative contribution of TNF alpha to tinnitus was published recently (Stein et al. 2014). In this report, a patient was diagnosed with Melkersson-Rosenthal syndrome (MRS), accompanying hearing loss and intermittent tinnitus. Upon off-label treatment with TNF alpha blocker (adalimumab), not only the remission of the main MRS symptoms was observed (orofacial edema, facial nerve palsy and furrowed tongue) but also total remission of hearing loss and tinnitus occurred. This case report provides evidence for the following subjects:

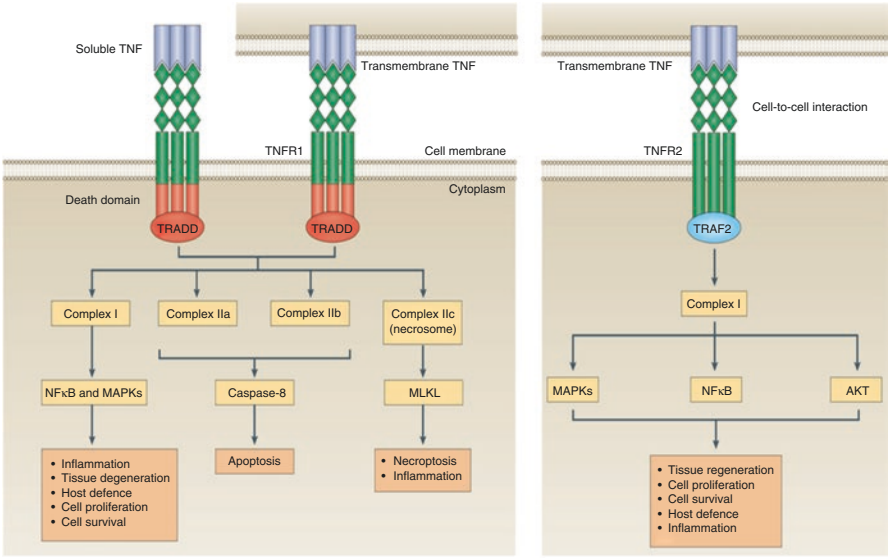

Fig. 6.4 (**a**) TNF receptor 1 (TNFR1) signalling is activated by both soluble and transmembrane TNF. TNFR1 bears a death domain that recruits the adaptor protein TNFR1-associated death domain protein (TRADD). Ligation of TNFR1 by soluble TNF or transmembrane TNF leads initially to the assembly of complex I, which activates nuclear factor κB (NFκB) and mitogen-activated protein kinases (MAPKs). TNFR1–complex I signalling induces inflammation, tissue degeneration, cell survival and proliferation, and orchestrates the immune defense against pathogens. Alternative signalling modalities, associated with programmed cell death, can also be activated downstream of TNFR1. The formation of the complexes IIa and IIb (also known as ripoptosome) results in apoptosis, whereas complex IIc (necrosome) induces necroptosis and inflammation. (**b**) TNFR2 is proposed to be fully activated primarily by transmembrane TNF, in the context of cell-to-cell interactions. TNFR2 recruits TNFR-associated factor 2 (TRAF2) via its TRAF domain, triggering the formation of complex I and the downstream activation of NFκB, MAPKs, and AKT. TNFR2 mediates primarily homeostatic bioactivities including tissue regeneration, cell proliferation and cell survival. This pathway can also initiate inflammatory effects and host defense against pathogens. MLKL, mixed lineage kinase domain-like protein. *Reprinted with permission from* (Kalliolias and Ivashkiv 2016)

1. **Diversity of diseases** that have tinnitus as a symptom
2. **Intermittent tinnitus** as an underestimated form of tinnitus, during which the precept could be successfully treated
3. **Inflammatory character** of diseases associated with tinnitus

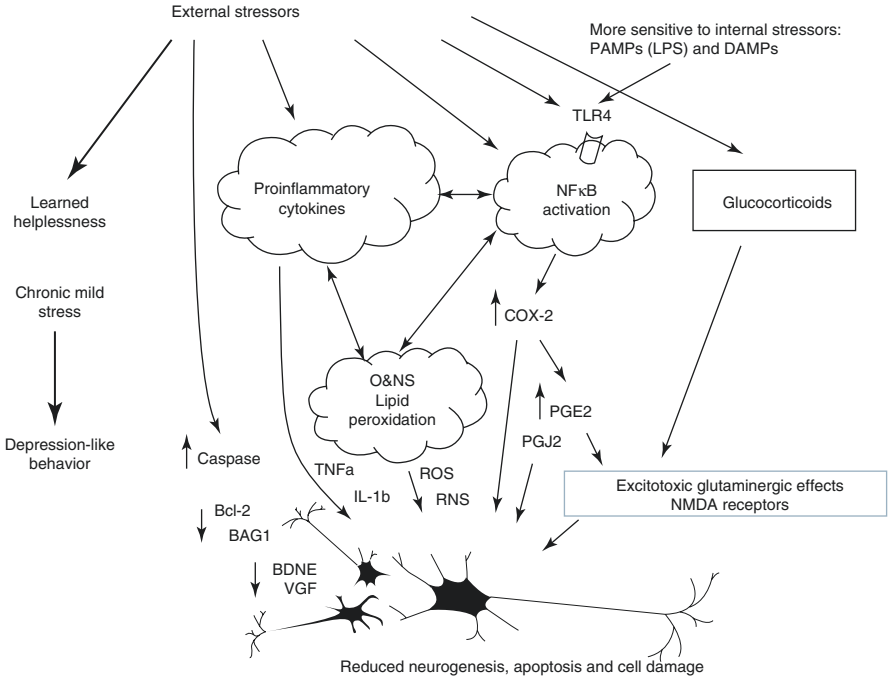

Fig. 6.5 External stress-induced depression-like behavior. External stressors in animals, such as chronic mild stress and learned helplessness, are accompanied by depressive-like behaviors. External stress-induced depression-like behavior is accompanied by peripheral and central inflammation, with increased levels of proinflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNFa) and IL-6. The external triggers and cytokines may induce nuclear factor κB (NFκB), which in turn induces the expression of proinflammatory cytokines, oxidative and nitrosative stress (O&NS) pathways, and cyclooxygenase (COX)-2. Through these pathways, external stress may cause increased amounts of reactive oxygen (ROS) and nitrogen (RNS) species, including $O2-$ and NO that results in the generation of peroxynitrite. COX-2 may generate prostaglandins (PG), such as PGE2 and PGJ2. External stressors also increase the expression of Toll-like receptors (TLR4), which increase the sensitivity to internal stressors, including pathogen associated molecular patterns (PAMPs), i.e., conserved microbial structural motifs, such as lipopolysaccharide (LPS), and damage-associated molecular patterns (DAMPs). External stressors increase glucocorticoids and glutamate release and consequently provoke activation of neuronal N-methyl-d-aspartate (NMDA) receptors. External stressors cause antineurogenic effects by downregulating neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and VGF. Finally, external stressors cause apoptosis with lowered levels of Bcl-2 and BAG1 (Bcl-2 associated athanogene 1) and increased levels of caspase-3. Cytokines, O&NS, NFκB, COX-2, prostaglandins, e.g., PGE2, excitotoxic glutaminergic effects, apoptotic pathways, and reduced neurotrophic substances contribute to the neurodegenerative processes and reduced neurogenesis which are observed in depression-like behaviors. *Reprinted with permission from* (Kubera et al. 2011)

Two of our earlier mentioned studies have scrutinized the usefulness of TNF alpha as a biomarker for tinnitus. In the first study, we demonstrated that not only tinnitus-related distress but also TNF alpha decreases in a group of tinnitus patients who performed relaxation exercises but not in those, who did not exercise (Weber et al. 2002). In the second study, using psychometric instruments, we measured the perceived stress

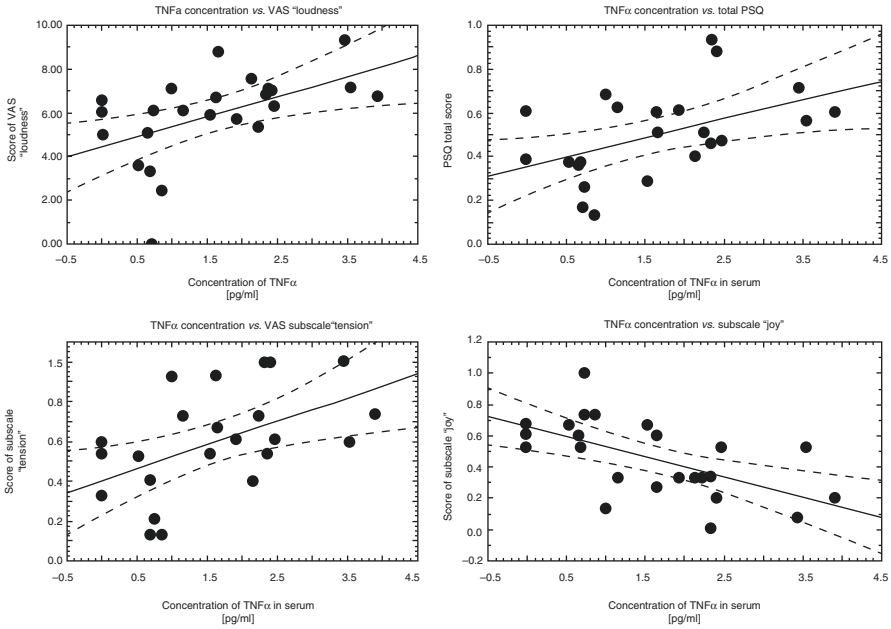

Fig. 6.6 Correlations between the concentration of circulating TNF α and psychometric scores. Shown are the *regression lines* indicating significant correlations between the concentration of circulating TNF alpha and the scores of VAS "loudness," total PSQ, and PSQ subscales "tension" and "joy." *Dotted lines* represent 95% confidence interval (CI). *Reprinted with permission from* (Szczepek et al. 2014)

and tinnitus-related distress. We found that the concentration of TNF alpha in serum obtained from tinnitus patients significantly correlates with the perceived loudness of tinnitus (as per analogue visual scale) and with the total score of perceived stress questionnaire PSQ (*for more on the PSQ questionnaire see* Chaps. 7 and 9) (Fig. 6.6).

One needs caution when designing and interpreting the results from these types of studies—the measured concentration of serum or plasma cytokines is below of what we consider "normal" inflammatory levels, consistent with lack of fever, which is only present then when there is a lot of circulating pyrogenic cytokines. The second problem is the choice of tools available for determination of cytokine concentration. There are several products on the market which can be purchased from various companies and the sensitivity and reproducibility of the tests differ between the products. We recommend using products labeled with "IVD" which stands for "in vitro diagnostic medical device." These products are rigorously controlled for their quality and licensed for human diagnostics.

6.3.2 Thrombocytes (Platelets)

Thrombocytes (or platelets) are anuclear components of blood and derivative of megakaryocytes residing in the bone marrow. Thrombocytes are indispensable for the repair of damaged blood vessels. Through the process of adhesion, activation,

and plug formation, they also initiate the process of blood coagulation and activate circulating white blood cells. Mean platelet volume (MPV) is used to determine the size of thrombocytes whereas platelet count is used to estimate their concentration. Both values are routinely included in the complete blood count (CBC).

Psychosocial or emotional stress was shown to affect the blood homeostasis and even lead to the coronary heart disease by expressing adhesion molecules (e.g., P-selectin) on the thrombocytes, which in turn activate the white blood cells. Bulk of evidence has accumulated in the last two decades to support the notion about acute and chronic stress contributing to platelet activation via HPA axis and elevated concentrations of glucocorticoids (see Chap. 2) or via impaired serotonergic function (Brydon et al. 2006).

Stressful situations contribute to the increase in numbers of thrombocytes (Baltrusch et al. 1990; Jern et al. 1989) and to the decrease of mean thrombocyte volume (Baltrusch et al. 1990; Gogcegoz Gul et al. 2014). Interestingly, few recent clinical studies determined increased numbers of thrombocytes and decreased mean platelet volume (MPV) in the blood of tinnitus patients [Kemal et al. 2016; Sarikaya et al. 2016a, b; Yuksel and Karatas 2016]. However, the studies assessed neither the coronary disease nor the level of stress in the subjects tested. Still, methodical study of the thrombocyte/platelet count and MPV in patients with tinnitus may prove in the near future to be cost-effective and a meaningful biomarker in the diagnosis and monitoring of tinnitus-related distress.

6.4 Neurotransmitters and Neurotrophins as Biomarkers of Stress

6.4.1 Serotonin (5-Hydroxytryptamine (5-HT))

Serotonin is a monoamine that serves as neurotransmitter. Serotonin is produced from a precursor, L-tryptophan and metabolized into 5-hydroxyindoleacetic acid (5-HIAA). Elevated plasma serotonin levels were found to correlate with stress and depressive symptoms (Tyano et al. 2006). Interestingly, in a cohort of 344 tinnitus patients, there were statistically significant more individuals who had elevated blood 5-HIAA serotonin metabolite than the control subjects; however, the only correlation found was between 5-HIAA and tinnitus duration (Kim et al. 2014). Another study connecting tinnitus with serotonin was a blood-based genetic analysis of the serotonin transporter gene polymorphism (promoter region) and various characteristics of tinnitus percept and tinnitus-related distress (Deniz et al. 2010). The authors found that those of tinnitus patients who have *ll*–type of allele encoding serotonin transporter gene promoter region (5-HTTLPR) are more sensitive to tinnitus-related distress (severity, frequency and duration, discomfort level, attention deficit, and sleep disorder) than those patients who had *sl* or *ss* allele. The *ll* allele correlates functionally with a quicker serotonin reuptake (Greenberg et al. 1999). Larger studies should address feasibility of adding 5-HTTLPR polymorphism into the tinnitus-related distress biomarkers.

6.4.2 Neurotrophins: Brain-Derived Neurotrophic Factor (BDNF)

Neurotrophins comprise a family of about fifty proteins that contribute to growth, differentiation, and survival of neurons. One of the early discovered neurotrophins is the brain-derived neurotrophic factor (BDNF). BDNF is a small (13.6 kDa or 27.2 kDa dimer) peptide produced not only in the brain (as the name suggests) but also in the skeletal muscle (Matthews et al. 2009), bone marrow megakaryocytes (Chacon-Fernandez et al. 2016), and peripheral blood mononuclear cells (Cattaneo et al. 2016). BDNF binds and signals through tropomyosin receptor kinase B (TrkB). It actions on neurons include neuroplasticity and neuronal regeneration. Substantial evidence links the alterations in BDNF expression with a variety of psychological conditions, including anxiety disorders and depressive symptoms. In addition, modulation of BDNF levels was seen in Alzheimer, Huntington, and Parkinson diseases (Zuccato and Cattaneo 2009), making BDNF almost a universal biomarker for neurodegenerative disorders.

Impact of emotional or psychosocial stress on the expression of BDNF in blood has been studied for several years (Cattaneo et al. 2016). According to the latest model, the changes in BDNF level induced by emotional or psychosocial stress vary depending on the quality and duration of stressor (Schmitt et al. 2016) where acute stress induces BDNF levels whereas prolonged, chronic stress decreases the BDNF levels (Fig. 6.7).

To date, three clinical studies with tinnitus patients have been performed, in which BDNF was attempted to be used as a biomarker. In the first study, Goto and colleagues included 43 patients and 30 control subjects (Goto et al. 2012). To determine the tinnitus-related distress, Tinnitus Handicap Inventory (THI) was used (see Chaps. 7–9); to determine the presence and degree of depressive symptoms, Hospital Anxiety and Depression Scale (HADS) was used; and to determine the concentrations of BDNF in blood, lithium heparin plasma was prepared from the whole blood, and a BDNF-specific ELISA was used. The authors found *significant differences in plasma BDNF* when the patients were split into two groups, depending on depressive HADS scores (high and low), suggesting that individuals with more depressive symptoms had less circulating BDNF and vice versa. Similarly, patients

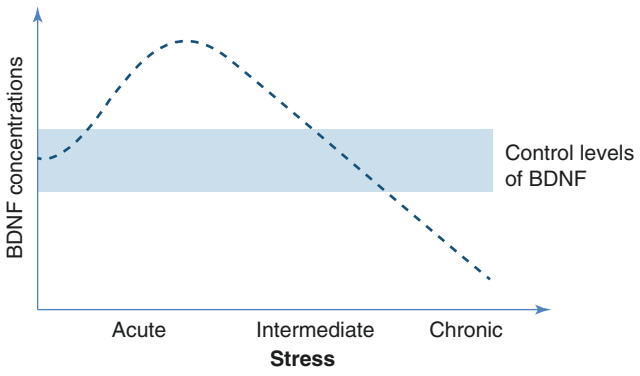

Fig. 6.7 Influence of stress on BDNF levels

with a mild tinnitus-related distress (as per THI) had higher levels of BDNF than the patients with severe tinnitus-related distress.

The second study, in which BDNF was measured in relation to tinnitus-induced distress, was our own work, published in 2014 (Szczepek et al. 2014). However, we have not observed correlation between any of the psychometric parameter measured (tinnitus-related distress, perceived stress, and depressive symptoms) and the BDNF concentration determined with specific ELISA. The explanation for this is that we used serum and not plasma, as it was the only blood product which we had available. During the coagulation process, platelets—the major source of BDNF in blood—release the BDNF and as a result, extinguish possible minor differences that could have existed in the BDNF concentration in full blood prior to coagulation.

In the third, recently published study, 82 patients were screened with the THI and visual analogue scale prior to and following the tinnitus retraining therapy (TRT) (for therapeutic protocols, see Chap. 8) (Xiong et al. 2016). Blood was collected in the EDTA tubes prior to TRT and 3 months after the therapy onset. The concentration of BDNF was assessed with specific ELISA. The authors found that on average, the tinnitus patients had higher levels of circulating BDNF than the control subjects. The second important finding was that the positive TRT effects could not only be seen with the use of THI scores or VAS scales (awareness, annoyance, loudness), but they were also reflected by significant changes in the concentration of circulating BDNF. However, all these changes were seen only in the group of patients with severe (decompensated) form of tinnitus. Depressive symptoms were not assessed.

Taken together, BDNF seems to be a promising biomarker that could be used in the longitudinal studies or for the monitoring of patients' progress in combination with measurement of psychometric parameters, such as tinnitus-related distress and depressive symptoms. We propose a hypothetical model, in which the level of tinnitus-related distress would be reflected by the concentration of circulating BDNF, where the patients with mild tinnitus-related distress (compensated) would have high concentrations of BDNF and patients with severe tinnitus-related distress (decompensated) would have lower BDNF concentrations (Fig. 6.8). Again, more studies would be needed to confirm this hypothesis.

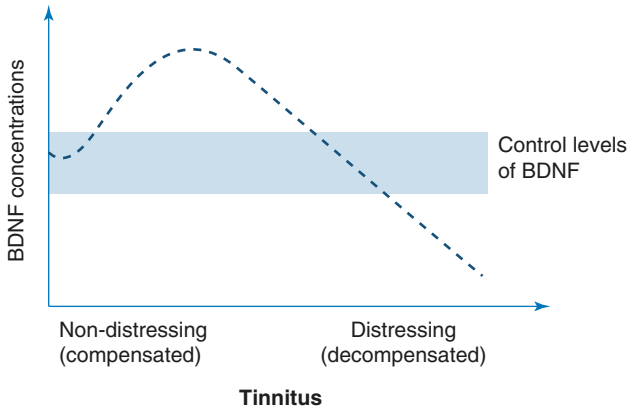

Fig. 6.8 Hypothetical association of tinnitus-induced distress severity with the BDNF levels

6.5 Other Biomarkers

6.5.1 Vitamin B12

Vitamin B12 (also known as cobalamin) is an essential coenzyme of various metabolic reactions and a key factor for neuronal health and regeneration. Vitamin B12 cannot be synthesized by people and is an exclusive product of bacteria and archaea. Lack of proper nutritional uptake of B12 may lead to deficits that are reflected by fatigue, depressive symptoms, and cognitive deficits and in the end may lead to irreversible neuronal degeneration.

A very large epidemiological study (sample size 9670 participants) determined associations between low intake of vitamin B12 and depressive symptoms (Sanchez-Villegas et al. 2009). Interestingly, vitamin B12 deficiency was determined in almost a 50% of relatively young (mean age 39 years) military personnel with noise-induced hearing loss *and* tinnitus and only in 27% of personnel with noise-induced hearing loss *without* tinnitus (Attias et al. 2002; Shemesh et al. 1993). Some attempts to supplement B12 deficiency in tinnitus patients produced results, which were not convincing (Berkiten et al. 2013), but in other studies, the decrease in tinnitus-related distress was statistically significant (Singh et al. 2016). Nevertheless, vitamin B12 seems to be a biomarker worth looking at and should be acknowledged on the potential blood biomarkers for tinnitus.

6.5.2 Prestin

Prestin is a transmembrane protein, expressed specifically by the outer auditory hair cells and responsible for their ability to move and therefore, to amplify the acoustic signal in the cochlea (Dallos 2008). During the noise exposure, some auditory hair cells are getting damaged and their proteins were proposed to get spilled to circulation. Prestin was suggested by Parham as a hypothetical serum biomarker indicating damage to the outer hair cells and predicting hearing loss as well as consequent tinnitus (Parham 2015). This hypothesis was supported by evidence obtained in animal model of noise-induced hearing loss (Parham and Dyhrfjeld-Johnsen 2016). It remains to be established how long does prestin circulate in blood following the acoustic injury and to what extend its presence would correlate with the presence of tinnitus percept and/or tinnitus-related distress.

6.6 Biomarkers for the Diagnosis and Monitoring of Tinnitus

Although no particular biomarkers have yet been approved as monitoring or diagnostic tool for tinnitus, the need to identify reliable blood biomarkers is growing. In a recent review, the outcome measures of 228 clinical trials were evaluated (Hall et al. 2016). Of all 228 studies, two used blood for a primary outcome measure and three for a secondary outcome measure; one study used saliva two studies used

urine. The collection of bodily fluids was performed for either safety reasons or to determine the levels of used medication.

Despite rather sparse reports about tinnitus-related distress blood biomarkers, the concept of using them is very appealing. Measuring concentrations of substances in blood is a *reliable objective* way of monitoring in many diseases. However, tinnitus is *not a disease* but a *symptom* accompanying various diseases. Nevertheless, there *are* symptoms, which can be very well measured objectively despite the disease they are connected with, for instance, fever or blood pressure, but these symptoms are also objective.

Tinnitus percept and the tinnitus-related distress are subjective and the tinnitus clinical research field has to deal with the same problems such as these; the pain research has to struggle with. In fact, pain researchers are step ahead of tinnitus and have determined blood biomarkers, to which belong the micro-RNA (Ramanathan and Ajit 2016) and proinflammatory cytokines family members (DeVon et al. 2014). Although the tools have been identified, the pain research found out that there are many types of pain and that each of them correlates with a specific set of biomarkers (Marchi et al. 2009).

Many clinical and basic scientists recently joined their forces in attempt to classify and characterize various types of tinnitus (Bruggemann et al. 2016; Chen et al. 2016; Figueiredo et al. 2016; Lopez-Escamez et al. 2016; Schlee et al. 2016). This classification is expected to yield a system, which should help to organize the tinnitus array based on selected domains. One can speculate that within defined tinnitus subgroups, a set of specific biomarkers can be found. It will not be easy to precisely define such a set, as there are several factors possibly affecting the biomarkers, such as age, gender, medical history, comorbid psychological and physical conditions, and many others (Fig. 6.9). Still, narrowing the tinnitus subgroups may help to develop tinnitus-subtype-specific biomarkers.

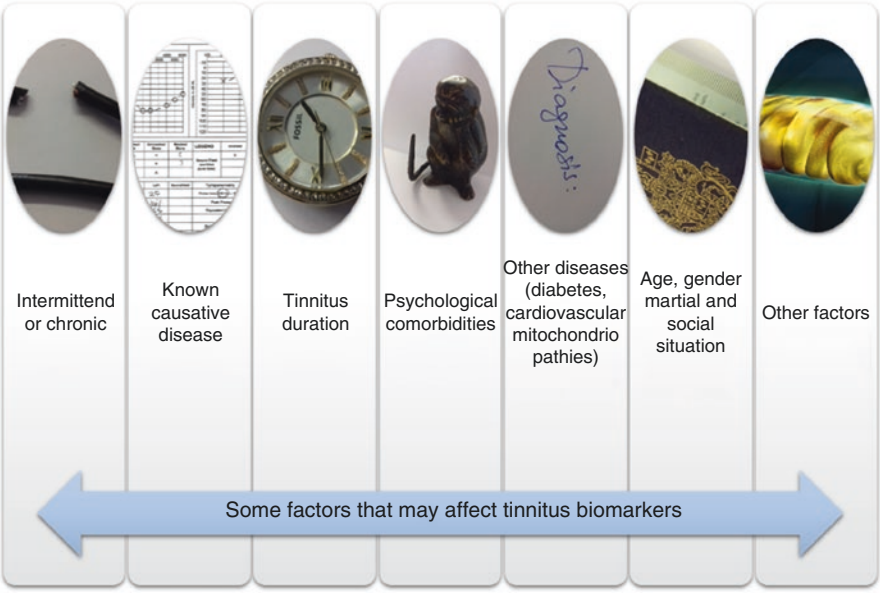

Fig. 6.9 Presence and levels of tinnitus biomarkers may be affected by variety of factors

The Holy Grail is to create *tinnitus index* comprising auditory, psychometric, and objective biological parameters. This goal will require multicenter studies, involvement of specialists from various disciplines, lots of subsidy, and of course willingness of tinnitus patients across the world to participate. We do believe that *tinnitus index* would provide an international platform for the diagnosis and monitoring of tinnitus patients and that the discovery of blood biomarkers is essential for this process.

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Psychometric Assessment of Tinnitus Patients Within Clinical Practice Settings

7

Petra Brüggemann and Matthias Rose

Abbreviations

BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CBT	Cognitive behavior therapy
DSM	Diagnostic and Statistical Manual for Mental Disorders
HADS	Hospital Anxiety and Depression Scale
PROM	Patient-reported outcome measure
PSQ	Perceived Stress Questionnaire
PSS	Perceived Stress Scale
STAI	State-Trait Anxiety Inventory
TQ	Tinnitus Questionnaire (German version-TF)
TRQ	Tinnitus Reaction Questionnaire
TRT	Tinnitus retraining therapy
VAS	Visual analog scale

7.1 Conceptual Framework

Interest in collecting patient-reported outcomes (PROs), such as health-related quality of life (HRQOL), health status reports, symptom assessment, patient-reported function or disability, patient satisfaction, and others, in clinical practice is on the rise. They are no longer just relevant endpoints of clinical trials and clinical

P. Brüggemann
Tinnitus Center, Charité University Hospital, Berlin, Germany

M. Rose (✉)
Department of Psychosomatic Medicine, Charité University Hospital, Berlin, Germany
e-mail: Matthias.Rose@charite.de

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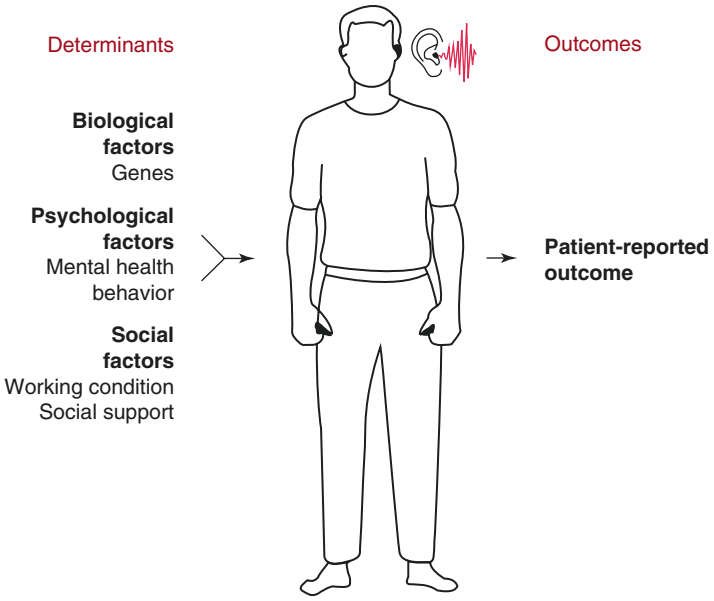

Fig. 7.1 Distinction of patient-reported health status information into prediction and outcome variables

research, but are increasing being collected in routine clinical practice (Kahneman et al. 2004). The potential uses of PROs in clinical practice are multifold: they can be used to screen for specific health disorders or to monitor individual patients, to evaluate relevant patient-reported outcomes in groups of patients, to assess quality of service, impact of an intervention, as part of quality assurance processes, and to assess needs of patients. To systematically include health status information derived directly from the patient, it needs to be identified which constructs are of interest and their potential use to improve the treatment or the prediction of the further course of the disease.

In general, patient-reported health information can be differentiated into "determinants/predictors" and "outcome" variables. Although health "outcomes" may become "predictive" for the further course of the disease, and "determinants" may become treatment targets as well, within each measurement situation, the intended purpose of the measure should be clear for an effective interpretation of patient-reported health status information within clinical practice settings (Fig. 7.1).

Within each group there are several variables of potential interest which can be further differentiated. Figure 7.2 shows an adaptation for tinnitus patients of a well-established theoretical framework for the assessment of patient-reported outcomes in chronic conditions published by Wilson and Cleary (1995).

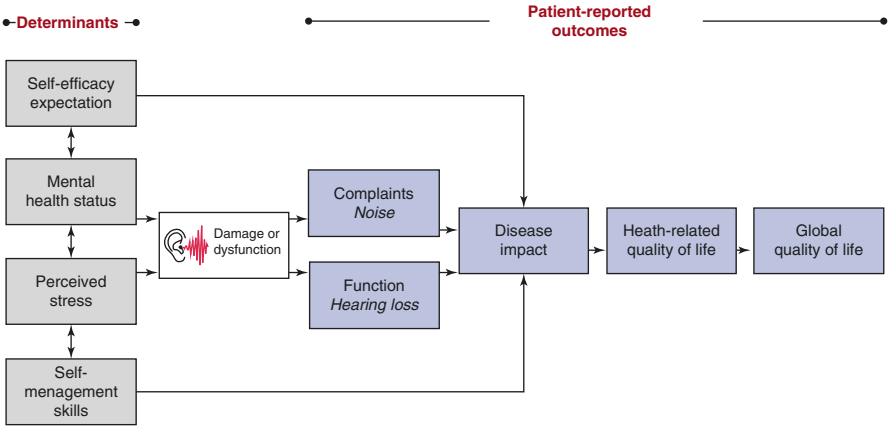

Fig. 7.2 Determinants for the development and the perception of the disease with common outcome variables and their relation (adapted from Wilson and Cleary 1995)

There is a large amount of literature investigating potential determinants for the development of tinnitus and the perception of tinnitus symptoms. Within a clinical practice setting, we believe it is important to limit the assessment to a reasonable number of constructs, which may either be important to monitor the treatment success or to assess potential predictors of the treatment success which may also be treatment targets, like the assessment of perceived stress, self-management skills, or the mental health status of the patient.

It seems important to distinguish between the assessments of tinnitus symptoms, e.g., noise sensation and hearing lost, and the impact of both symptoms on the patient, his health-related quality of life, or even patient's global quality of life perception.

On the outcome side of the measurement model, it seems important to distinguish between the assessments of tinnitus symptoms, e.g., noise sensation and hearing lost, and the impact of both symptoms on the patient, his health-related quality of life, or even his global quality of life perception. Whereas the assessment of the *symptoms* should be descriptive, the assessment of the *disease impact* on the patient's life inherently includes the appraisal and coping processes of the patients. Both are important treatment targets in particular in situations when the primary symptoms cannot be reduced. Although almost 10–15% of the population suffer from tinnitus (Henry et al. 2005), just 1% report a serious impact on their quality of life (Axelsson and Ringdahl 1989) which demonstrates the relevance to distinguish conceptually different treatment outcomes in clinical settings.

7.2 Overview of Commonly Used Assessments

7.2.1 Patient-Reported Outcomes

There are several disease-specific outcome measurement tools, which are frequently used for scientific research questions. However, measurement properties of psychometric assessments in clinical practice settings need much higher standards. Whereas in clinical research, larger sample sizes can account for measurement error, this is not possible in clinical practice with a sample size of $n = 1$. In addition, instruments need to provide a suitable, real-time report with reference values to enable clinical decision-making. As it will be further discussed below, an ideal situation would be to have different tools for different purposes but still measuring the same construct on the same scale, to make scores comparable between different settings. By today, this goal has not yet been achieved. Thus, at this time we need to choose between different tools to apply the most feasible for clinical practice settings.

7.2.1.1 Symptoms

There are two established tools measuring primarily *the tinnitus severity*: Tinnitus Severity Index and Tinnitus Severity Questionnaire. Both instruments are discussed in Chap. 8.

7.2.1.2 Disease Impact

Five commonly used tools provide an assessment of the impact of tinnitus, with some using composite scores, including the assessment of tinnitus symptoms. All are discussed in detail in Chap. 8.

7.2.1.3 Health-Related Quality of Life

There is a plethora of different tools assessing the generic self-reported health status. Within the scope of this chapter, we would only like to mention the Short Form 36 Health Survey (**SF-36®**), which is the mostly used tool of all psychometric instruments that has been applied in over 10,000 published studies.

The SF-36 (Bullinger 1995) is an interdisciplinary measuring instrument for recording the health-related quality of life of patients and in tinnitus studies already regarded as an important survey instrument (Muluk 2009). A total of eight dimensions are assessed and can be classified into the areas of "physical health" and "mental health" and the areas "physical function," "physical function," "physical pain," "general health awareness," "vitality," "social functioning," "emotional role," and "mental well-being," The evaluation is made by adding the crossed responses per subscale. A computerized program is available for the evaluation. In order to facilitate the interpretation, all scales are usually reproduced on a 50/10 scale standardized by means of representative population data. A value of 50 corresponds to the mean value of the normal population. A higher value corresponds to a better health condition. The inner consistency of the subscales is between $r = 0.57$ and $r = 0.94$.

With the SF-12, a short form is available to measure the physical and mental component score allowed. The SF-8 short form is not suitable for clinical use but rather for large epidemiological studies.

7.2.1.4 Global Quality of Life

Global quality of life is an emergent and idiosyncratic construct, i.e., it is perceived as more than a compilation of different subcomponents. Thus, the assessment of the overall quality of life is typically being measured by one single item, with a considerable measurement error. However, large discrepancies between the HRQL assessment and the global quality of life score may add in particular situations valuable information for the clinical encounter.

One of the theoretically best grounded global quality of life assessments is the Anamnestic Comparative Self-Assessment (ACSA). The ACSA is a visual analog scale (VAS), but different to similar tools, both extremes are anchored to individual reference points (best and worst time in the patient's life). We believe avoiding normative anchoring (e.g., comparing to others) is the most consequent approach to access this construct. Although being a highly abstract measurement, still the ACSA has shown to be effective with for the assessment of tinnitus patients (Kamalski et al. 2010; Mazurek et al. 2006). It has been shown that in many cases, tinnitus patients experience a considerable limitation in their quality of life. The measurement of the global quality of life is carried out by means of an open question, such as "What is your current quality of life compared to the most beautiful and the worst time in your life?". Factors such as the social desirability or rehabilitation, which result from comparative processes, are circumvented because of the individual reference in the test. The coding is numeric. Validity was performed on the basis of a pilot study with cancer patients (Bernheim 1986). The scale achieves high interrate and retest reliability (Ledure et al. 1981).

7.2.2 Determinants

There are several parameters which have shown (or are supposed) to influence the development of tinnitus symptoms or the success of tinnitus treatment. Within the scope of this chapter, only a few domains can be mentioned which are comparatively easy assessable with patient self-assessments or with standardized clinical interviews.

7.2.2.1 Comorbidities

Many studies have shown a close correlation between the subjective tinnitus exposure and psychological comorbidity (Hiller and Goebel 1999; Langguth et al. 2007; Weber et al. 2008). Affective disorders such as depression and dysthymia, somatization, anxiety, panic, and obsessive-compulsive disorder are both comorbidities and operative factors in the rehabilitation or habituation process (Andersson and Westin 2008; Stobik et al. 2005; Hesse 2008; Schaaf and Gieler 2010).

The use of self-report measures for case identification, severity assessment, and treatment monitoring of depression has been advocated by a growing number of practice guidelines for different chronic conditions. The benefit of self-report questionnaires is that they may help to identify mental comorbidities in busy practice setting without large effort for the healthcare provider. In general such screening tools are useful for mental health disorders with a higher prevalence.

There are dozens of well-validated, self-report questionnaires available for depression screening in clinical care. They differ from each other with respect to their theoretical background, or content, but—unfortunately—also with respect to their screening results (Thombs et al. 2008; Cameron et al. 2008; Kendrick et al. 2009). Whereas some instruments favor measurement precision, or range, others focus on respondent burden (Kroenke 2001; Kroenke et al. 2003). For example, the updated National Clinical Practice guideline (2009) of the National Institute for Health and Clinical Excellence (NICE) recommends the use of two questions about depressed mood and anhedonia in the past month for case finding of depression in primary care patients and patients with physical illnesses (National Collaborating Centre for Mental Health 2010a, b; Whooley et al. 1997; Mitchell and Coyne 2007).

One instrument with the most favorable screening properties is the PHQ-9. It has been developed to capture the nine key aspects of depressive disorders as defined in the DSM-V or ICD-10 classification system with one item each. The PHQ-9 self-rating has recently also been recommended for depression measurement by the International Consortium for Health Outcomes Measurement (www.ichom.org).

Another commonly used tool is the Center of Epidemiological Studies Depression Scale (CES-D, in Germany ADS). Unfortunately, several different versions of this scale are being used. However, all of them show favorable psychometric characteristics. Different to the PHQ-9, the CES-D was constructed to measure a more purely defined depression construct. Thus, items assessing physiological symptoms of depression, e.g., appetite lost, which are included in the PHQ-9, are missing. The long version of ADS (Hautzinger and Bailer 1993; Fuhr et al. 2016) contains 20 items. The total value of all responses can vary between 0 and 60 points. It serves as a characteristic value of the depressive symptoms. Increased ADS score (>23 points) indicates a depressive disorder. The response is based on a four-step response scale (Fig. 7.2). ADS has already been used for the treatment evaluation of chronic tinnitus in order to determine the presence of depressive symptoms (Seydel et al. 2010). The ADS is a valid and reliable measuring instrument, whose long form has an internal consistency of $r = 0.89$. Longer instruments which also have been used frequently, like the BDI (Titov et al. 2011), did not show to our knowledge a clear added benefit for use with tinnitus patients over the instruments just being mentioned.

The state of the art for the assessment of present mental health conditions are structured diagnostic interviews, like the Composite International Diagnostic Interview (CIDI) (Wittchen 1994). Both require an trained interviewer, and thus, only in rare cases, clinical practice setting will have the resources available to use standardized diagnostic interviews for all their patients. However, they are very

useful tools to confirm a screening result from patient self-reported assessment, like the ones mentioned above. We have used the CIDI and identified depressive disorders in 37%, anxiety disorders in 32%, and somatoform disorders in 27% of our tinnitus patients (Zirke et al. 2013).

Patients with severe (decompensated) tinnitus-induced distress had significantly more affective and anxiety disorders than patients with compensated tinnitus.

7.2.2.2 Perceived Stress

One of the most important self-assessments, next to assessment of the tinnitus symptoms themselves, is the assessment of the perceived stress. There are several instruments, which have shown to be effective in patients with tinnitus. The most commonly used instruments are presented and discussed in Chap. 9.

Although theoretically "stress" has to be seen as a determinant for the development or perception of tinnitus symptoms, clearly, it is also one of the treatment targets. Thus, monitoring of perceived stress scores also helps to determine the efficiency of our treatment attempts in clinical practice. Figure 7.3 shows that within a sample of 192 patients receiving a structured, 7-day inpatient treatment, stress levels and the depressive symptoms decrease in parallel to tinnitus-induced distress.

7.2.2.3 Personalities

There are number of personality traits which interfere with the mental health status of the patient, as well as with their ability to cope with the occurrence or persistence of tinnitus. Among them, we find that the assessment of the self-efficacy expectation and optimism of the patients may add important information to other constructs that were mentioned before. However, if a respondent burden is a limiting factor, those additional assessments may be omitted.

One simple tool to assess the self-efficacy expectation and possibilities of coping is the SWOP. The SWOP measures self-efficacy, optimism, and pessimism as independent scales and represents a further development of the SWO (Scholler et al. 1999). It comprises a total of nine items, of which five items record the "self-efficacy" of a person and each two items "optimism" and "pessimism." Finally, the evaluation is carried out by means of the formation of mean values for the individual scales. Self-efficacy and optimism are meaningful parameters for the evaluation of therapy. In various clinical studies, the self-efficacy expectation with regard to health behavior and pain management has been demonstrated as a significant influencing factor (Buckelew et al. 1994; Litt et al. 1993). An investigation by Sirois et al. (2006) showed that a tinnitus subset and apoptosis could be better achieved with a rather severe tinnitus stress if the patient had a higher self-efficacy expectation. The test quality criteria prove to be satisfactory.

A related construct which we find informative is the assessment of the sense of coherence as one potential stress buffer.

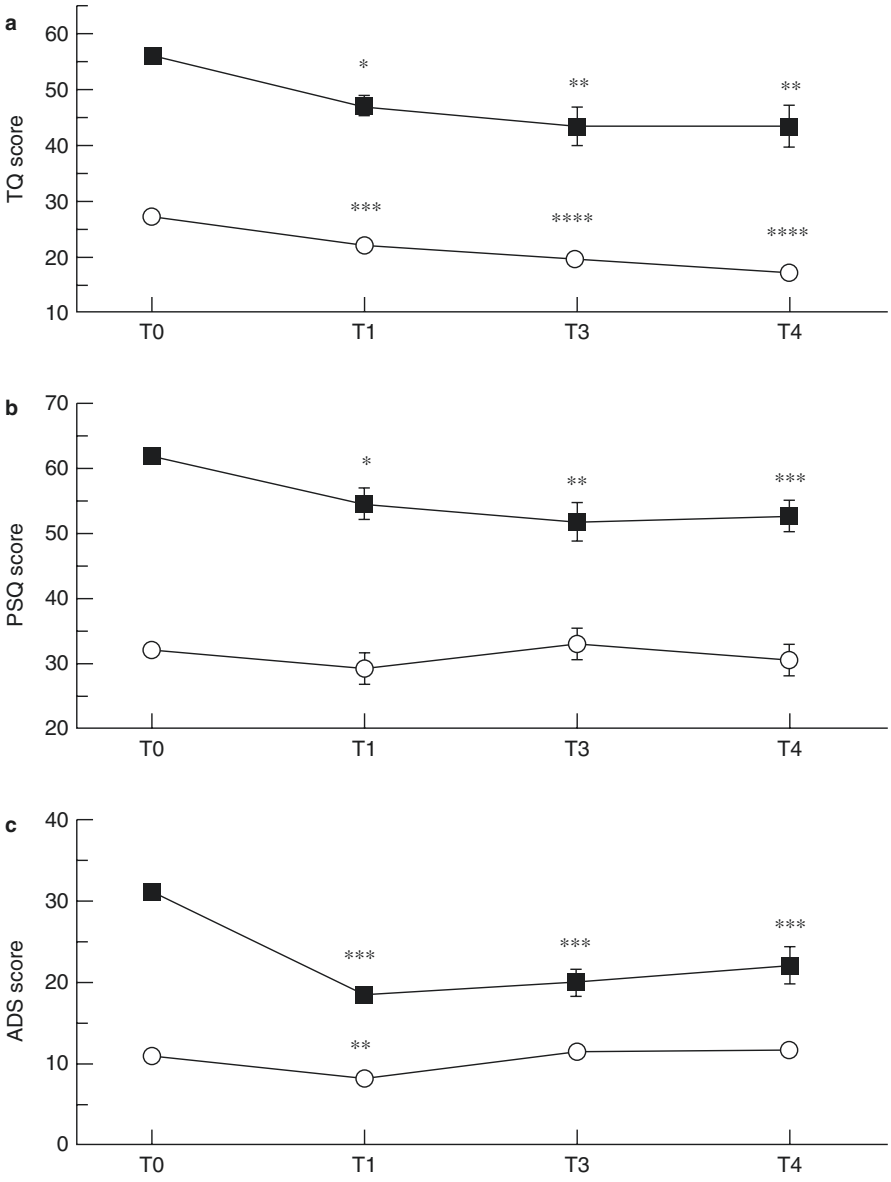

Fig. 7.3 Example of treatment-related changes in tinnitus patients measured by self-rating instruments for tinnitus (**a**) (TQ) (Goebel and Hiller 1994), stress (**b**) (PSQ) (Fliege et al. 2005), and depression (**c**) (ADS) (Hautzinger and Bailer 1993). Filled squares – patients with disturbing (non-compensated) tinnitus, open circles – patients with non-disturbing (compensated) tinnitus; T0 – study onset, T1 – 7 days after therapy onset, T3 3 month after therapy, T4 – 12 months after therapy

The SOC-L9 is based on the model of the salutogenesis of Antonovsky (1993, 1995), which focuses on factors that keep people healthy despite stress and stress. It is a relationship between health, stress, and coping. The SOC-L9 is a short circuit

with nine items (Antonovsky 1995; Scholler et al. 1999) and measures coherence, which is defined as a global orientation that reflects the extent to which a person is a generalized and persevering and has dynamic feeling of the confidence that its own inner and outer environment is predictable and that it is very likely that things will develop as one might reasonably expect.

The measured items can be grouped into the three scales of "understandability" (two items), "manageability" (three items), and "meaningfulness" (four items) and are considered subcomponents of the coherence feeling (Schneider et al. 2004). A raw sums value is calculated for all items, which can be compared with the mean value of a standard sample. The questionnaire has a sufficiently high degree of reliability and validity. Schumacher et al. (2000), during a statistical evaluation of the SOC-L9 on a representative sample of the German population ($n = 2005$), have determined a separation severity coefficient with values between $r = 0.56$ and $r = 0.68$, which is exactly the same as the calculated one. Internal consistency (Cronbach-$\alpha = 0.87$) can be considered as good. The normalized values obtained by Schumacher et al. (2000) from a German representative survey are similar to the results of Hannover et al. (2004). Investigations by Söderman et al. (2001, 2002) reported that the SOC had an influence on the results in the HADS in Meniére disease and tinnitus patients and proved to be a relevant influencing factor of psychosocial dimensions. There was a high correlation between the SOC and the quality of life. This questionnaire is particularly useful when choosing the individual design of therapeutic measures.

7.3 The Next Generation of Instruments

Clinical assessments of PROs typically call for short, yet very precise measurements. Thus, the psychometric requirements for instruments used for this purpose are high. Among these, measurement precision is of crucial importance, while small changes over time must be interpreted and a vast array of different sources of variance that can hardly be controlled under real-life conditions.

Today, many validated outcomes tools could be used (McDowell et al. 2004) and allow for increasing specification of a range of domains related to health and well-being of tinnitus patients. However, the use of these tools has important limitations. One is that all of the tools mentioned above and in the following chapters were not developed for clinical practice. Thus, the most precise and comprehensive questionnaires are rather lengthy and complex, leading to a level of respondent burden that hampers their use in clinical routines.

An additional major limitation has been that results from different questionnaires are difficult to compare, even when two similar instruments are used to assess the same outcomes. The situation is as if body temperatures assessed in different settings were not comparable with one another but were dependent on the particular thermometer used (Ware 1993, 2008). To make the measurement of psychological constructs more similar to biomedical ones, a standardized, efficient approach for a variety of applications including clinical practice and clinical trial research needs to be developed, so that results can be compared across conditions, therapies, trials, and patients.

7.3.1 Common Metric

The use of the so-called item response theory (IRT) for the development of PRO tools provides a solution to many of the limitations of existing instruments. IRT methods were developed more than four decades ago (Lord 1965; Rasch 1966), and numerous attempts have been made to exploit their potential (Bech et al. 1978; Fisher 1993). Today, IRT-based tests are well established in the educational field (Haley et al. 2004; Anonyms 1988) but have just been widely introduced into health care during the past decade (Ware et al. 2003; Cella and Chang 2000; Ware et al. 2000; Bjorner et al. 2003a).

Like factor analysis, IRT models assume that the measured construct is a latent variable, referred to as the IRT score, theta, or θ, which cannot be observed directly, but can be estimated based on responses to different items measuring the construct. An IRT item bank consists of items measuring the same construct and a mathematical description of the items' measurement properties (Bjorner et al. 2003b). The IRT model (Martin et al. 2007; Fischl and Fisher 2007) describes the probability of choosing each response on a questionnaire item as a function of theta (Embretson 2000, 2006). One important distinction of all IRT methods from classical test theory methods is that theta can be estimated from the responses to *any* subset of items in the bank (Bjorner et al. 2003b). Accordingly, researchers or clinicians can select items that are most relevant for a given group or an individual patient and score the responses on one *common metric* that is independent of the choice of items. If the item bank contains items from established questionnaires, the scores of these questionnaires can be predicted from estimates of theta even if the questionnaires themselves have not been used. Thus, comparisons of results from different questionnaires are expected to be facilitated with the introduction of comprehensive IRT item banks (Bjorner et al. 2003c). There a few of such common metrics already available for key health constructs, like depression, and some websites can assist to report theta scores or corresponding scores of similar tools (www.common-metric.org, www.prosettastone.org). Figure 7.4 shows an easy to use lookup table.

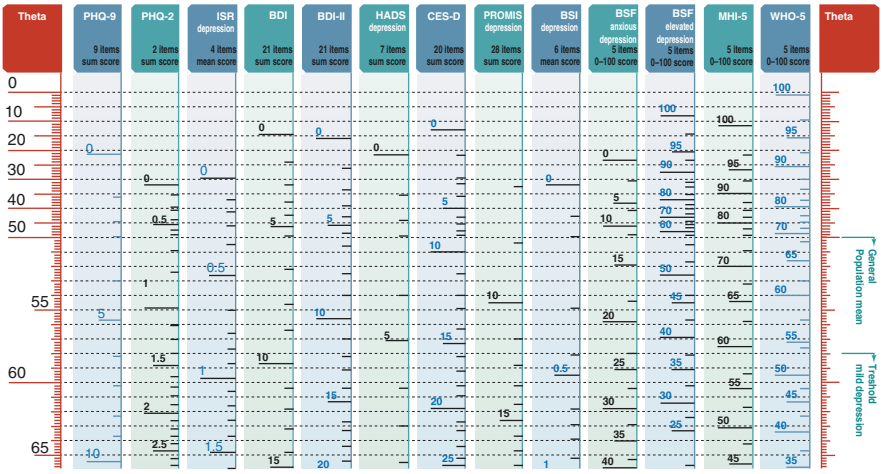

Fig. 7.4 Example how to score different depression instruments on one common metric (Wahl et al. 2014)

7.3.2 Individually Tailored Tests

This new generation of PRO tools also promises to provide very short but still reliable assessments (Haley et al. 2004; Ware et al. 2003; Embretson 2000, 2006; Bjorner et al. 2003c; Revicki and Cella 1997). The goal of the so-called computerized adaptive test (CAT) is to select and administer only the most informative items from an IRT item bank for every individual patient according to her or his estimated theta value. After each item has been administered, an IRT score is reestimated to choose and apply the next best suited item for the current score estimate. By omitting irrelevant, uninformative items, higher measurement precision is achieved, while at the same time, respondent burden can be controlled (Cella and Chang 2000; Hambleton 2006; Hays et al. 2000). CATs generally use two different ways to end the assessment ("stopping rules"): the CAT either stops after a predefined measurement precision (confidence interval) has been achieved or after a predefined total number of items have been administered.

7.3.3 Assessment Across Different Settings

Whereas clinical researchers can limit their research questions to a specific setting, clinical practice applications need to be embedded within the healthcare delivery system to be useful. To connect different assessment points, one could imagine, for instance, that future patients might be asked to assess their most relevant symptoms regularly at home, e.g., on a smartphone (Fig. 7.5). If self-reported health status declines, a case manager could be automatically alerted to call the patients for further evaluation and may send them to the doctor's office. At the office, a second test might be used to confirm the home assessment. If the patients are transferred to other settings, more comprehensive health assessments also could be applied. Each setting calls for the use of different tools. At the patients' home, practicality and low

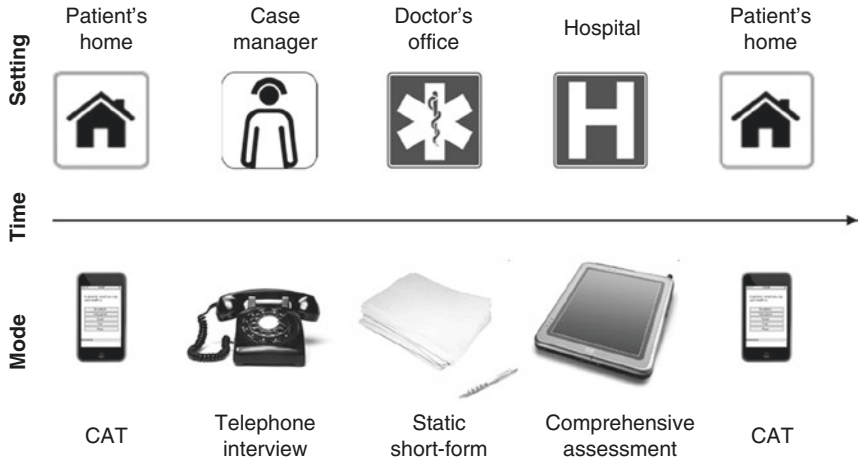

Fig. 7.5 Distinction of patient-reported health status information into prediction and outcome variables

respondent burden will be the priorities, and lower measurement precision generally will be acceptable, whereas in a clinical setting, more comprehensive tests will be favored. Ideally, all instruments used in this chain of healthcare delivery would be scalable on the same metric as described above.

7.4 Logistics

Once the decision has been made to collect one or more PROs in clinical practice, and the intent and application of that collection have been considered, the attention needs to turn to the logistics of collecting them, so that they indeed serve the purpose that was intended. The logistical issues that require particularly careful consideration and implementation are (1) the methodology of collecting PROs itself and (2) the support that will be needed for the collection of data in clinical practice.

7.4.1 Mode of Assessment

There are several methods of administering standardized questionnaires to collect PROs in clinical practice. The traditional methods are face-to-face interviews and paper-and-pencil completion of questionnaires. More commonly, computerized methodologies are used, as they provide date entry, administration, analysis and, printout of data in real time, to make assessment results immediately available for the clinical encounter. Computerized technologies include traditional personal computers (PCs) (which may be situated, e.g., in the clinic waiting room), mobile tablet PCs, handheld computers, smartphones, or personal digital assistants (PDAs) given to patients for one-time use or to keep them for the duration of the evaluation (e.g., over an entire treatment or follow-up period). A variation of the computer method is the use of SmartPen technology. Instead of typing or pressing buttons, a pen-like device is used to check boxes on an individually printed paper questionnaire, which uniquely identifies the patient as well as the assessment. From the users' perspective, this assessment mode is alike traditional paper-pencil methods but still maintaining the advantages of computerized data entry.

Whereas the mentioned technologies are primarily used for the assessment within a clinical practice setting, a new field of PRO assessments for individual case management emerges with the assessment and monitoring of the subjective health status of the patients at home; this requires different technical solutions. Telephone is still the most common way to collect PRO data at the patients' home, either via traditional interview (i.e., a person posing questions to the patient over the telephone) or via automated telephone interviews, using interactive voice recognition (IVR) or pressing a number to select answers to questions (Fig. 7.6).

Generally, most studies comparing *paper-and-pencil* and *computerized* administration modes (PDA, online, pen, tablet, touch screen) suggest psychometric equivalence between both modes of administration (Bettinville et al. 2005; Folk et al. 2006; Norman et al. 2010; Webb et al. 1999; Heuser and Geissner 1998; Velikova

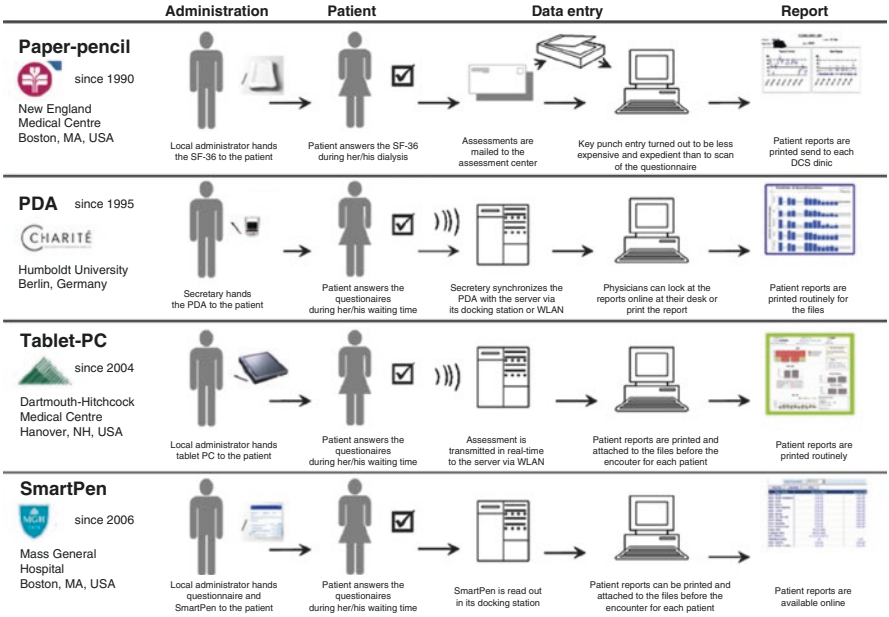

Fig. 7.6 Distinction of patient-reported health status information into prediction and outcome variables

et al. 1999; Cook et al. 2004; Schaeren et al. 2005; Bliven et al. 2001; Kleinman et al. 2001; Ryan et al. 2002; Saleh et al. 2002; Wilson et al. 2002), but some studies also report differences (Beebe et al. 2006; DeAngelis 2000). The literature on mode effects between *paper-pencil* versus *phone* administration is more heterogeneous. Some studies suggest no mode effects (Duncan et al. 2005; Hepner et al. 2005; de Vries et al. 2005); others report and account for them (Powers et al. 2005; Beebe et al. 2005; Kraus and Augustin 2001). Literature on mode effects using *IVR technology* is rare, probably due to the novelty of IVR; one large-scale study reports IVR mode effects (Rodriguez et al. 2006) and suggests to adjust for it. A significant limitation is that many studies were underpowered to detect small but meaningful clinical differences.

Given a lack of evidence of superiority of one mode of administration of questionnaires to collect PROs over another, the choice of methodology is more dependent on the ability to provide appropriate support for the various options, cost issues, and most importantly the reasons why PROs are being collected. If the PROs need to be immediately available to the healthcare provider(s), a methodology that includes immediate availability of data will be needed (i.e., a printout of the answers and/or scores). This may also include comparison with previous data from that patient or comparison with norms. In both of those situations, a computerized collection is clearly superior to a pen-and-paper collection. If PRO data are collected in order to be summarized for groups of patients at a later date, then traditional non-computerized collection can be adequate. Another issue to consider is whether the

PRO data need to be connected to other clinical or demographic data, in which case connectivity with the clinical record is required. Another critically important issue is what is the technological sophistication of patients—that includes their age (with some groups experiencing more difficulties with elderly patients, although that is not universally observed and may be changing with time), literacy (are they able to read the questions on their own, or should someone read the questions to them), reading level (i.e., are the questions worded at an appropriate level of complexity, so that they can be understood by all patients), visual ability (including font size), language fluency (i.e., can they read in the language of the questionnaire, or will questions have to be provided in several languages), familiarity with touch screen computers (e.g., are they used for banking and other activities of daily living by the target group), availability of home computers if that is a method being considered, or manual dexterity (e.g., if contemplating the use of PDAs).

Critically important issue is what is the technological sophistication of patients that includes their:

- *Age*
- *Literacy*
- *Reading*
- *Visual ability*
- *Language fluency*
- *Familiarity with touch screen computers*
- *Availability of home computers*
- *Manual dexterity*

Finally, the frequency of clinic visits in relationship to the desired frequency of PRO assessments will influence the choice of the most appropriate method of PRO administration—if assessments need to be done outside scheduled clinic visits, home completion, and whether by mail, telephone, computer, or in person interview. Table 7.1 shows a summary of some of the key features of different modes of assessment for use within clinical settings.

7.4.2 Infrastructure

Regardless of which method of PRO data collection is chosen, a considerable amount of attention needs to be given to the appropriate level of support for the successful collection and usefulness of these data. Support is needed at several levels, including technical level, patient level, and healthcare provider level, as well as overall system support. Technical support in setting up and supporting the administration of the PROs may be obvious for computerized assessments but is indeed needed in all methods (such as preparing the questionnaire packages, resolving any

Table 7.1 Characteristics of different modes of assessments within a clinical setting

	Paper-pencil	PDA/smartphone	Tablet PC	SmartPen
Mobile	++	+++	+	++
Easy to handle	++	++	++	+
Fill out time independent from staff time	++	++	++	++
Data entry time	– –	++	++	+
Immediate patient reports	– –	++	++	++
WLAN	– –	+	++	– –
Mail in/out option	++	– –	– –	– –
Development of new questionnaires	++	+	+	–
Computerized adaptive tests	–	+	+	–
Visually impaired patients	–	– –	+	–
Hardware investments	++	–	+	–
Administrative costs	– –	++	++	+
Total costs	– –	+	++	–

PDA personal digital assistant

copyright/authorization issues, ensuring that all materials are appropriate for the patient population—e.g., font size, language, etc.) and then troubleshooting and providing ongoing technical support. Decisions are required regarding funding, availability of software, and whether the software needs to be adapted or customized (e.g., with the institution logo, appropriate preamble, specific ad hoc items, etc.). At the patient level, a dedicated or at least knowledgeable and motivated individual is required to introduce the concept to the patients, explain the rationale and logistical issues, direct them to the actual collection format, answer questions, and try to ensure compliance. If an interview or pen-and-paper method is chosen, data will need to be transcribed, entered, and analyzed. Computer and telephone methods may require more up-front investment, but data collection and entry are integrated, and analysis is automated (at least on a patient level but for most software solutions also on an aggregate level). If adequate resources are not dedicated to collecting PROs in clinical practice, the data obtained will be incomplete and almost certainly biased toward more compliant patients, who are healthier and do not represent the entire patient group. Thus, suboptimal compliance will result in misleading information about the patients' real health status on an aggregate level (Fig. 7.7).

The most important barriers to the introduction of PRO assessments into daily care today seem to be attitudinal barriers. Typically healthcare providers, such as doctors and nurses, are not familiar with the questionnaires and question their applicability and clinical usefulness. One regular concern is that the process will be time-consuming and interfere with the usual clinic flow and that questionnaires are too long for patients to complete. Even when those concerns are addressed, the involved individuals need to be made aware of the purpose of PRO collection. Efforts should be placed to get the "buy-in" of all stakeholders as well as participants. Why is this

Fig. 7.7 Different software platforms being used at the Charité following technical advances

information being collected, and how will it potentially affect the healthcare provider, is a particular issue that requires careful attention. Although surveys of physicians indicate favorable attitudes toward QOL information (Bezjak et al. 2001), there are clearly views to the contrary. This may especially be an issue for collection of patient satisfaction data, as that data could potentially reflect in a negative way on the performance of the healthcare team or its individual members, and there may be concerns on whether such data could jeopardize their evaluation and/or employment.

Thus, at the healthcare provider level (physician, nurse, etc.), considerable efforts need to be put, preferably up front, before the collection of PROs commences, to educate the healthcare providers on how to look at the data and how to interpret them. Critical questions that need to be addressed regard the display of results:

- Graphs with scores?
- Individual questions with answers?
- Comparison to previous answers/scores of that patient?
- Comparison to norms?
- Which norms—of that patient population from the literature? from that center?
- Comparison to healthy population?

All of these questions again relate to the aim of the collection of PROs—reflecting on the reason and on how will the results be used often provides answers to how results should be displayed. Depending on the particular environment, some users may prefer an individualized PRO assessment; others may prefer one of the available of-the-shelf solutions.

Another issue of supporting healthcare providers is whether to start with a small number of dedicated and interested individuals, and let the program expand as the providers themselves find added value in it, or whether to mandate that all doctors or nurses in a group/clinic/hospital be part of the program of receiving and asking to review PROs. There is no doubt that even with a good support offered to healthcare providers, the rate of adoption varies, with early adopters, the "middle pack," and individuals who remain resistant to change even when most of their colleagues have adopted the new technology.

Finally, there needs to be some consideration of support at a "systems level," for the collection of PROs to be successful. Some discussion needs to take place on how does this fit within the existing processes and structure in that institution (clinic, hospital, or office), how are the initiatives communicated, who supports it (financially and administratively), and how do they support it.

Conclusion

There are a number of issues and potential barriers that need to be addressed before PRO assessments can be implemented into clinical routines. To choose the appropriate constructs, the best instruments and the most suitable mode of assessment are just some of them. Up to now, PRO assessments have not been established in clinical practice on a wide scale. One of the reasons for this may be that the scientific evidence for the benefits of PRO assessments in clinical practice is still scarce. Greenhalgh and Meadows (1999), Espallargues and Alonso (1998), and Donaldson (2004) have reviewed the literature and found that including psychological assessments in clinical practice facilitated the doctor-patient communication and expanded the scope of communication toward psychosocial aspects which was perceived as beneficial by the patients (Detmar et al. 2002; Rubenstein et al. 1995; Velikova et al. 2004).

Incorporation of psychological assessments into clinical practice facilitates the therapist-patient communication and expands the scope of communication toward psychosocial aspects, which is perceived as beneficial by patients.

However, to our knowledge there are still no large randomized studies, which would demonstrate that PRO assessments in clinical practice positively impact medical decision-making or objective treatment outcomes. In our opinion, there are two key reasons for this situation: (1) commercial ePRO software for clinical practice has just been made available for a larger public, and (2) the psychometric instruments typically used still have a number of important shortcomings. We discussed some of them in Sect. 7.3. However, with the emerging new generation of tools, it seems likely that psychometric assessment can meet the standards of biomedical assessments in the near future. We believe that a precise monitoring of the patient subjective health status within the clinic as well as at the patients home will provide highly valuable information for a successful treatment of the patients which cannot be assessed by other means.

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Stress-Related Tinnitus Treatment Protocols

8

New Treatment Approaches for Chronic Tinnitus-Related Distress

Rilana F.F. Cima

Abbreviations

ACT	Acceptance and commitment therapy
CBT	Cognitive behavioral therapy
CR	Conditioned response
CS	Conditioned stimulus
FA	Fear avoidance
FTQ	Fear of Tinnitus Questionnaire
HR-QoL	Health-related quality of life
MBSR	Mindfulness-based stress reduction
NP	Neurophysiological
PVAQ	Pain Vigilance and Awareness Questionnaire
TAQ	Tinnitus Acceptance Questionnaire
TCS	Tinnitus Catastrophizing Scale
TDI	Tinnitus Disability Index
T-FAS	Tinnitus Fear-Avoidance Scale
THI	Tinnitus Handicap Inventory
THQ	Tinnitus Handicap Questionnaire

R.F.F. Cima
Department of Clinical Psychological Science, Behavioural Medicine Section i.s.o. Unit, Maastricht University, Maastricht, The Netherlands

Adelante, Centre of Research and Expertise in Rehabilitation and Audiology, Hoensbroek, The Netherlands
e-mail: r.cima@maastrichtuniversity.nl

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TQ	Tinnitus Questionnaire
TRQ	Tinnitus Reaction Questionnaire
TRT	Tinnitus retraining therapy
TSI	Tinnitus Severity Index
TFI	Tinnitus Functional Index
TSQ	Tinnitus Severity Questionnaire
TVAQ	Tinnitus Vigilance and Awareness Questionnaire
UR	Unconditioned response
US	Unconditioned stimulus

8.1 Stress, Distress, and Tinnitus Suffering

Stress as a concept cannot be adequately defined using a single unified definition. There is the biological perspective, underpinning the biological responses and markers following stressful events. On the other hand, there is the biopsychological perspective describing stress as the experiential and emotional state of being confronted with "stressors," the coinciding bio-psycho-physiological responses, and the emotional and behavioral efforts toward adaptation (Baum 1990; Mazurek et al. 2012). For the purpose of this chapter, as a working definition of stress, we will adopt the following description: stress is the internal state that occurs when an organism experiences (or perceives to experience) a disturbance in usual equilibrium of homeostasis, which in turn evokes subsequent responses of the systems in an effort to return to the homeostatic equilibrium.

In order to understand the several concepts underlying most of the tinnitus therapy models, it is imperative to differentiate between the concepts of *stress* and *distress.* Consider that an internal stressful state and the subsequent response sets can be induced by either positive or negative events (stressors). This stress response might even be considered adaptive and not unequivocally considered or perceived to be negative or unwanted. If we look at the definition of *distress*, this concept is usually defined as the very negative and aversive state when the processes of adaptation and the efforts thereto have failed to return the organism to said calmness of homeostasis. *Distress* happens when the organism fails to assimilate to stressors and experiencing *distress* is therefore intrinsically maladaptive and unwanted. When studying tinnitus and the associated suffering, which happens often but not always, it can be purported that in the case of suffering, tinnitus-related *distress*, as opposed to the more general term stress, might be the more appropriate point of focus when describing treatment avenues.

Distress happens when the organism fails to assimilate to stressors and experiencing distress is therefore intrinsically maladaptive and unwanted.

The term "tinnitus" is usually defined as the perception of sound in the absence of an external (or adequate) source. Though adequately describing the instance of perceiving a tinnitus, this definition fails to recognize that for a fairly large group of people, this perception, even though continuously present, is perceived as fairly harmless, while for others it coincides with severe anguish. Contemplating as to why the one and not the other is suffering from the tinnitus, it might be stated that in most cases, tinnitus is indeed a stressful event, which in the suffering person evokes maladaptive responses, leading to tinnitus-related *distress*.

In most cases, tinnitus is indeed a stressful event, which in the suffering person evokes maladaptive responses, leading to tinnitus-related distress.

Furthermore, tinnitus is not a disease, but merely a symptom, evidenced by the fact that the experience of tinnitus is not equal to tinnitus *distress*, which might add to the confusion in terminology about the condition. In analogy with observations in chronic pain research (Gatchel et al. 2007; Turk and Monarch 2002), one might view tinnitus as being a perception *of disease/harm,* rather than a disease, i.e., a biological disorder of structure or function, in itself. When bothersome, tinnitus is, next to the mere perception of a sound, a very *distress*ing experience occurring through a set of maladaptive psychological responses. In order to address and include the intrinsic psychological component of the *distress*ing tinnitus experience, a description of tinnitus suffering might be formulated as follows:

Bothersome (distressing) tinnitus is a negative emotional and auditory experience, associated with or described in terms of actual or potential physical or psychological harm.

This definition (Cima 2015) well describes a group of individuals who find themselves unable to habituate the seemingly "harmless" signal and often end up having a chronic *distress*ing tinnitus. In this group, tinnitus represents harm, or at least potential harm in their perception, since it has led to severe disability in functioning on almost all life domains. Most of the contemporary tinnitus treatment protocols are mainly focused on reducing the tinnitus-related *distress* and, consequently, its disabling influence on life and not so much on eliminating or decreasing the tinnitus signal in itself. The latter has been a focus of research, but convincing results are yet to be found or are considered to be of experimental value and not yet clinically relevant. The focus of this chapter will lie on the former, the clinical treatment avenues concerned with decreasing the tinnitus-related *distress*.

First, the psychological nature of tinnitus suffering is discussed. It is of importance to highlight the psychological nature of tinnitus suffering and distress, since it is still a largely neglected area in tinnitus treatment protocols. Second, the main theoretical models will be discussed, as well as the psychological mechanisms

which are assumed to be predictive for chronic tinnitus *distress*. Next, the different treatment approaches will be described and finally, some of the most commonly used instruments to assess tinnitus-related distress and the associated psychological constructs will be presented.

8.2 The Psychological Nature of Tinnitus Suffering

Residing within and confined to the individual's subjective perceptual experience, tinnitus is not measureable or quantifiable by objective physical recordings and is furthermore not traceable to disease, injury, or pathology in the brain or elsewhere. Indeed, up to this day, a medical or pharmacological cure for Tinnitus is unavailable (Elgoyhen and Langguth 2010; Elgoyhen et al. 2012). Likewise, audiometric properties of the tinnitus-percept itself (the quality of the tinnitus sound, e.g., loudness or pitch) hardly predict the level of tinnitus annoyance or severity (Andersson 2003; Coccia et al. 2014; Hiller and Goebel 2006). Rather, the more psychologically intrusive and threatening the sound becomes in the perception of the individual, the more severe is the suffering (Coccia et al. 2014; Hiller and Goebel 2006). Following these observations, one may conclude that tinnitus suffering is fundamentally and foremost explained by psychological processes.

Tinnitus suffering is fundamentally and foremost explained by psychological processes.

Evidence corroborates the idea of cognitive misinterpretations, negative emotional reactivity, and dysfunctional attentional processes being of main importance in dysfunctional tinnitus habituation, contributing to tinnitus severity (Andersson et al. 2006; Andersson and McKenna 2006; Andersson and Verblad 2000; Cima et al. 2011a; Erlandsson and Hallberg 2000; Kroner-Herwig et al. 2003; Westin et al. 2008b; Zachriat and Kroner-Herwig 2004). Important to note is that for 16–21% of the adult population, tinnitus is a fairly common auditory sensation (Krog et al. 2010). These people report to perceive a tinnitus but are not bothered by it. It is only for a subgroup of 3–8% (Davis and Refaie 2000; Ahmad and Seidman 2004) that tinnitus becomes a chronic bothersome incapacitating symptom (Cima et al. 2011b). The coinciding extreme anguish and suffering of these patients is evident and has resulted in the widespread notion among clinicians and researchers that all tinnitus treatments should target psychological suffering. Indeed, it is in fact hard to find a single treatment approach without at least one element aimed at decreasing psychological distress.

Theories about the nature and cause of tinnitus suffering have been developed and can be categorized according to their focal point of study: the sound, i.e., the actual acoustic perception of the sound, or the suffering caused by it, i.e., the impact the sound has on the individual, or both. Current treatment approaches roughly follow these two lines, either placing emphasis on aiming treatment at alleviating the

perceptional experience by masking it (partly or completely) for habituation or soothing purposes, to decrease awareness of the sound by attentional training and cognitive interventions, or aimed mainly at decreasing the maladaptive responses and distress resulting from it. Current theoretical frameworks have been explanatory on some level, and the resulting treatment approaches have alleviated complaints leading to reports of occasional recovery to a satisfactory daily life in some patients. However, despite these advances, tinnitus remains for many persons a disabling complaint.

The approaches described above will provide the framework for the present chapter, in particular two specific theoretical frameworks: the cognitive models of tinnitus distress and the cognitive behavioral account. Both will be presented and discussed below. The question as to why a small group of individuals enters a vicious circle of incapacitation whereas the larger part remains unaffected is a major challenge in tinnitus research and clinical practice. Interestingly, although both frameworks share the same basic assumptions, they might initiate contrasting treatment approaches.

8.3 The Cognitive Approaches

8.3.1 The Habituation Model

The habituation model proposed by Hallam et al. (1984) is often considered the first attempt to offer a psychological account for troublesome tinnitus. It was proposed that the habituation of negative signal interpretation and the related heightened autonomic arousal levels would lead to dysfunctional cognitive processing. Hallam proposed that for most people, repeated perception of the tinnitus sound teaches them that it is not worth their attentional resources. In other words, to function effectively, the "normal" neuronal pathways select which stimulus is "worth" paying attention and which is not. Hallam claimed that most people learn that the tinnitus sound is of low informational value and, thus, does not require a reaction. Consequently, tinnitus does not pose a problem for the majority of affected people. However, tinnitus-related *distress* occurs when these attentional processes are malfunctioning, which is more likely at times of increased stress and arousal, which in turn restrains cognitive resources.

The habituation model claims that tinnitus-related distress occurs when the attentional processes are malfunctioning, which is more likely at times of increased stress.

The habituation model has remained largely theoretical, although tinnitus treatment approaches, such as relaxation therapy, attention diversion techniques (directing attention away from tinnitus), and stress reduction by means of cognitive restructuring methods (aimed at altering beliefs about the tinnitus), have been based

on its main premises. For example, the habituation model suggests that following the perception of tinnitus and coinciding *distress*, a person might actively avoid exposure to tinnitus and as a result experience relief from it (this being an example of negative reinforcement where the tinnitus-related distress is relieved by the preceding, avoidant action). Difficulties arise when significant or continuous resources (cognitive or otherwise) are needed to avoid the tinnitus to experience relief. To treat tinnitus-related distress (or to facilitate habituation to tinnitus), it was recommended that stress levels as well as arousal levels of or in the central nervous system should be reduced. In addition, an attempt to change the meaning of the tinnitus percept for the patient should be made (Hallam et al. 2004). Current research indicates mixed evidence in support of the habituation model (Baguley et al. 2013).

8.3.2 The Neurophysiological Model

The habituation model has inspired (Jastreboff 1990; Jastreboff et al. 1988a), who postulated that the association between tinnitus and an aversive emotional state emerges through classical conditioning. Classical (or Pavlovian) conditioning (Pavlov 1927) refers to a process whereby two stimuli are repeatedly presented together (famously illustrated by the dog, presented with both a bell and meat). While doing this, the animal or individual learns that the two stimuli are associated (i.e., "if bell, then meat"). Subsequent presentations of the principal stimulus alone (the bell, which is the conditioned stimulus), even without the meat (the unconditioned stimulus), proved to suffice to trigger the same response (salivating, which was the conditioned response).

The neurophysiological tinnitus model (NP model) is based on the idea that conditioned fear responses elicited by the tinnitus precept are the cause for tinnitus becoming bothersome (Fig. 8.1) (P. J. Jastreboff 1990; P. J. Jastreboff and Hazell 1993). This reasoning stems from animal research, in which conditioning paradigms were used to

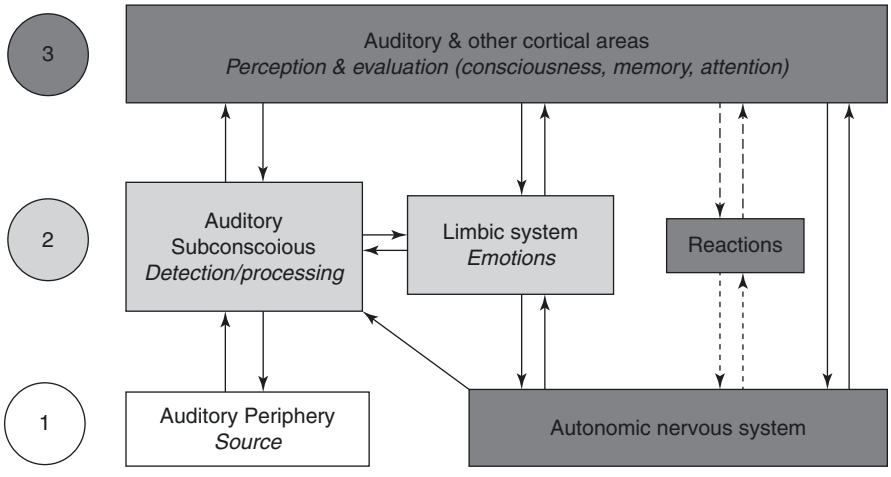

Fig. 8.1 The neurophysiological model

induce tinnitus-like fearful behavior in rats (P. J. Jastreboff et al. 1988a, b). The NP model distinguishes three stages: stage one, generation of the auditory stimulus in the auditory periphery; stage two, detection of the tinnitus-related signal; and stage three, perception evaluation of tinnitus. The neurophysiological model demonstrates tinnitus generation/detection, based on neurophysiological mechanisms.

The neurophysiological model is based on the idea that conditioned fear responses elicited by the tinnitus precept are the cause for tinnitus becoming bothersome.

8.3.3 The Cognitive Model

A conceptual cognitive model proposed by McKenna et al. (2014), incorporates a cognitive model of distress to explain tinnitus-associated insomnia (Harvey 2002). McKenna et al. argue that the tinnitus-signal distress and bodily arousal are provoked mainly through negative cognitive misinterpretations, leading to inaccurate evaluations of sensory activity and distorted perceptions (see Fig. 8.2). It is

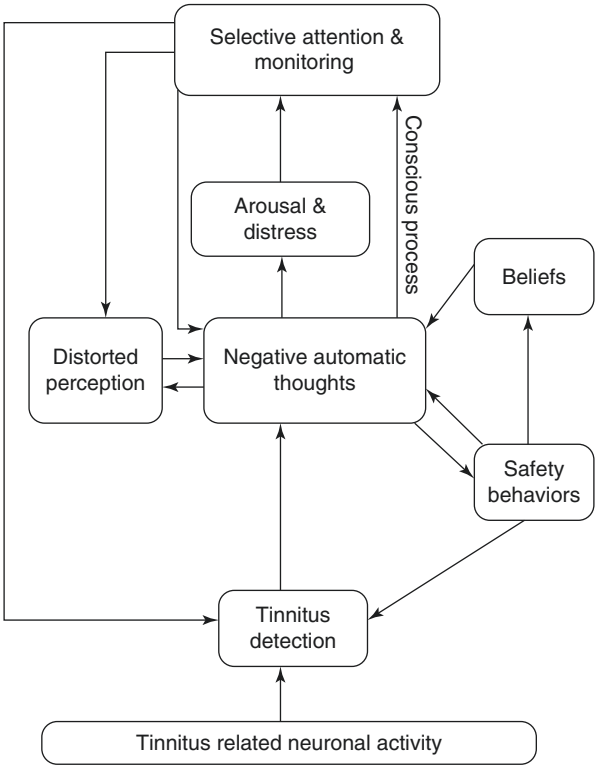

Fig. 8.2 Cognitive model—reproduced from (McKenna et al. 2014)

proposed that the resulting stress and hypervigilance contribute to a feedback cycle that exacerbates the distress associated with flawed sensory processing, of which tinnitus may be a major component. The model attributes a fundamental role to the negative evaluation of tinnitus. The negative evaluation of the tinnitus percept can be viewed as comprised of primary and secondary appraisals. For example, a person might initially appraise the tinnitus as being threatening to their health and then make a secondary appraisal of their (in)ability to cope with it.

The cognitive model attributes a fundamental role to the negative evaluation of tinnitus.

Clinical trials in which this model is applied to treatment, by which the clinical relevance of the model can be tested, have not taken place yet. However, evidence exists that cognitive processes, such as interpretation, attention, and memory, are indeed involved in chronic tinnitus suffering (Andersson et al. 2013; Conrad et al. 2011; Rossiter et al. 2006; Stevens et al. 2007), though these studies were not specifically aimed at validating the model.

8.4 The Cognitive Behavioral Approach

Several so-called "cognitive behavioral" accounts for tinnitus have been postulated (Cima et al. 2011a; Hallam et al. 1984; Kleinstauber et al. 2012; McKenna et al. 2014). A promising one is based on a fear-avoidance model (FA model) of chronic pain (Vlaeyen and Linton 2000, 2012), since in this model, predictions about the behavioral components in the maintenance of tinnitus distress are included. The FA model (Fig. 8.3) for chronic tinnitus offers explanatory predictions about both the

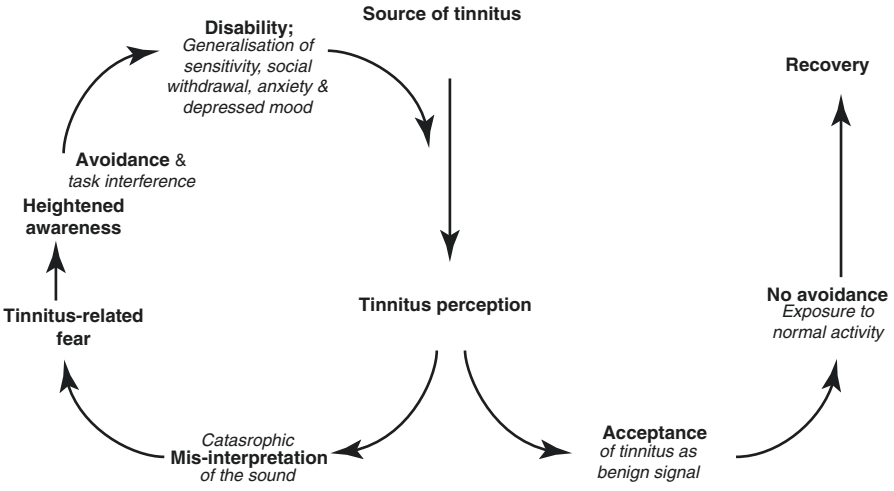

Fig. 8.3 The fear-avoidance model

cognitive processes and the behavioral mechanisms. It predicts that individuals perceiving the tinnitus signal are subject to automatic emotional and sympathetic responses. These symptoms are misinterpreted as harmful or threatening. If the signal persists, the coinciding threatening (alarm) states, which indicate malignance of the signal, elicit conditioned, both classical and operant, fear responses, i.e., fear, increased attention, and safety seeking, i.e., avoidance and escape behaviors. These safety behaviors become negatively reinforced through instant decreased fear, which is adaptive in the acute phase. In other words, by avoiding, or not exposing themselves to tinnitus-related perceptions, patients learn that their fear instantly diminishes. However, in the long run, through persistent avoidance of tinnitus percept as well as tinnitus-eliciting or tinnitus-increasing stimuli, the heightened fear and fear responses, such as hypervigilance and safety seeking, are maintained. Avoidance behaviors subsequently lead to task interference and functional disability (Blaesing and Kroener-Herwig 2012; Hesser et al. 2009). The maintained high threat value of the tinnitus leads to increased tinnitus severity and distress, feeding into an endless circle of increased disability (Cima et al. 2011b).

The cognitive behavioral model predicts that the tinnitus signal invokes automatic sympathetic and emotional responses, which are misinterpreted as harmful or threatening, leading to safety behaviors.

A typical feature of the FA model is its prediction; next to the maladaptive pathway (leftward), an alternative and more adaptive pathway (turning right) is proposed, whereby a positive or neutral evaluation of the tinnitus results in no or low fear of the tinnitus and in partially or completely decreased distress. In other words, the tinnitus sound is accepted by the system as being benign; therefore, no unwanted attentional resources are needed. In turn, avoidance and/or escape behaviors do not interfere with daily tasks, resulting in lack of severe disability due to tinnitus.

Accumulating evidence indicates that a cognitive behavioral treatment, based on this fear-avoidance notion, which targets reappraisal of and exposure to the tinnitus sound, significantly reduces tinnitus distress as well as tinnitus suffering and improves the quality of life and daily functioning of tinnitus patients (Andersson 2002; Andersson and Lyttkens 1999; Andersson et al. 2002; Cima et al. 2012; H. Hesser et al. 2011; Hoare et al. 2011; Martinez-Devesa et al. 2010). However, the cause-effect relationships of specific learning mechanisms are still unknown (Cima et al. 2011a; J. A. Henry et al. 2005a; Kleinstauber et al. 2012).

8.5 Comparing the Models

In overview, consensus among the theoretical models exists regarding the evidence that a neutral acoustic signal receives negative valence by means of classical conditioning, in which an individual learns that the signal becomes predictive for negative

states ("false alarms") as a result of automatic negative responses elicited by this signal (Pawel J. Jastreboff and Jastreboff 2006; Vlaeyen and Linton 2000). Both cognitive models highlight the importance of cognitive processes, and although behavioral consequences are mentioned and recognized as important, they are considered secondary for the maintenance and therefore also for the treatment of chronic tinnitus suffering. Conscious cognitive processes are emphasized, as these constitute the main therapeutic targets in treatments stemming from these models, hypothesizing that the classical (involuntary) learning mechanisms are of lesser importance.

Following the lines of theoretical reasoning, it can be postulated that conditioned negative responses are the main cause of the suffering (Jastreboff and Jastreboff 2006) and that these aversive responses toward the tinnitus sound lead to misinterpretations feeding back into negative evaluations and fear responses (Hallam et al. 1988; Hallam et al. 1984; P. J. Jastreboff 2007; McKenna et al. 2014). Building on these principles, the FA model offers predictions about fearful responses (emotional and attentional) and behaviors (Cima et al. 2011a), which explain the maintained tinnitus distress. This latter premise is based on an operant component in learning theory terms and remains unexplained, though mentioned, both in the neurophysiological model as well as the cognitive model. The FA model provides specific predictions on this level, which leads us to the main difference between the models.

While the NP model deals mainly with tinnitus generation and detection and the habituation and cognitive models emphasize the voluntary conscious processing of the tinnitus, the FA model is predictive beyond that and picks up there where the other models stop being explanatory. The main conceptual overlap might lie at the level of the detection/perception and interpretation level, and the classical learning principles are involved purportedly, as was described above. The models differ in explaining how these learning principles—both classical and specifically the operant learning mechanisms—may play a role. The NP model is mainly based on neurophysiological processes and attempts to explain the psychological path in neurophysiological terms. This provides only general descriptions of classical and operant conditioning mechanisms. The habituation and cognitive models both state that the conscious alteration of negative interpretations will decrease arousal and distress as a result of tinnitus, with less emphasis on the behavioral processes. As opposed to this, the FA model is based on associative learning and operant principles and offers explanatory predictions about the classical and the behavioral mechanisms. This fear-avoidance approach integrates previous concepts and might prove helpful in discovering new venues of investigations, as well as in offering means to determine why not only cognitive but also behavioral treatment approaches are repeatedly found to be successful (Tutorial 8.1).

Tutorial 8.1 Theoretical models

Theoretical models leading to psychological treatment approaches for tinnitus distress can be roughly divided into two categories: the cognitive approaches and the cognitive behavioral approaches

Cognitive approaches	
Neurophysiological model	*Main hypothesis* Dysfunction is hypothesized on the following levels • Detection • Perception/evaluation Based on two fundamentals of brain functioning in general 1. Plasticity 2. Habituation
Hallam's habituation model	*Main hypothesis* Malfunctioning attentional processes disturb habituation
McKenna's cognitive model	*Main hypothesis* Cognitive appraisal of the tinnitus signal and selective attention distort the tinnitus perception
Cognitive behavioral approaches	
Fear-avoidance model	*Main hypothesis* Safety behaviors, negatively reinforced in the short term (instant temporary decrease in fear), maintain tinnitus complaints (maintenance of underlying fear)

8.6 Treatment Approaches for Tinnitus-Related Distress

Next to the theoretical frameworks, a short overview of developments within the cognitive behavioral therapies (CBT) during the past decades is necessary, to provide the background for the development of treatments for reducing tinnitus-related distress. To answer the question as to what is meant by the cognitive behavioral therapies, we will take a short journey in the past.

8.6.1 The History of CBT

The first wave of CBT, or the first revolution, started with Wundt's (1832–1920) experimental methods and findings, in combination with the emergence of the behavioral traditions of the classical- or respondent- (Pavlov 1927) and operant- or instrumental- (Skinner 1938) conditioning principles. A class of psychological interventions emerged and converged theory, evidence, and experimental methods. Noteworthy is that at that time, it was a new and a very exciting field in psychology.

A second major impulse was given by the so-called cognitive revolution (second wave), not surprisingly by cognitive sciences and entailed the empirical study of how the thinking (cognitions) and the interpretations (attributions) affected the emotions and behavior. Methods were mainly aimed at the conscious and voluntary altering of interpretations and thought processes, by means of elaborate narrative therapeutic methods (cognitive therapy). Examples include rational emotive therapy (RET) introduced by Albert Ellis in the 1950s, which focused on the associations between cognitions and emotions (Ellis and Grieger 1977). Aaron Beck (1976) introduced cognitive therapy (CT) for the identification and modification of thought "errors" (Gopinath et al. 2010). Another major influence on the cognitive revolution was the major discoveries in computer science and programming, where a computer software gave almost a perfect analogy for understanding the "programming rules" in human brains. During the early 1970s, the behavioral and cognitive approaches merged (Dobson 2010; Hofmann et al. 2012), and the term "integrated cognitive behavior therapies" (CBT) was invented.

The new CBT treatments, such as mindfulness-based stress reduction (MBSR), or simply mindfulness, and acceptance and commitment therapy (ACT), have been classified as "third-wave" CBT approaches (Dobson 2010; Hayes 2004). Some discussion exists as whether they are a new form of therapy altogether, or whether they are still grounded within the traditional CBT family (Ost 2008). For the purpose of this chapter, they will be considered the third revolution in CBT. Although the third-wave CBT treatments contrast with the cognitive tradition by accepting the existence of negative thoughts and emotions rather than trying to modify them, a major similarity is the assumption that human suffering is caused by learning, dysfunctional beliefs, and behavior, all leading to emotional distress and disability. Effects of both ACT and MBSR have been investigated in different populations, including patients with different psychological disorders (e.g., anxiety and depression), with chronic symptoms (e.g., chronic fatigue and chronic pain), and in the healthy population (Bohlmeijer et al. 2010; Powers et al. 2009; Veehof et al. 2011).

The cognitive behavioral therapies (first, second, and third wave) share the idea about psychological *distress* and resulting problems being based in malfunctioning information processing, emotional reactivity, and behavioral mechanisms. CBT has led to a plethora of evidence-based cognitive behavioral treatments for mental and somatic health disorders (Hofmann et al. 2012). In sum, CBT is an integrative and pragmatic treatment approach aimed at modifying dysfunctional behaviors and beliefs in order to reduce symptoms, increase daily life functioning, and ultimately recover from the disorder (Dobson 2010).

8.6.2 Tinnitus Retraining Therapy

Although tinnitus retraining therapy (TRT) is not usually categorized as a form of CBT, it is nevertheless a treatment with a main cognitive component and is therefore at least in part a form of *first-wave* CBT.

As was introduced earlier, TRT is the implementation of the NP model, which is a theory of neurophysiological processes considered to be relevant for tinnitus

perception. TRT is based on two fundamental principles of brain functioning: (1) plasticity and (2) habituation. The basis of the NP model is that the actual source (the tinnitus sound) is not causing the annoyance, but it is the subjective experience and interpretation of the individual which determine whether the tinnitus is experienced as aversive or not.

Two main components make up TRT. The first component is a form of cognitive therapy, so-called retraining counselling or teaching. Through verbal instruction patients are expected to reinterpret the tinnitus, thereby decreasing negative thoughts and beliefs about the tinnitus. The second entails sound therapy, which is either instructing the patient to wear tinnitus maskers[1] or to enrich sound environment, avoiding silence at all costs. It is hypothesized that sound therapy (and avoidance of silence) will decrease the detection of tinnitus and therefore facilitate sustained habituation (Jastreboff and Jastreboff 2000). Changes in tinnitus interpretation and evaluation are postulated to be generated automatically by instruction and sound enrichment. The resulting emotional and behavioral consequences are not the aim of therapy, nor are there specific predictions about these in the NP model. Additionally, TRT postulates that once the conditioned associations are removed, by said interventions, habituation should occur (Jastreboff and Hazell 2008). Although there is a specific prediction about what is the unconditioned stimulus, the conditioned stimulus and conditioned responses are not clearly specified in the NP model (Cima 2013). The effectiveness of TRT remains inconclusive (Hoare et al. 2011; Hobson et al. 2010; Phillips and McFerran 2010), though TRT, and specifically the use of sound generators, is still a popular form of treatment for tinnitus distress, mainly among audiologists.

8.6.3 Cognitive Therapy and Cognitive Behavioral Therapy

Confusion often exists about the differences between cognitive and cognitive behavioral therapy (CBT), since both terms are used interchangeably. Since CBT stems from the convergence of two distinct theoretical schools, the radical behavioral school (first wave) and the cognitive school (second wave), CBT entails a diversity of both cognitive and behavioral principles and methods, and usually a combination of these is used in therapeutic sessions. Therefore, both cognitive and behavioral treatment elements can be found when reviewing CBT procedures in general as well as in tinnitus intervention. Cognitive behavioral theory and treatment has been applied in tinnitus research for decades (Hallam et al. 1988; Scott et al. 1985; Sweetow 1986), and CBT approaches for tinnitus have been repeatedly shown to be effective in decreasing tinnitus distress, anxiety, and tinnitus annoyance and improving daily life functioning. Although there are the discernible common elements across CBT-based treatments for tinnitus, the investigated tinnitus CBT approaches vary in numbers of treatment sessions, hours spent in therapy, group versus individual formats, face-to-face versus

[1] Tinnitus maskers are ear-level devices (much like a hearing aid) which generate a "neutral" sound. It is emphasized that the tinnitus itself should remain audible when using the maskers.

internet based self-help therapies, combinations of different treatment elements, and tinnitus diagnostics and outcome assessments.

8.6.4 The Cognitive Approach

In line with the evolution of CBT in general, during the development in CBT for tinnitus, cognitive therapeutic procedures have been applied plentifully. The main idea of the cognitive approach is that psychological distress is maintained by cognitive factors. Typical cognitive therapeutic interventions (or so-called "talking" therapy) are aimed at (Ellis and Grieger 1977; Beck 1976):

1. Correcting/changing "erroneous" beliefs or thought processes (cognitions)
2. Dealing with current problems and thought processes (and not so much with the past)
3. Advising the patients to perform behavioral experiments in order to test the validity of maladaptive thoughts and beliefs

In line with the cognitive tradition, the cognitive model (McKenna et al. 2014) postulates that therapeutic strategies used to change maladaptive cognitions lead to automatic changes in emotional distress and in problematic behaviors. These cognitive techniques seem to be helpful in the short term. Techniques, next to educational counselling, include but are not limited to "Socratic dialog," thought control, rational thought formulation, exploring automatic thoughts, and testing of thoughts and beliefs through behavioral experiments.

8.6.5 A Fear-Avoidance Approach

Recently, *exposure* therapy, which is a behavioral therapeutic strategy, entered CBT treatment protocols for tinnitus (Cima et al. 2012), next to the much more known cognitive ("talking") interventions. *Exposure* therapy, also applied in chronic pain CBT treatments (Volders et al. 2011), is a clinical application of what is called "extinction" of the association between two stimuli in classical terms of learning theory. It is assumed that tinnitus patients *learned to be fearful* of the tinnitus percept. That is, in the distressed tinnitus patients, the initially neutral tinnitus signal became associated with sympathetic arousal (alarm detection) (Jastreboff 1990; Wilson 2006). According to fear-avoidance reasoning (see Fig. 8.4), the neutral tinnitus signal (CS) became a predictor of aversive interoceptive stimuli (US), hereby receiving a very negative value (danger). Patients interpret the signal as a sign of harm or injury, which is why they are so fearful, selectively single out the tinnitus signal, are interrupted, and engage in safety-seeking behavior (CR). These mechanisms are likewise at work in arachnophobias, for example. The spider, which is harmless, becomes a sign of great danger, leading to the extreme fear.

For arachnophobia, exposure procedures consist of repeated confrontations with spider-related images, objects, and eventually real spiders, which evoke the greatest fear in the patient. As a result of repeated exposure to the most feared stimuli, the

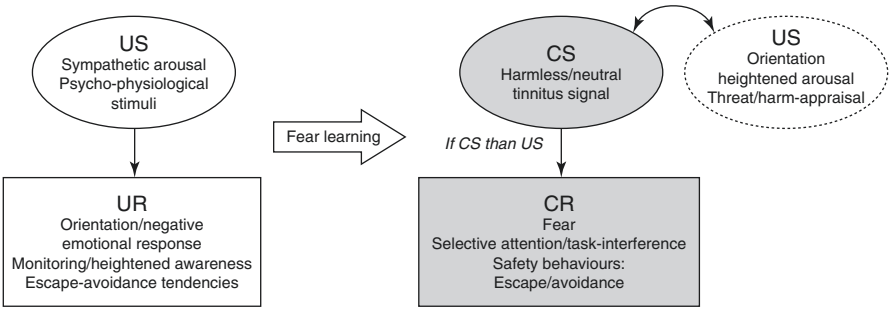

Fig. 8.4 A new fear-learning paradigm: applying the classical conditioning to tinnitus-related distress (Cima 2013)

patient learns that confrontation with spiders is not life-threatening, and therefore they are not in danger. In the end, the fear of spiders dissipates (extinction). Analogically speaking, tinnitus patient is extremely fearful of perceiving the tinnitus. Even though the tinnitus is continuously present, the involuntary response is to not hear it and to try to be minimally confronted with the tinnitus sound (avoidance). Patients do this by trying to control sound environment, or not thinking about tinnitus (which is contradictory: "white bear effect"), and direct their attention elsewhere, but consequently they increase the monitoring and awareness of tinnitus. Cognitive resources by consequence are depleted, leading to task interruptions, more avoidance (safety seeking), and eventually disruptions in functional activities. The sustained consequences are severe disabilities disrupting all life domains and severe dysphoria (dissatisfaction with life).

This "new" form of CBT for tinnitus typically includes the third-wave forms of therapy (see Tutorial 8.2) to enhance internal observations, to increase moment-to-moment consciousness (exposure to) of the tinnitus, and to provide the ability of observing tinnitus-related emotions, sensations, and cognitions in a nonjudgmental way. *Exposure* therapy for tinnitus patients involves exposing them to their tinnitus sound, the interceptive sensations associated with the tinnitus, as well as their moment-to-moment narrative. In order to provide an appropriate context, *exposure* is performed in quiet circumstances. This way, the patient experiences that the tinnitus sound is harmless, not dangerous, and listening to it in silent environments will not have catastrophic consequences. They also learn that the aversive interoceptive stimuli are not always triggered and threat expectancies are adjusted. These experiences lead to a neutralization of tinnitus by extinction of tinnitus-related fears; consequently the more the tinnitus becomes less intrusive and bothersome, the more they engage in *exposure*. In classical learning theory terms, if the patients are exposed to the conditioned stimulus, without the unconditioned stimulus always occurring, extinction of the unwanted conditioned responses occurs (see Fig. 8.4).

8.6.6 Comparing the Treatments

As has been stated before, the theoretical frameworks are fundamentally based on the idea that the initially neutral tinnitus signal receives an "alarm" value, through

Tutorial 8.2 The "third-wave" CBT treatments

Mindfulness-based stress reduction (MBSR)

Mindfulness is a type of psychological treatment aimed at psychological distress, depressive symptoms and anxiety, initially developed for individuals suffering from chronic disease. MBSR was developed by Kabat-Zinn (1982), Ludwig and Kabat-Zinn (2008). MBSR protocols typically consist of up to 10 group sessions. The focus lies on training of the skill of being mindful, which is a moment-to-moment awareness, and observing emotions, sensations, and cognitions nonjudgmentally. Sessions are built up around meditational skills, bodily exercises, and psycho-education. Initially MBSR was developed for chronic pain sufferers and later adapted for chronic diseases such as heart disease and recently for tinnitus as well (Bohlmeijer et al. 2010; Kauth et al. 2010; Philippot et al. 2012). As a stand-alone treatment approach, mindfulness has been applied to a large number of psychological disorders (Fjorback et al. 2011; Shapiro et al. 2011). Mindfulness is also an important component of other psychological treatments such as ACT, some forms of behavioral treatment, and cognitive therapy (Hayes et al. 1999, 2006; Teasdale et al. 2001)

Acceptance and commitment therapy (ACT)

According to its founder (Hayes et al. 2006), ACT has its roots in the behavioral tradition. Interestingly, ACT does not emphasize the accuracy or the content validity of cognitions and behaviors, as is the case in the more cognitive approaches, described earlier. Focus in ACT lies on functional usefulness of thoughts and actions and not on the "right- or wrongfulness" (Hayes et al. 2006; Hofmann et al. 2010). One of the key elements of ACT is to decrease "experiential avoidance" (Hayes and Wilson 1994); i.e., ACT advocates experiencing psychological events (thoughts, perceptions, emotions) in a nonjudgmental way, not trying to change or modify those events, leading to a more functional awareness of how thoughts, emotions, and behaviors create and maintain distress. Since MBSR approaches advocate present moment awareness and observation in a nonjudgmental way, which results in decreased rumination and worry, it has been an integrated part of the ACT protocol

classical conditioning. In turn, this negative tinnitus valence exacerbates negative responses in cognitions, emotions, and behaviors, hindering the "normal" process of habituation. Tinnitus distress—which is the very negative and aversive state—arises when processes of adaptation and the efforts to that have failed to return the organism to equilibrium or homeostasis.

Important to note is that the treatment avenues have been contradictory. The TRT approach suggests that next to extensive education, a (partial) masking of the signal (avoidance of the signal, by avoiding silence at all costs) is the road to habituation. The habituation model and cognitive approaches reason that thought control and attention diversion techniques (altering thoughts/beliefs about the tinnitus and actively directing attention away from the tinnitus) will be beneficial for habituation. For a short-term habituation, these strategies might be useful.

On the other hand, the FA approach leads to the complete opposite approach. The FA's main aim is extinction of CS-US associations and therefore sustained extinction of conditioned responses, instead of enforcing short-term habituation. If we look at Fig. 8.4, the FA approach aims at dissolving the dotted arrow between the CS and US.

In other words, the FA model contradicts the habituation approaches by predicting that doing the exact opposite (confrontation instead of avoidance, exposure instead of masking, tinnitus awareness instead of attention diversion, observing thoughts/beliefs instead of altering/challenging) will lead to sustained recovery of distress. Indeed, strong associations between avoidance behaviors and perceived tinnitus handicap have already been found (Kleinstauber et al. 2013).

Implementing the new concepts in CBT, using mindfulness-based exercises as well as ACT methodology (see Tutorial 8.2) for *exposure* toward tinnitus, has indeed proven successful in effectively decreasing tinnitus-related distress (Cima et al. 2012; Hesser et al. 2012, 2014; Philippot et al. 2012; Westin et al. 2011).

8.7 Measuring Tinnitus-Related Distress

As it has been described in the previous sections of this chapter, distress is an aversive state, which is the result of the organism failing to adapt to stressors. Tinnitus-related distress, and the treatment thereof, hardly focusses on the tinnitus sound itself, since indeed emotional distress is the main and the most significant factor in predicting the variability in quality of life of tinnitus patients is psychological *distress* (Cima et al. 2011a, b; Erlandsson and Hallberg 2000). In individuals with persistent tinnitus, the acoustic characteristics of tinnitus percept (e.g., loudness or pitch) are hardly associated with tinnitus severity or treatment outcome (Jastreboff 1990; Jastreboff and Hazell 1993). The initial negative evaluation and subsequent fear responses leading to the overall distress might be more relevant in defining the severity of complaints than the tinnitus percept itself.

Accumulating evidence suggests that fear responses, cognitive misinterpretations, negative emotional reactivity, attentional processes, and misappropriated behavioral strategies are crucial in dysfunctional habituation leading to severe tinnitus-related distress (Andersson and McKenna 2006; Erlandsson and Hallberg 2000; Kroner-Herwig et al. 2003; Zachriat and Kroner-Herwig 2004). In other chronic disorders, like irritable bowel syndrome, chronic fatigue syndrome (Deary et al. 2007), and chronic pain disorder (Gatchel et al. 2007), psychological mechanisms, predicting or promoting dysfunctional responses to symptoms, have similarly shown to be significant predictors of suffering (Crombez et al. 1999; Rief and Broadbent 2007).

8.7.1 Tinnitus Severity in Terms of Distress

Tinnitus severity can be defined as a function of the level of averseness of the state tinnitus patients are in, in other words, the level of distress. As mentioned earlier, only for a small group of patients (3–8%), tinnitus is distressing and therefore disabling (Davis and Refaie 2000; Ahmad and Seidman 2004). Since distress is a term which coins the general aversive state, instruments to measure this construct usually include subdomains, which are hypothesized to be of importance for tinnitus severity. These

instruments are therefore hybrid in that they measure several concepts as a means to capture tinnitus distress. There are several instruments in use for assessing the level of severity of tinnitus complaints. In a review on disease-specific health-related quality of life (HR-QoL) instruments used to measure outcomes in tinnitus trials, six commonly used HR-QoL tinnitus instruments were identified (Kamalski et al. 2010; Meikle et al. 2007) and will be shortly described below. The instruments specifically used to measure the outcome of treatment are described in Chap. 9.

The Tinnitus Handicap Inventory (THI) (Newman et al. 1996) is an instrument that presumably measures the impact of tinnitus on a daily life. It has three subscales, functional, emotional, and catastrophic responses to the tinnitus, the second being psychological distress related. Both overall and subscale internal consistency were found to be good. The Tinnitus Questionnaire (TQ) (Hallam et al. 2004) has six predominantly distress-related domains: emotional distress, cognitive distress, intrusiveness, auditory and perceptual difficulties, sleep disturbances, and somatic complaints as a result of the tinnitus. The TQ items are internally consistent; however, the subscales lack internal consistency. The Tinnitus Reaction Questionnaire (TRQ) (Wilson et al. 1991) was intended to specifically measures distress related to tinnitus. TRQ incorporates four different domains: general distress, interference, severity, and avoidance of the tinnitus. The three questionnaires focus mainly on measuring patient's perception, on impaired individual functioning, or on specific functions as a result of tinnitus.

The Tinnitus Severity Index (TSI) (M.B. Meikle et al. 1995) was introduced as a unified measure of tinnitus severity. Two items specifically address the interference of the tinnitus in daily life activities. The Tinnitus Handicap Questionnaire (THQ) (Kuk et al. 1990; Meikle et al. 1995) was intended to measure patient's perceived degree of handicap due to tinnitus. The THQ has three domains: physical health/emotional status/social consequences, hearing and communication, and personal viewpoint on tinnitus. Seven items specifically address the interference of tinnitus on the daily activities: four of them address hearing difficulties, two address social interactions, and one item addresses sleep difficulties due to tinnitus. The THQ subscales fails on internal consistency.

The Tinnitus Severity Questionnaire (TSQ) (Coles et al. 1991) is a short unified measure, with two items specifically addressing interference of tinnitus, one item regarding sleeping habits and one the impairment of concentration.

More recently, the Tinnitus Functional Index (TFI) was introduced as a new measure for scaling the severity and negative impact of tinnitus, both for use in diagnostic assessment and for measuring treatment-related changes in tinnitus (responsiveness) (M. B. Meikle et al. 2012; Henry et al. 2014). What is unique about this instrument is that it is a measure of tinnitus severity as perceived "over the last week," therefore asking patients to reflect about only a short timeframe (1 week). The TFI is also a hybrid, measuring tinnitus-related distress/severity as a function of predominantly psychological construct such as attention, worry, anxiety, and depression as well as the more functional constructs such as hearing, social life, and activity level. Table 8.1 lists these seven instruments along with their characteristics and psychometric quality.

The above mentioned psychometric instruments were developed to assess tinnitus suffering or burden for clinical diagnostic purposes and are commonly used to evaluate clinical trials in tinnitus research. All of the seven instruments incorporate

Table 8.1 Characteristics and psychometrics of existing tinnitus HR-QoL instruments

Instrument	Items	Scoring	Construct validity	Reliability (test-retest)	Subscales
Tinnitus Handicap Inventory (THI)	25	(0) Never (2) Sometimes (4) Yes	+	+	Functional, emotional, catastrophic responses
Tinnitus Questionnaire (TQ)	52	True Partly true Not true	=/− Subscales not reliably tested, therefore invalid	+	Emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance, somatic complaints
Tinnitus Reaction Questionnaire (TRQ)	26	(0) Not at all (4) Almost	+	+	General distress, interference, severity, avoidance
Tinnitus Severity Index (TSI)	12	(0) Never (4) Always	_	+	None
Tinnitus Handicap Questionnaire (THQ)	27	(0) Strongly disagree (100) Strongly agree	+	+	Physical health/ emotional Status/social consequences, hearing and communication, personal viewpoint
Tinnitus Severity Questionnaire (TSQ)	10	(0) Not affected (4) Always affected	_	_	None
Tinnitus Functional Index (TSQ)	25	(0) Not affected (10) Always affected	+	+	None

items assessing psychological distress resulting from tinnitus. Items about hearing difficulties, social interactions, and sleep quality are included as well. Three of the six specifically address the interference of tinnitus on the specific daily life activities. Interestingly, an assessment of the tinnitus interference with specific daily life activities without the confounding of psychological distress/dysfunction is less common. The question as to which domains are usually addressed when assessing tinnitus severity as an outcome measure in clinical trials has been recently investigated in a systematic review (Hall et al. 2016) and in Chap. 9.

8.7.2 Tinnitus Distress: The Psychological Constructs

Psychometric instruments described below assess the psychological constructs of importance as predictors for tinnitus-related distress and typically used when providing CBT for tinnitus. These instruments have all been used in previous research and have been clinically tested. They serve as examples to be used for psychological

screening purposes, to measure treatment effects, as well as to monitor changes in psychological distress over time.

8.7.2.1 Measuring Tinnitus Catastrophizing

In the context of the FA model, catastrophic (mis)interpretations of the tinnitus signal trigger a cycle that leads to elevated levels of fear. Fear of tinnitus may lead to safety behaviors, which in the long run increase interference in daily life activities and result in severe disability. The Tinnitus Catastrophizing Scale (TCS) was developed to assess the level of overly negative (catastrophic) misinterpretations of the tinnitus. The TCS, a modification of the Pain Catastrophizing Scale (Sullivan et al. 1995), is a 13-item self-report measure that allows respondents to indicate the extent to which a series of statements applies to them on a five-point Likert scale as follows: *0 = not at all*, *1 = to a small extent*, *2 = to some extent*, *3 = to a large extent*, and *4 = always.* The TCS is a reliable and valid measure to assess the extent to which people catastrophically misinterpret tinnitus perceptions. The TCS is a unitary measure, and evidence indicates that catastrophizing about tinnitus is a strong predictor of daily interference (Cima et al. 2011a). The TCS is sensitive and responsive over time (Cima et al. 2012) and has good test-test reliability. See Appendix 1.

Weise and colleagues (2008) used the subscale "catastrophizing" (H. Flor et al. 1993) included in the pain-related self-statements scale (Flor et al. 1993). This subscale was adapted to fit the tinnitus population, has nine items, assesses situation-specific catastrophic cognitions, and has been used in other studies (Flor et al. 2004).

8.7.2.2 Measuring Tinnitus-Related Fear

The FA model applied to tinnitus proposes that in people with bothersome tinnitus, fear of tinnitus is a product of catastrophic interpretations of the tinnitus sound and that it subsequently leads to safety behaviors that are not functional in the long term and contribute to sustained impairment and distress. Items for the fear of Tinnitus Questionnaire (FTQ) were derived from the Tampa Scale for Kinesiophobia (Jeffrey Roelofs et al. 2011) and the Pain Anxiety Symptom Scale (Mccracken et al. 1992), two commonly used measures of fear used in pain research. The TFQ is a reliable and valid measure for assessing fear of tinnitus (Cima et al. 2011a), proved to be an excellent predictor of tinnitus-related distress, is sensitive and responsive over time (Cima et al. 2012), and has good test-test reliability. See Appendix 2.

8.7.2.3 Measuring Increased Awareness of Tinnitus

The Tinnitus Vigilance and Awareness Questionnaire (TVAQ) has 18 items and is based on the 16-item Pain Vigilance and Awareness Questionnaire (PVAQ) (Roelofs et al. 2003). Items 2, 3, 4, 6, 7, 8, 9, 10, 13, and 14 are PVAQ items, in which the word "pain" was substituted with the word "tinnitus." The remaining items were believed to capture amplified awareness of tinnitus. Items are to be rated on a six-point scale (0 = never, 5 = always). The TVAQ is still an experimental instrument though it has already been tested on tinnitus patients (Bånkestad 2012; Cima et al. 2011a; Nascimento 2015). See Appendix 3.

8.7.2.4 Measuring Tinnitus Avoidance

Recently, a Tinnitus Fear-Avoidance Cognitions and Behaviors Scale (T-FAS) was developed and validated (Kleinstauber et al. 2013). The 15-item T-FAS aims at assessing the levels of fear-related avoidance behavior and catastrophizing cognitions in individuals with chronic tinnitus on three subscales: catastrophizing about tinnitus, fear-related avoidance of activities that might damage hearing and avoidance of activities, and situations that might amplify tinnitus. Each item is rated on a six-point Likert scale indicating the degree of agreement (1 = strongly disagree, 2 = disagree, 3 = somewhat disagree, 4 = somewhat agree, 5 = agree, 6 = strongly agree). High scores indicate a high level of fear-avoidance cognitions and behaviors. The T-FAS has good psychometric properties.

8.7.2.5 Measuring Tinnitus Acceptance

Tinnitus acceptance can be conceptualized as the opposite of tinnitus avoidance, since acceptance or, more specifically, psychological acceptance has been defined as the active perception of sensations, cognitive processes, and emotions, without trying to control, change, or avoid them (Hayes et al. 1996). The Tinnitus Acceptance Questionnaire (TAQ) is a 12-item instrument based on the Chronic Pain Acceptance Questionnaire (McCracken et al. 2004) and the Acceptance and Action Questionnaire (Hayes et al. 2004). Items in the forms of statements are scored on a seven-point Likert scale (0 = never true to 6 = always true) and have two subscales: activities engagement and tinnitus suppression (Weise et al. 2013; Westin et al. 2008a). The TAQ has good psychometric properties. The higher the TAQ scores, the lower the tinnitus-related disability and distress.

8.7.2.6 Measuring Tinnitus-Related Disability

Only three of seven so-called health-related quality of life (HR-QoL)-related instruments (summarized above) specifically address the interference of tinnitus with specific daily life activities. An assessment of the interference of tinnitus with specific daily life activities without the confounding of emotional, physical, or attentional dysfunctioning is the Tinnitus Disability Index (TDI). The TDI is a reliable and valid measure for assessing tinnitus-related disability. A principal component analysis revealed a single factor. TDI scores are significantly associated with general health status and ratings of tinnitus distress. Moreover, TDI has the advantage of not being confounded by tinnitus-related distress and tinnitus severity (Cima et al. 2011b). See Appendix 4.

8.8 Take-Home Messages

To serve the purpose of this chapter, the term *distress* was introduced as the operationalization of the term *stress*, within the context of clinical tinnitus treatments. The main points that have been discussed in the previous sections will be highlighted shortly below.

The concepts of *stress* and *distress*

- *Stress* was defined as the internal stressful state, and the subsequent responses can be induced by either positive or negative events (stressors). This stress response might even be considered adaptive and not unequivocally considered or perceived to be negative or unwanted.
- *Distress* was defined as the negative and aversive state when processes of adaptation have failed; in other words *distress* happens when the organism fails to assimilate to stressors and experiencing *distress* is therefore intrinsically maladaptive and unwanted.

In case of suffering, tinnitus-related *distress*, as opposed to the more general term stress, was decided to be the more appropriate point of focus when describing treatment avenues.

The psychological nature of tinnitus suffering

Tinnitus can be defined in terms of acoustical characteristics, damage to the ear and brain, or malfunctioning or deficient physiological functioning and/or processes, when addressing tinnitus distress. By definition, this distress is predicted by psychological reactivity of the patient, which are:

- Cognitive functions (attention, memory, interpretation, or attribution)
- Emotional states or reactivity (fear, anxiousness, depression)
- Behavioral responses (task interference, avoidance, and escape tendencies)

These psychological factors are of most value when predicting overall well-being (perceived disability, quality of life, social involvement) in tinnitus patients and are therefore mostly the target of tinnitus treatment strategies aiming to decrease tinnitus-related distress.

The main theoretical models of tinnitus distress

Cognitive approach	
Neurophysiological model	*Main hypothesis* Tinnitus is a dysfunction on the levels of detection (of the signal) and the perception/evaluation of this signal This assumption is based on the two main fundamentals of brain function in general: plasticity and habituation
Hallam's habituation model	*Main hypothesis* Malfunctioning attentional processes disturb habituation.
McKenna's cognitive model	*Main hypothesis* Cognitive appraisal of the tinnitus signal and selective attention distort the tinnitus perception
Cognitive behavioral approach	
Fear-avoidance model	*Main hypothesis* Safety behaviors, negatively reinforced in the short term (instant temporary decrease in fear), maintain tinnitus complaints in the long run (maintenance of underlying fear)

The main treatments

Tinnitus retraining therapy

Two main components

- Cognitive therapy, "retraining counselling" (or "teaching"): patients are verbally instructed how to reinterpret the tinnitus, thereby decreasing negative thoughts and beliefs about it.
- Sound therapy: either instructing the patient to wear tinnitus maskers[2] or to enrich sound environment, avoiding silence at all costs.

Cognitive therapy

Therapeutic "talking" interventions aim at changing maladaptive cognitions in order to change the emotional consequences, which next to educational counselling include but are not limited to "Socratic dialog," thought control, rational thought formulation, exploring automatic thoughts, and testing of thoughts and beliefs through behavioral experiments.

Cognitive behavioral therapy

Includes third-wave forms of therapy to benefit *exposure* therapy for tinnitus:

Exposure to tinnitus sound, to the interceptive sensations associated with the tinnitus, as well as patients' moment-to-moment narrative, quiet circumstances. Exposure leads to a neutralization of tinnitus by extinction of tinnitus-related fears; consequently the tinnitus becomes less distressing.

Classical learning theory terms: patients are exposed to the conditioned stimulus (tinnitus sound), without the unconditioned stimulus (aversive interceptive states) always occurring; as a result, extinction of the unwanted conditioned responses (fear and avoidance) occurs.

The assessment of distress-related tinnitus variables	
Distress/severity: General measures of severity which are mostly hybrid, since they are intended to capture the multifaceted nature of tinnitus distress	
THI	Tinnitus Handicap Inventory
TQ	Tinnitus Questionnaire
TRQ	Tinnitus Reaction Questionnaire
TSI	Tinnitus Severity Index
THQ	Tinnitus Handicap Questionnaire
TSQ	Tinnitus Severity Questionnaire
TFI	Tinnitus Functional Index
Psychological mechanisms: instruments designed to assess the specific psychological domains which are considered predictive for tinnitus distress/severity	
TCS	Tinnitus Catastrophizing Scale
FTQ	Fear of Tinnitus Questionnaire
TVAQ	Tinnitus Vigilance and Awareness Questionnaire
PVAQ	Pain Vigilance and Awareness Questionnaire
T-FAS	Tinnitus Fear-Avoidance Scale
TAQ	Tinnitus Acceptance Questionnaire
TDI	Tinnitus Disability Index

[2] Tinnitus maskers are ear-level devices (much like a hearing aid) which generate a "neutral" sound. It is emphasized that the tinnitus itself should remain audible when using the maskers.

Effective management of tinnitus-related distress has been a difficult assignment requiring a multitude of disciplines and usually prolonged fragmented trajectories (Cima et al. 2012; Greimel et al. 1999; J. A. Henry and Meikle 2000; Hoare et al. 2012). As the psychological correlates of tinnitus (i.e., emotional, cognitive, and attentional) influence the tinnitus suffering, cognitive behavioral therapy (CBT) treatment elements have been increasingly incorporated in tinnitus management (Andersson et al. 2000; Andersson and Lyttkens 1999; H. Hesser et al. 2011; Martinez Devesa et al. 2007). Next to these CBT approaches, other therapies aimed at decreasing the acoustic characteristics of tinnitus, such as tinnitus masking therapy (TM) or tinnitus retraining therapy (TRT), are offered widely as well. These sound-based approaches aim to ameliorate tinnitus distress by means of education, counselling, and exposure to a neutral external sound, by the use of a sound-generating device, based on a specific protocol (Henry et al. 2005a, b; Jastreboff 1999; Jastreboff and Hazell 1993; Schechter and Henry 2002).

Throughout the literature dealing with tinnitus management, it is hard to find either CBT or sound-based approaches as a sole treatment. In order to effectively manage complex tinnitus problems, multimodal treatment packages usually consisting of a mixture of treatment approaches, combining counselling, sound therapy, and additional CBT approaches, have been proposed to effectively reduce the impact of the tinnitus on functioning (Asmundson et al. 2007, 2008). However, none of the above approaches have led to the implementation of **one specific treatment strategy on a large scale**. Moreover, studies of sufficient methodological quality generating comparable outcomes have been scarce (Cima et al. 2009; Hoare et al. 2012), thereby unfavorably leaving patients and professionals alike with a myriad of options and combinations of treatment approaches.

Next to the highly diversified treatment approaches, many different outcome measures and clinical assessment batteries can be found, whether it concerns audiometry, severity, intensity, acoustic properties, daily life impact, or psychological distress associated with tinnitus, leading to difficulties in reaching consensus and in comparable research outcomes (Hoare et al. 2011).

In an evaluation of contemporary tinnitus management in the United Kingdom (Hoare et al. 2012), this lack of standardized practice and consensus in tinnitus services was clearly illustrated as leading to difficulties in determination of key factors for best practice, establishing quality of care, problems in equal access to care for patients, and limited translational research outcomes. Evidence is accumulating that other countries are having comparable issues. All these problems are currently addressed by a group of tinnitus specialists (including researchers, clinicians, and patients), who try to establish **consensus on assessment, treatment, and referral paths for all tinnitus patients** (http://tinnet.tinnitusresearch.net/).

Appendix 1

Tinnitus Catastrophizing Scale (TCS)

We are interested in your thoughts en feelings when experiencing tinnitus. With this questionnaire we want to investigate what influence tinnitus has on you; on your mood, your behaviour, your attitude. Below you can find 13 statements describing different thoughts and feelings which might be related to your tinnitus. Please try to indicate to what extent these thought or feelings apply to you by using the following rating scale: *0 = Not at all; 1 = to a small extent; 2 = to some extent; 3 = to a large extent; 4 = Always*

If I experience Tinnitus …

☐… I worry all the time about whether the tinnitus will end
☐… I feel I can't go on
☐… It's terrible and I think it's never going to get any better
☐… It's awful and I feel it overwhelms me
☐… I feel I can't stand it anymore
☐… I become afraid the tinnitus will get worse
☐… I keep thinking about other times I experienced tinnitus
☐… I anxiously want the tinnitus to go away
☐… I can't seem to keep it out of my mind
☐… I keep thinking about how strong my tinnitus is
☐… I keep thinking about how badly I want the tinnitus to stop
☐… There is nothing I can do to reduce the intensity of the tinnitus
☐… I wonder whether something serious may happen

Appendix 2

Fear of Tinnitus Questionnaire (FTQ)

This questionnaire will help us understand how you think and feel about your tinnitus condition. It enables us to examine how tinnitus affects you, what effect is has on your mood, your behaviour, your attitude. Below you will find 17 statements. Please check the box next to each statement that you think applies to your current situation.

☐	**1**	I am afraid that my tinnitus will deteriorate my hearing
☐	**2**	I am afraid that my tinnitus will become worse
☐	**3**	I fear that my tinnitus is the result of a tumour
☐	**4**	Even though my tinnitus is getting worse, I do not think it points to a serious disease
☐	**5**	I am afraid that my tinnitus will drive me crazy
☐	**6**	The fact that I have tinnitus does not mean that my health is at risk
☐	**7**	I am afraid my tinnitus will leave me deaf
☐	**8**	I am afraid the moment will come that my head cannot withstand tinnitus anymore
☐	**9**	My mental condition will become severely affected by my tinnitus
☐	**10**	I am afraid that tinnitus will stop me from ever having a normal life again
☐	**11**	I am afraid that I will never be able to experience silence again because of tinnitus
☐	**12**	I am afraid that loud noises will aggravate my tinnitus
☐	**13**	I am afraid I will not be able to do anything anymore because of my tinnitus
☐	**14**	It worries me to think I may never be able to learn how to cope with this condition
☐	**15**	It would be terrible if my tinnitus proved a life-long condition
☐	**16**	I am concerned that tinnitus may be a risk to my physical health
☐	**17**	I am afraid that tinnitus may be a preliminary sign of brain haemorrhage or similar

Appendix 3

Tinnitus Vigilance and Awareness Questionnaire (TVAQ)

Below you find 18 sentences describing how people react on their tinnitus. . With this questionnaire we want to investigate what influence tinnitus has on you; on your mood, your behaviour, your attitude. Please indicate how often a statement applies to you by circling a number between 0 (never) and 5 (always).

		Never					Always
1	I am very aware of changes in my tinnitus	**0**	**1**	**2**	**3**	**4**	**5**
2	I am quick to notice changes in the intensity of my tinnitus	**0**	**1**	**2**	**3**	**4**	**5**
3	I am quick to notice the effects of medication on my tinnitus	**0**	**1**	**2**	**3**	**4**	**5**
4	I am quick to notice changes in sound or intensity of my tinnitus	**0**	**1**	**2**	**3**	**4**	**5**
5	The tinnitus keeps me constantly occupied	**0**	**1**	**2**	**3**	**4**	**5**
6	I notice the tinnitus even if I am busy with another activity	**0**	**1**	**2**	**3**	**4**	**5**
7	I find it easy to ignore my tinnitus	**0**	**1**	**2**	**3**	**4**	**5**
8	I know immediately when my tinnitus starts or increases	**0**	**1**	**2**	**3**	**4**	**5**
9	When I do something that increases my tinnitus, the first thing I do is check to see how much my tinnitus was increased	**0**	**1**	**2**	**3**	**4**	**5**
10	I know immediately when my tinnitus decreases	**0**	**1**	**2**	**3**	**4**	**5**
11	I must attend to my tinnitus a lot	**0**	**1**	**2**	**3**	**4**	**5**
12	I carefully monitor how intense my tinnitus is	**0**	**1**	**2**	**3**	**4**	**5**
13	I become preoccupied with my tinnitus	**0**	**1**	**2**	**3**	**4**	**5**
14	I do not dwell on my tinnitus	**0**	**1**	**2**	**3**	**4**	**5**
15	Sometimes I'm able to ignore the tinnitus, even if it is present	**0**	**1**	**2**	**3**	**4**	**5**
16	I am aware of my tinnitus from the moment I get up till the moment I go to sleep	**0**	**1**	**2**	**3**	**4**	**5**
17	The tinnitus distracts me, no matter what I do	**0**	**1**	**2**	**3**	**4**	**5**
18	Often, my tinnitus is so bad that I cannot ignore it	**0**	**1**	**2**	**3**	**4**	**5**

Appendix 4

Tinnitus Disability Index

The rating scales below are designed to measure the degree to which several aspects of your life are presently disrupted by the tinnitus. In other words, we would like to know how much the tinnitus is preventing you from doing what you normally do, or from doing it as well as you normally would. Respond to each category by indicating the overall impact of the tinnitus in your life, not just when the tinnitus is at its worst.

For each of the 7 categories of life activity listed, please circle the number on the scale which describes the level of disability you typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your tinnitus.

1. Family/home responsibilities

This category refers to activities related to the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favours for other family members (e.g. driving the children to school).

0	1	2	3	4	5	6	7	8	9	10
No disability										Total disability

2. Recreation

This category includes hobbies, sports, and other similar leisure time activities.

0	1	2	3	4	5	6	7	8	9	10
No disability										Total disability

3. Social activity

This category refers to activities which involve participation with friends and acquaintances other than family members. It includes parties, theatre, concerts, dining out, and other social functions.

0	1	2	3	4	5	6	7	8	9	10
No disability										Total disability

4. Occupation

This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or a volunteer worker.

0	1	2	3	4	5	6	7	8	9	10
No disability										Total disability

5. Sexual behaviour

This category refers to the frequency and quality of one's sex life.

0	1	2	3	4	5	6	7	8	9	10
No disability										Total disability

6. Self-care

This category includes activities which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed, etc.).

0	1	2	3	4	5	6	7	8	9	10
No disability										Total disability

7. Life-support activity

This category refers to basic life-supporting behaviours such as eating, sleeping and breathing.

0	1	2	3	4	5	6	7	8	9	10
No disability										Total disability

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Outcome Measures Associated with Perceived Stress

9

Deborah Ann Hall

Abbreviations

ACT	Acceptance and commitment therapy
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CBT	Cognitive behaviour therapy
DSM	Diagnostic and Statistical Manual for Mental Disorders
HADS	Hospital Anxiety and Depression Scale
PROM	Patient-Reported Outcome Measure
PSQ	Perceived Stress Questionnaire
PSS	Perceived Stress Scale
STAI	State-Trait Anxiety Inventory
TRQ	Tinnitus Reaction Questionnaire
TRT	Tinnitus retraining therapy

9.1 Clinical Trial Designs

This chapter describes a number of outcome measures associated with the perceived stress experienced by people with tinnitus and that are used in clinical research. Such measures are used to determine whether an intervention aimed at alleviating tinnitus leads to a meaningful patient benefit. The choice of outcome is one of the

D.A. Hall
National Institute for Health Research Nottingham Biomedical Research Centre, Nottingham, UK

Otology and Hearing Group, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, UK
e-mail: deborah.hall@nottingham.ac.uk

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most important fundamental aspects of clinical trial design, but that choice is often driven by the type of clinical trial, in particular whether it is an explanatory or a pragmatic trial (see Tutorial 9.1).

The choice of outcome is one of the most important fundamental aspects of clinical trial design.

Types of clinical trial designs are broadly outlined in Tutorial 9.1. Feasibility and pilot trials typically answer questions about the process and procedures of how a trial might be run, but they don't directly test patient benefit. Explanatory and pragmatic trials do. Explanatory trials are most common in the tinnitus field. They typically answer the question about whether a particular treatment for tinnitus works 'under ideal conditions'. For these trials, outcomes are often condition-specific. A good example of this would be the measurement of the perceived stress associated with tinnitus. Pragmatic trials are broader in scope since they typically answer the question about whether a particular treatment for tinnitus works in everyday clinical practice. For these trials, outcomes tend not to be restricted to any single health condition. Good examples of this would be the measurement of general perceived stress, generalised anxiety or depressive symptoms, or even health-related quality of life.

Tutorial 9.1 Clinical Trial Designs

Clinical trial designs typically fall into four broad levels or categories (Arain et al. 2010; Williams et al. 2015):

Feasibility. A feasibility study tries out pieces of an explanatory clinical trial in order to answer the question about whether that main study can be done. Feasibility is used to test important parameters that are needed to design the main study: (1) scientific basis, (2) process, (3) resources and (4) management.

Pilot. A pilot study is a 'miniature' version of the main study that is run to test whether the components of the main study can all work together. Unlike a feasibility study, a pilot resembles the main study in many respects, including an assessment of the primary outcome. However, hypothesis testing is considered inappropriate because a pilot tends to be underpowered.

Other terms for feasibility and pilot trials are 'proof of concept' or 'Phase I' trials.

Explanatory. An explanatory trial typically answers the question 'can this treatment work under ideal conditions?' It is deliberately designed to give the maximum chance of showing an effect, if one is present. For example, the sample is often a highly selected and homogenous group exhibiting good compliance, the intervention is tightly defined, the comparator may be a

placebo, outcomes are often condition-specific and may include biomarkers as well as condition-specific questionnaires, and the study end point tends to be short term (e.g. 6 weeks).

Pragmatic. A pragmatic trial typically answers the question 'we now know the intervention can work, but how well does it work in everyday clinical practice?' The design aims to test an intervention in a study environment that is closer to real life in terms of sample, intervention, active comparator and outcomes. Outcomes are generic rather than specific and often quality of life questionnaires. Another aim of a pragmatic trial is to ensure that the intervention can be implemented in routine healthcare settings and that the primary outcome is clinically important and easily understood by a range of users, including clinicians, patients, policy makers and health commissioners. The study end point tends to be longer term (e.g. 6 months).

9.2 Definition of Perceived Stress

General situations in life are appraised as stressful when they are unpredictable, uncontrollable or overloading. In the context of this chapter, perceived stress reflects the experienced level of stress as a function of objective stressful events, coping processes and personality factors (Cohen et al. 1983). This perspective is based on Lazarus's (1966) transactional model of stress which argues that the experience of a stressor is influenced by evaluations on the part of the person as to how well they can manage a stressor given their coping resources.

Stress therefore specifically refers to the subjective components of stress. There is an overlap in the operational definitions of perceived stress and the symptomatology of anxiety and depression. Stress can be manifest in a variety of patient-reported complaints about tinnitus and include the person's emotional state, physical state, their performance and behaviours in everyday life, relationships with others and overall quality of life. **Stress-related outcome** directly refers to one of these domains of complaint. It is important to acknowledge that there are physiological characteristics of stress, such as biomarkers like pupillary dilation and salivary cortisol and amylase. These have rarely been used in explanatory or pragmatic trials of tinnitus interventions and so are not considered further. Another term used throughout this chapter is **stress-related outcome instrument**. This refers to the way in which a stress-related outcome is measured or quantified. Instruments relating to perceived stress are typically questionnaires made up of a number of items. On each item, the person is asked to rate the frequency or severity of a complaint, or the degree to which he/she agrees or disagrees with a statement. Such instruments are sometimes called Patient-Reported Outcome Measures (PROMS). PROMS are important for measuring and improving the quality of patient care.

9.3 Patient-Reported Complaints About Tinnitus

For some people with tinnitus, their experience way exceeds the perception of a sound inside the head or ears and causes problems in daily life such as sleep disturbance, difficulties concentrating, and poor psychological well-being (Tyler and Baker 1983; Jakes et al. 1985), ultimately impairing overall quality of life. For counselling purposes during clinical management, it may be informative to identify perceptual attributes of the tinnitus (e.g. pitch and loudness). However, it is more clinically meaningful to identify the symptoms and functional impacts for each individual patient since these are most likely to determine joint decision-making about preferred management options (Henry et al. 2005).

Patient-reported complaints about tinnitus are many and varied. Some of the most influential studies to identify patient-reported complaints of tinnitus were those published before the advent of any tinnitus-related questionnaire measures. Two studies (Tyler and Baker 1983; Jakes et al. 1985) are worthy of note because they have informed decisions about the construction of many of the tinnitus-related questionnaires that have followed. Decisions informed by these data have been the choice of questionnaire subscales, empirical support for their validity to patients (content validity), as well as the selection and wording of individual questionnaire items. I also summarise findings from a third study which is more contemporary, but nevertheless addresses the same issue. Coincidentally, all three studies just so happen to have been conducted in the UK.

The first is a patient-centred study published in 1983 by Tyler and Baker. Data were collected from 72 people who were members of a tinnitus self-help group. People were asked to list the difficulties that they had as a result of their tinnitus. Instructions were 'Please make a list of the difficulties which you have as a result of your tinnitus. List them in order of importance, starting with the biggest difficulties. Write down as many of them as you can' p. 150. Respondents reported between one and 13 complaints. Subjective evaluation of the free-text response data demonstrated the diversity of tinnitus complaints. Four thematic categories were described: (1) effects of hearing (e.g. understanding speech, appreciation of music and localising sounds), (2) effects on lifestyle (e.g. getting to sleep, family problems and avoiding quiet situations), (3) effects on general health/healthcare (e.g. pain/headaches, tiredness and giddiness/imbalance/fuzzy head) and (4) emotional problems (e.g. concentration/confusion, despair/frustration/depression and annoyance/irritation/inability to relax).

The second is a patient-centred study published in 1985 by Jakes and colleagues. Data were collected from 82 patients who attended a neuro-otology clinic and whose main presenting symptom was tinnitus. Patients were asked to

complete a questionnaire concerning 19 different features of tinnitus and other symptoms. These were presented as closed questions requiring a rating of the frequency or severity, according to predefined descriptors given by the authors. Illustrative examples are (1) 'I find the noises are now/bearable/unbearable' and (2) 'The noises are affecting me to the extent that I am now/not depressed/somewhat depressed/extremely depressed'. The authors also collected audiometric data about the hearing status of all patients. Statistical analysis of the quantitative response data using factor analysis confirmed the multifactorial nature of tinnitus complaints. Eleven factors explained 86% of the variance. These categories were (1) hearing loss, (2) tinnitus-related distress, (3) intrusiveness of tinnitus, (4) interference on music and TV, (5) tinnitus loudness, (6) sleep disturbance, (7) vertigo, (8) use of medication, (9) impact on work, (10) bilaterality of tinnitus and (11) auditory thresholds, in descending order of percentage variance explained.

Our team in Nottingham has conducted a contemporary assessment of the same issue, but using a much larger clinical sample (Watts et al. 2016). Through collaboration with Jacqueline Sheldrake, we had the good fortune to obtain anonymised clinical interview data from 988 patients whom attended the Tinnitus and Hyperacusis Centre (London, UK) between 1989 and 2014. All patients answered the open-ended question 'Why is tinnitus a problem?' Thematic analysis was used to code and collate individual responses into groups or themes according to the domain of the patient-reported problem. Complaints covered the person's emotional state, physical state, their performance and behaviours in everyday life, relationships with others and overall quality of life. Each domain included only those responses that were judged to relate to the same theoretical construct. We can think of these domains as stress-related outcomes that are relevant to tinnitus. Overall, the free-text response data indicated 18 distinct domains of tinnitus-associated complaints. The domains 'tinnitus-related fear' and 'constant awareness' had the highest number of mentions by individual participants indicating that it was a very frequent complaint. The top five also included 'loss of quiet', 'annoyance' and 'effects on quality of life'. Many of the 18 domains were those identified in the two previous studies. However, four particular domains were not highlighted by the two prior studies. These were (1) 'feeling deficient because of tinnitus', (2) 'sense of loss of control', (3) 'concerned by lack of knowledge about what tinnitus is' and (4) 'loss of sense of self'.

The number and diversity of patient-reported complaints about tinnitus are illustrated in Fig. 9.1, encircled within the green box. These examples have been collated from those patient responses reported by the above three independent pieces of research.

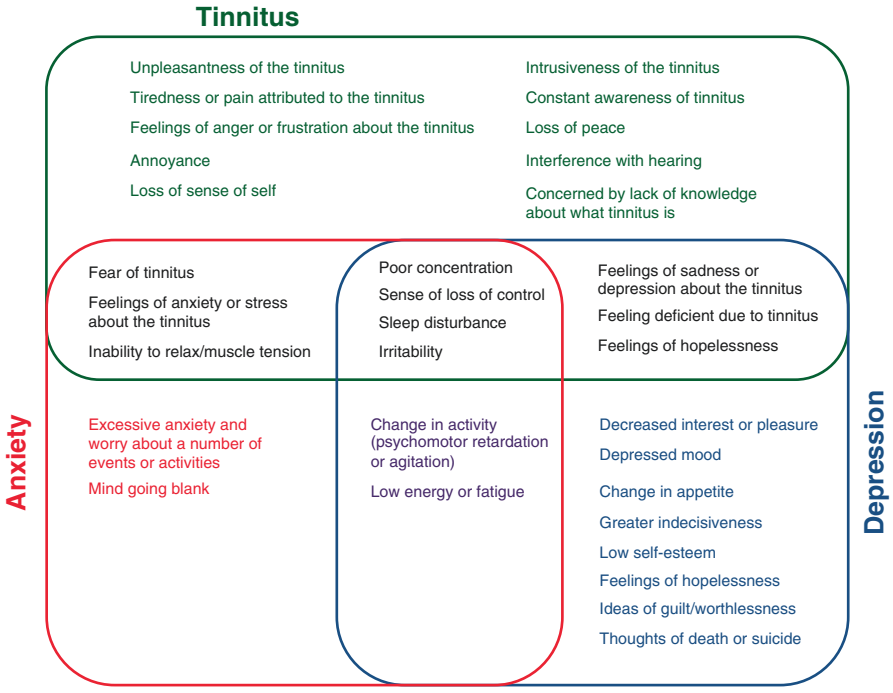

Fig. 9.1 Correspondence between patient-reported symptoms of tinnitus and the diagnostic symptoms of anxiety and depression. Symptoms of tinnitus are based on a qualitative analysis of patient-reported complaints collated by Watts et al. (2016) and Tyler and Baker (1983). Mental health symptoms are based on DSM-5 criteria for generalised anxiety and persistent and major depression (American Psychiatric Association 2013). Functional impacts that impair quality of life are not included here, but are common to all conditions. These impacts include but are not restricted to avoidance behaviours, reduced social participation and negative effect on work

9.4 Measuring Perceived Stress Associated with Tinnitus

The Tinnitus Reaction Questionnaire (TRQ) was constructed in Australia in 1991. It was designed specifically to measure a single attribute of tinnitus: the perceived stress related to tinnitus (Wilson et al. 1991). The TRQ selectively measures perceived stress associated with tinnitus. It has 26 items which all start off with the phrase 'My tinnitus has…' (see Fig. 9.2 for examples). Ratings for each item are made on a 5-point Likert scale (scored 0–4) with the category labels (not at all/a little of the time/a good deal of the time/almost all of the time). Scoring involves the simple addition of the category score selected by the respondent. This gives a range of scores from 0 to 104, with a high score representing greater distress. There is very little literature on the psychometric properties of the TRQ. Although Wilson et al. (1991) describe four factors resulting from their factor analysis (general distress, interference, severe distress, avoidance behaviours), the statistical outputs from the

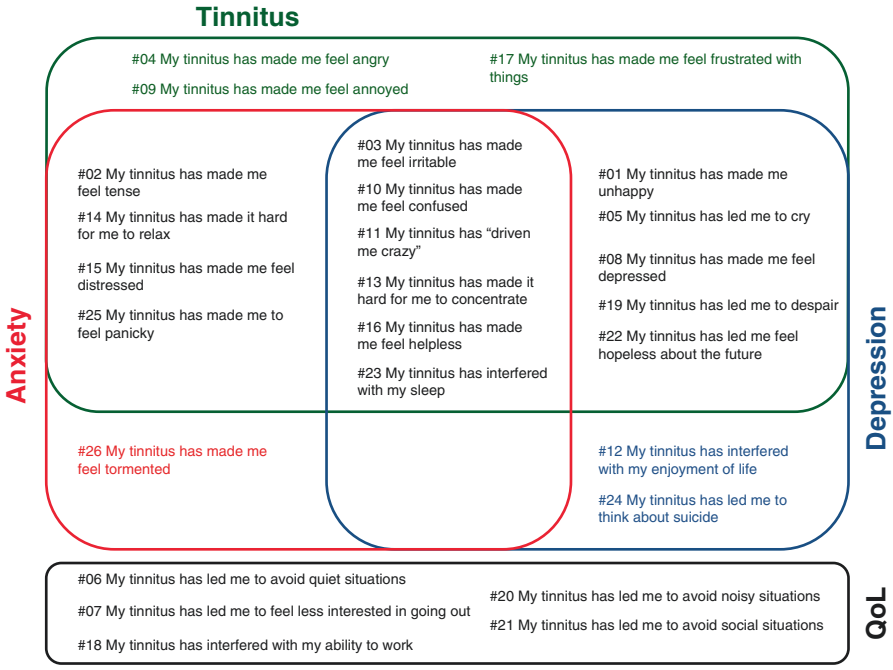

Fig. 9.2 Items taken from the Tinnitus Reaction Questionnaire (Wilson et al. 1991) and mapped onto the symptoms of tinnitus and the symptoms of anxiety and depression. Symptoms of tinnitus are based on Watts et al. (2016) and Tyler and Baker (1983). Mental health symptoms are based on DSM-5 criteria for generalised anxiety and persistent and major depression (American Psychiatric Association 2013). Functional impacts are not included here, but are common to all conditions. These impacts include but are not restricted to avoidance behaviours, reduced social participation, negative effect on work and impaired quality of life

factor analysis show that most of these items are very closely related to one another. So there is little value in treating this questionnaire as if it has multiple subscales. A single global score is adequate.

If a questionnaire looks like it is going to measure what it is supposed to measure, then it has what is termed 'face validity'. To assess the face validity of the TRQ, Fig. 9.2 illustrates how the 26 items map onto the framework of stress-related complaints already presented in Fig. 9.1. The wording of each item was carefully evaluated for its meaning, and it was ascertained whether it would fit within one of the symptom domains. Only 3 of the 26 items appear to be restricted to tinnitus-related stress (#04 My tinnitus has made me feel angry, #09 My tinnitus has made me feel annoyed, #17 My tinnitus has made me feel frustrated with things). Section 8.5 considers how many of the remaining tinnitus-related complaints share characteristics with impaired psychological well-being.

The impetus for the construction of the TRQ came from a need for a reliable measurement instrument for evaluating the effects of psychological interventions on the ability of people to cope with tinnitus (Ireland et al. 1985). Up until this point,

tinnitus-related questionnaires were purposefully broad in scope, and they included items that asked patients about a wide variety of complaints. The Tinnitus Questionnaire (Hallam et al. 1988) and the Tinnitus Handicap Questionnaire (Kuk et al. 1990) are both good examples of broad-ranging multi-attribute questionnaire instruments that were constructed before the TRQ, but they measure much more than simply perceived stress.

The Tinnitus Questionnaire has 52 items. Ratings for each item are made on a 3-point Likert scale (scored 0–2) with the category labels (true/partly true/not true). Only 41 items are scored, and the total score is scaled so that the global score ranges from 0 to 82, with higher score indicating greater severity of tinnitus symptoms. The first assessment of the psychometric (statistical) properties of the Tinnitus Questionnaire, using factor analysis techniques, identified three orthogonal factors covering (1) emotional distress, (2) auditory difficulties and (3) sleep disturbance (Hallam et al. 1988). A later reinvestigation by Hallam in 1996 using data from a different sample of tinnitus patients identified five orthogonal factors covering (1) emotional and cognitive distress, (2) intrusiveness, (3) auditory perceptual difficulties, (4) sleep disturbance, and (5) somatic complaints. Hence, there is some uncertainty about what domains of tinnitus-related complaints are measured by the Tinnitus Questionnaire.

The Tinnitus Handicap Questionnaire has 27 items. Ratings for each item are made on a 100-point numerical scale (from 0 = strongly disagree to 100 = strongly agree). The total score is scaled so that the global score ranges from 0 to 100, with higher score indicating greater severity of tinnitus symptoms. The Tinnitus Handicap Questionnaire has three subscales covering (1) social, emotional and physical effects of tinnitus, (2) hearing ability and unease and (3) the individual's perception of tinnitus. It has been pointed out that items on the first two subscales are very closely related to one another, both in terms of the semantic content (i.e. meaning) of the items and the statistical outputs from the factor analysis (see Kennedy et al. 2004; Fackrell et al. 2014). These observations indicate that the Tinnitus Handicap Questionnaire is particularly sensitive to the social, emotional and physical functioning aspects of tinnitus-related distress, but arguably this subscale actually covers three different discrete domains.

Although this summary of tinnitus-related questionnaires is not exhaustive, it serves to highlight the general emphasis on questionnaires that measure a broad range of dimensions of tinnitus complaint. Later questionnaires are little different in this respect (e.g. Tinnitus Handicap Inventory, Newman et al. 1996). Unlike these broad-scope questionnaires, the developers of the TRQ were explicit in their aim to assess a narrow range of tinnitus characteristics. In other words, their aim was to create a single-attribute questionnaire instrument that focused on perceived stress associated with tinnitus.

Given the overlap in patient-reported complaints for tinnitus, anxiety and depressive symptoms, one should expect a high degree of association between tinnitus-related questionnaire scores and questionnaire scores for anxiety and/or

depression. Convergent validity is a term that describes the extent to which the underlying construct of one questionnaire corresponds to other questionnaire constructs that are theoretically similar. It is measured by calculating the correlation coefficients between the questionnaire scores and assessing the strength of the association. Convergent validity is indicated by a strong Pearson correlation coefficient ($r > 0.60$) (Andresen 2000). The TRQ has been examined by correlating with scores for depression and anxiety questionnaires. TRQ has strong convergent validity with the Beck Depression Inventory (BDI) (Beck et al. 1961). Wilson et al. (1991) reported correlations of $r = 0.63$ and $r = 0.87$ for two independent samples of participants, while Robinson et al. (2003) reported a correlation of 0.66. With respect to anxiety, TRQ also correlates well. Correlation coefficients reported by Wilson et al. (1991) were 0.60 and 0.74 for state anxiety and 0.58 and 0.71 for trait anxiety, as measured by the State-Trait Anxiety Inventory (STAI) (Spielberger et al. 1970). Overall, the TRQ seems to be measuring similar theoretical constructs associated with general perceived stress. These findings raise an important question about whether the TRQ measures any sufficiently distinct aspect of tinnitus-related stress that is not captured by measures of general psychological well-being.

These results set the TRQ apart from the Tinnitus Questionnaire (Hallam et al. 1988) and the Tinnitus Handicap Questionnaire (Kuk et al. 1990). For comparison, the Tinnitus Questionnaire and Tinnitus Handicap Questionnaire generally had weaker correlations: BDI ($r = 0.51$ and $r = 0.62$, respectively) and Hamilton Rating Scale for Depression (Hamilton 1960) ($r = 0.48$ and $r = 0.57$, respectively) (Robinson et al. 2003). Overall, the Tinnitus Questionnaire and Tinnitus Handicap Questionnaire may therefore be measuring different theoretical constructs. One might speculate that this difference reflects the other (non-stress) outcome domains contained within these broad-scope multi-attribute tinnitus instruments.

9.5 Associations Between Tinnitus and Psychological Well-Being

From the patient-reported complaints (Sect. 9.3), it is clear that tinnitus is associated with considerable perceived stress manifest as feelings of anxiety, sadness or depression, irritability, inability to relax, etc. These symptoms are not restricted to tinnitus. Symptom overlap in tinnitus, depression and anxiety can act as a confounder in estimating the severity of either condition. Figure 9.1 illustrates this point by mapping out the correspondence between patient-reported symptoms of tinnitus and the diagnostic symptoms of generalised anxiety and depression according to the Diagnostic and Statistical Manual for Mental Disorders (DSM) edition 5 (American Psychiatric Association 2013). Four of the patient-reported complaints reported by people with tinnitus seem common to all three conditions (poor concentration, sense of loss of control, sleep disturbance and irritability).

Three further complaints are common to tinnitus and anxiety (fear, feelings of anxiety or stress and inability to relax), and three more are common to tinnitus and depression (feelings of sadness or depression, feeling imperfect and feelings of hopelessness). This high degree of association is also seen in the construction of the TRQ. Turning to Fig. 9.2, one can see how 18 of the 26 items from the TRQ appear to map onto domains relating to general anxiety or depression (or the intersections thereof). Associations between tinnitus and psychological well-being have important implications when we turn to discuss how perceived stress is measured.

9.6 Measuring General Perceived Stress

One of the most widely used measures of stress is the Perceived Stress Scale (PSS), developed in the USA (Cohen et al. 1983). This questionnaire was designed specifically to measure global perceived stress. Up until this point, measurements of stress typically focused on objective indicators (e.g. frequencies) of specific stressors such as chronic illness, bereavement, and retirement. But this focus on external life event stressors and the cumulative minor stressors of everyday life overlooked the influence on individual's subjective interpretation of that stressor.

The PSS therefore asks questions about whether a person feels under pressure from specific worries. It has 14 items which ask individuals to rate how often they experienced particular feelings and thoughts *in the past month*. Items were designed to tap into how unpredictable, uncontrollable and overloaded people find their lives. An example item is 'In the last month, how often have you felt that you were unable to control the important things in your life?' Ratings on each item are made on a 5-point Likert scale (scored 0–4) with the category labels/never/almost never/sometimes/fairly often/very often. Seven of the items are positively worded and seven are negatively worded. The positive items are reverse scored, and then the global score is the sum across all 14 items. A high score therefore reflects a high degree of perceived stress with the global score ranging from 0 to 56.

The first major assessment of the psychometric properties of the PSS, using factor analysis techniques, identified two orthogonal factors covering (1) the negatively worded items (e.g. been upset, unable to control things, felt nervous and stressed) and (2) the positively worded items (e.g. dealt successfully with hassles, effectively coping, felt confident) (Cohen and Williamson 1988). Informed by this dataset, a shorter 10-item version was produced, and again this had the same two-factor structure.

Results for convergent validity have been usefully summarised as part of a systematic review of the psychometric properties of the PSS (Lee 2012). Overall findings support the conclusion that the questionnaire score is either moderately or strongly correlated with scores for depression and anxiety questionnaires, as measured using the BDI, Hospital Anxiety and Depression Scale (HADS) (Zigmond

and Snaith 1983), STAI, and Depression, Anxiety and Stress Scale (DASS) (Lovibond and Lovibond 1995). These findings indicate that the PSS seems to be measuring similar theoretical constructs associated with stress.

The Perceived Stress Questionnaire (PSQ) is also concerned with the cognitive appraisal about aspects of everyday life and the emotional reaction to them (Levenstein et al. 1993). Many of the questions have the format 'you feel…'. For example, 'You feel that too many demands are being made on you/You feel frustrated'. The original PSQ comprised 30 items, spanning seven factors (harassment, irritability, lack of joy, fatigue, worries, tension and overload). Ratings for each item are made on a 4-point Likert scale (scored 1–4) with the category labels/almost never/sometimes/often/usually. Raw scores are transformed into a *stress index* from 0 (lowest possible level of stress) to 1 (highest possible level of stress). Just as in the PSS, one version of the PSQ asks individuals to rate how often they experienced particular feelings and thoughts *in the past month*. A second version of the PSQ asks about events *in the past 2 years*.

The 'past month' version of the PSQ demonstrated acceptable convergent validity with the PSS ($r = 0.73$) and trait anxiety measured using the STAI ($r = 0.75$), but weaker correlations with depression ($r = 0.56$).

In 2001, the PSQ was translated into German and re-evaluated on a broad sample of participants (Fliege et al. 2001). The resulting German version has a reduced set of 20 items, covering four factors (joy, worries, tension and demands). Although the labels given to three of the factors are equivalent across languages, it is important to note that the items that correspond to the factors are different. Thus, any subscale scores should not be directly compared across the English and German versions.

The DASS (Lovibond and Lovibond 1995) is another widely used questionnaire that includes a measure of perceived stress. This questionnaire comprises 42 items covering three separate scales of stress, anxiety and depression over the past week. Each scale has 14 items. For example, one of the stress scale items is 'I found myself getting upset by quite trivial things'. Ratings for each item are made on a 4-point (scored 0–3) with the following category labels: did not apply to me at all/applied to me to some degree, or some of the time/applied to me to a considerable degree, or a good part of time/applied to me very much, or most of the time. Scores of depression, anxiety and stress are calculated by summing the scores for the relevant items and are interpreted according to five symptom severities (normal, mild, moderate, severe and extremely severe).

There is relatively little data on the DASS in tinnitus. However, one article does report questionnaire findings in a sample of 100 patients with tinnitus attending an out-patient otorhinolaryngology clinic (Gomaa et al. 2014). Severe to extremely severe stress was observed in 33% of patients. The proportion of patients with severe to extremely severe depression and anxiety was somewhat greater (51% and 54%, respectively). Figure 9.3 shows the pattern of stress, anxiety and depressive comorbidities in this sample, plotted as a function of tinnitus 'severity'. Tinnitus severity was measured using a Visual Analogue Scale.

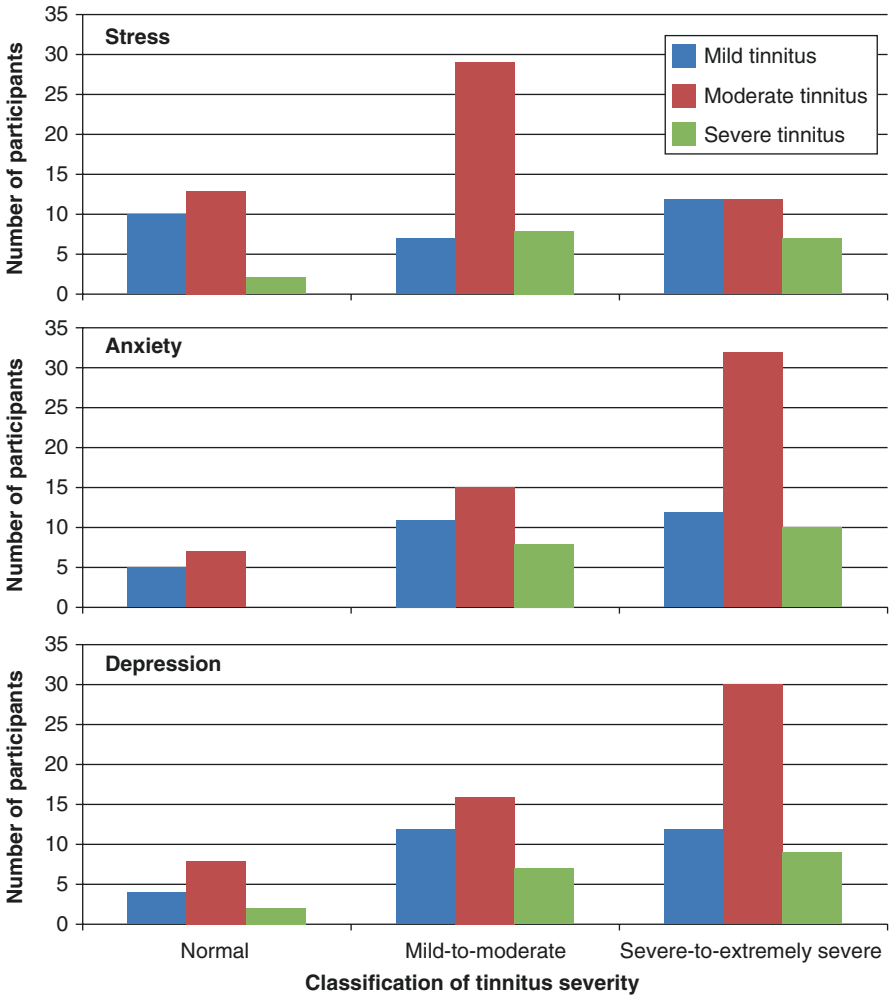

Fig. 9.3 Comparisons between level of stress, anxiety and depressive symptoms assessed in a sample of 100 tinnitus patients, using the DASS (Gomaa et al. 2014). Score classifications for the DASS are stress (normal, 0–14; mild-to-moderate, 15–25; severe-to-extremely severe, 26+), anxiety (normal, 0–7; mild-to-moderate, 8–14; severe-to-extremely severe, 15+) and depression (normal, 0–9; mild-to-moderate, 10–20; severe-to-extremely severe, 21+)

9.7 Applications of Stress-Related Questionnaire Instruments

The discussion so far has shown how patient-reported complaints have informed the construction of questionnaire instruments and has demonstrated the commonalities between complaints of tinnitus, stress, anxiety and depression. None of the issues so far concerning questionnaire construction are necessarily restricted to outcomes

used to evaluate treatment-related change. They are equally applicable to the purposes of screening, diagnosis and prognosis. However, the way that a questionnaire is constructed should be informed by the purpose for which it is intended. Tutorial 9.2 explains more about these different applications. This section considers how the intended application of each stress-related questionnaire defines what statistical properties of the instrument are most important during its creation.

Tutorial 9.2 Purpose of Questionnaires

Potential applications of such questionnaires typically fall into three broad categories (Kirschner and Guyatt 1985):

Discrimination. A discriminative tool is used to distinguish between individuals or groups, generally as part of a screening or diagnostic procedure. For example, to quantify the burden of stress on individual tinnitus patients so that healthcare provision can be tailored more effectively.

Prediction. A predictive tool is used to classify individuals into predefined categories generally as part of a screening or diagnostic procedure. For example, to identify clues to a prognosis.

Evaluation. An evaluative tool is used to measure the magnitude of change over time in an individual or group on the complaint of interest. For example, to quantify treatment benefits in clinical trials and for measuring quality-adjusted life years in cost-utility analysis.

It is not unusual for developers of tinnitus-related questionnaires to claim that theirs is a multipurpose instrument. For example, on the TRQ, Wilson et al. (1991) claimed 'such a scale may provide a useful assessment device in clinical practice and in further research on psychological aspects of tinnitus. It may be useful as a screening instrument in the selection of distressed samples, as a means to distinguish tinnitus sufferers who cope with the problem from those who do not cope well, and as a measure of psychological distress before and after treatment' p. 198.

For questionnaires assessing how a person feels and functions in day-to-day activities, the psychometric (statistical) requirements to maximise the discriminative, predictive or evaluative properties of the questionnaire are often at odds with one another. Table 9.1 describes key issues to be considered when devising a strategy for constructing a questionnaire for discrimination or for evaluation. Prediction is not discussed further because it is not an issue that has been widely investigated in the tinnitus field.

For those readers particularly interested in the measurement properties of patient-reported outcome instruments, the COSMIN checklist (http://www.cosmin.nl/) is a useful generic tool for evaluating the methodological quality of studies reporting the construction of an instrument.

While a discriminative strategy places an emphasis on attempting to sample all important, relatively stable aspects of functional status common to most members of each functional class, an evaluative strategy places an emphasis on restricting

Table 9.1 Major issues for consideration in the construction and evaluation of outcome instruments (informed by Kirschner and Guyatt 1985)

Issue to consider	Discriminative strategy	Evaluative strategy
Selecting the questionnaire items	Complaints are: • Important to patients with tinnitus • Universally applicable to people with tinnitus • Stable over time	Complaints: • Are likely to change • Will be responsive to a clinically significant change, as a result of the intervention of interest
Choosing the format of the response options available to patients	• Short response sets which facilitate the same interpretation from person to person	• Response sets have sufficient gradations to register change
Reducing the total item pool based on performance in the relevant setting	• Remove items where variability between-subjects is not related to tinnitus • Consider time and effort needed by the subject	• Remove unresponsive items
Ensuring measurement of true differences relative to the overall variance	• Variation between subjects is large and remains stable across testing intervals	• Variation within-individuals remains stable across testing intervals
Validity	• Include all characteristics of tinnitus that are common to most people • Relationship between the instrument score and external measures at a single point in time	• Include only characteristics that are salient with respect to clinically important treatment-related change. • Relationship between changes in the instrument score and external measures over time
Responsiveness	• N/A	• Known power of the test to detect a minimal clinically important difference (i.e. all parameters for computing the sample size required to observe a predefined change in the population)

measurement only to those salient activities and feelings that are subject to clinically important treatment-related change. Kirschner and Guyatt (1985) point out that this distinction has often been neglected in the health status measurement literature. An outcome instrument for measuring stress-related symptoms in people with tinnitus before and after (psychological) treatment should certainly *not* be seeking to assess all of the 20 distinct domains of tinnitus-associated complaints that are given in Fig. 9.1. Criticism of tinnitus questionnaires that 'measure a limited number of constructs' (p. 144) (Newman et al. 1996) is not a valid criticism for questionnaires that are primarily to be used for an evaluative (outcome) purpose.

Suffice it to say that few tinnitus-related questionnaires have been developed specifically according to an evaluative strategy (Fackrell et al. 2014). And the TRQ, PSS, PSQ and DASS are no exceptions. Their psychometric properties as outcome instruments in the tinnitus population are not yet established.

9.7.1 Use of Questionnaires for Diagnosing Perceived Stress

Just like other chronic conditions, tinnitus in the general population is associated with perceived stress and its associated symptoms of anxiety and depression. Table 9.2 lists some of the instruments that have been used for assessing stress,

Table 9.2 List of instruments used for assessing stress, anxiety and depression in clinical research

Instrument for assessing stress, anxiety and depression	Reference	Instrument used for diagnosis	Instrument used as primary outcome	Instrument used as secondary outcome
		Number of studies out of 16	Number of studies out of 228	
Perceived stress associated with tinnitus				
Tinnitus Reaction Questionnaire (TRQ)	Wilson et al. (1991)	2 (13%)	11 (5%)	2 (<1%)
General perceived stress				
Perceived Stress Scale (PSS)	Cohen et al. (1983, 1988)	0	1 (<1%)	0
Perceived Stress Questionnaire (PSQ)	Levenstein et al. (1993)	0	3 (1%)	0
Depression, Anxiety and Stress Scale (DASS)	Gomaa et al. (2014)	0	0	1 (<1%)
Anxiety and depression				
Anxiety Sensitivity Index	Reiss et al. (1986)	1 (6%)	0	1 (<1%)
Beck Anxiety Inventory (BAI)	Beck et al. (1988)	1 (6%)	0	1 (<1%)
Beck Depression Inventory (BDI)	Beck et al. (1961)	5 (31%)	7 (3%)	13 (6%)
Composite International Diagnostic Interview Short Form	World Health Organization	1 (6%)	0	0
Comprehensive Psychopathological Rating Scale	Asberg et al. (1978)	1 (6%)	0	0
Hopkins Symptoms Checklist (HSCL)	Derogatis et al. (1974)	1 (6%)	0	0
Hospital Anxiety and Depression Scale (HADS)	Zigmond et al. (1983)	5 (31%)	7 (3%)	27 (12%)

(continued)

Table 9.2 (continued)

Instrument for assessing stress, anxiety and depression	Reference	Instrument used for diagnosis	Instrument used as primary outcome	Instrument used as secondary outcome
		Number of studies out of 16	Number of studies out of 228	
M.I.N.I.—International Neuropsychiatric Interview	www.medical-outcomes.com/index/mini	2 (13%)	0	0
Major Depression Inventory	World Health Organization	0	0	5 (2%)
State-Trait Anxiety Inventory (STAI)	Spielberger et al. (1970)	2 (13%)	3 (1%)	3 (1%)
Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (DSM)	American Psychiatric Association	5 (31%)	0	0
Symptom Checklist 90 Revised	www.pearsonclinical.com	1 (6%)	1 (<1%)	0

Instruments used for diagnosis of stress, anxiety and depression comorbid with tinnitus are taken from Pinto et al. (2014). Instruments used for evaluation of treatment-related outcome are taken from an unpublished systematic review (Hall et al. 2015)
Note that only the 'most typical' are reported here. Occasional use of other questionnaires is reported, but these constitute <1% when combined across diagnosis and treatment outcome studies

anxiety and depression in tinnitus research. Consistent with the previous descriptions, these are classified according to measures of perceived stress associated with tinnitus, general perceived stress, anxiety and depression.

Those questionnaires used for diagnosis of tinnitus-related comorbidities are given in column 3. It is not an exhaustive list, but instead reflects data reported by Pinto et al. (2014) in a systematic review focusing on the *diagnosis* of mental disorders associated with tinnitus. Using such measures, it was confirmed that the prevalence of anxiety and depression is high in patients with tinnitus (Pinto et al. 2014). Indeed, this pattern was reported in 15 of the 16 included studies. Seven studies reported a significant positive correlation between the presence and severity of depression and the severity and annoyance of tinnitus, while four reported a similar pattern for anxiety. On the basis of this evidence, the authors conclude that the presence of a comorbid depression or anxiety worsens the prognosis of tinnitus-related stress. It is important to note that only five out of the 16 included studies used a psychiatric diagnosis of a mental health disorder according to the Structured Clinical Interview for the DSM edition 3 or 4 (Table 9.1). Patient-reported questionnaires, namely, the HADS and the BDI, were equally popular. But detection of depressive symptoms by self-report scales does not automatically mean the diagnostic criteria for a psychiatric disorder are fulfilled (Langguth et al. 2011).

9.7.2 Use of Questionnaires for Evaluating Treatment-Related Change in People with Tinnitus

A number of co-workers and I have recently completed a systematic review of clinical trials assessing the treatment of adults with tinnitus (Hall et al. 2016). Only trials with ≥20 participants were eligible, thus excluding the majority of feasibility and pilot studies. The objective was to identify and evaluate the current reported outcome domains and instruments. There was no restriction on inclusion criteria for participants in the trial, for the type of intervention or for the type of outcome evaluation. From 1574 articles and trial registrations published since July 2006 to March 2015, 228 met our inclusion criteria for the review. Overall for the primary evaluation of treatment benefit (i.e. the primary outcome), 78 different instruments were used. For the secondary evaluation of treatment benefit (i.e. the secondary outcome), 108 different instruments were used. Perhaps, unsurprisingly, the most popular instruments were condition-specific, i.e. they were assessing multiple attributes related to the impact of tinnitus. The Tinnitus Handicap Inventory (Newman et al. 1996) was most frequently used.

The other interesting questionnaire instruments with respect to the aim of this review are the TRQ which was used in 13 studies, the PSS which was used in one study, the PSQ which was used in three studies and the DASS which was used in one study and was scored separately for each of the three subscales (Table 9.2).

Table 9.3 reports some of the characteristics of these studies including the trial design, type of intervention(s), description of the outcome domain, end points, definition of the minimal clinically important difference, details of the sample size calculation and the sample size itself. For controlled trials, Table 9.3 also reports whether a statistically significant difference between groups was detected ($p < 0.05$).

As expected from the description of clinical trial designs given in Sect. 9.1, explanatory trials formed the majority of studies using the TRQ as a condition-specific stress outcome. Eight of the 13 studies using the TRQ were of this design, with another being a pilot trial for a later planned explanatory trial. Only one study was described as a pragmatic trial, and this used a general perceived stress outcome, as would be expected.

In general, definitions of the minimal clinically important difference and details of the sample size calculation were poorly reported (Table 9.3). This may reflect a lack of awareness on the part of the investigators or (for the change measure) a paucity of knowledge about what these parameters should be for the target population. These pieces of information are crucial aspects of good trial design for explanatory and pragmatic trials. The interested reader is directed to Tutorial 9.3 for more details. Whatever the reason, there is a risk that many of these trial designs are underpowered.

Many (but not all) of the interventions being assessed using the TRQ, PSS, PSQ and DASS were psychological interventions. This is consistent with the purpose of these questionnaires to measure complaints associated with perceived stress. In other words, investigators tended to describe an interest in reducing patient distress or stress and most therefore tended to choose a stress-related questionnaire as a

Table 9.3 Table reporting details of clinical trials conducted and/or reported between 2006 and 2015, using stress-related outcomes

Reference	Clinical trial design	Type of intervention(s)	Author-defined outcome domain	Primary or secondary outcome?	Sample size	Minimal clinically important difference	Sample size calculation	End points	Group diff.
Tinnitus reaction questionnaire									
ClinicalTrials. gov ID: NCT00724152	Pilot—randomised controlled trial	1-Tinnitus education, 2-Tinnitus education plus CBT, 3-Standard care (not defined)	Not reported	Secondary	66	Not reported	Not reported	6, 14 and 30 weeks	Protocol only
Abbott et al. (2009)	Explanatory—cluster randomised trial	1-Internet-based CBT 2-Internet-based information only	Tinnitus distress	Primary	1–32 2–24	Not reported	Not reported	6 weeks	n.s
Davis et al. (2007)	Explanatory—randomised controlled trial	1-Neuromonics one-stage protocol 2-Neuromonics two-stage protocol	Tinnitus distress	Primary	1–16, 2–19	A threshold for a clinically significant improvement was set at 40% of pretreatment TRQ	Not reported	2, 4, 6 and 12 months	n.s.
Kaldo et al. (2007)	Explanatory—randomised controlled trial	1-Tinnitus self-help book and telephone calls 2-Delayed tinnitus self-help book	Tinnitus annoyance and distress	Primary	1–34 2–38	50% reduction in TRQ mean score = clinically significant improvement	Not reported	6 weeks	sig.
Kaldo et al. (2008)	Explanatory—randomised controlled trial	1-Internet-based CBT 2-Group-based CBT	Tinnitus annoyance and distress	Primary	1–26 2–25	Not reported	Not reported	Not clearly defined	n.s.
Malouff et al. (2010)	Explanatory—randomised controlled trial	1-Tinnitus self-help book (Henry and Wilson) 2-Delayed tinnitus self-help book	Psychological distress specifically associated with tinnitus	Primary	1–84 2–78	Not reported	Not reported	2 months	n.s.

Robinson et al. (2008)	Explanatory—randomised controlled trial	1-Immediate CBT 2-Delayed CBT	Psychological distress related to tinnitus	Primary	1–38 2–27	Not reported	'We conducted a power analysis and identified a goal of recruiting 60 patients total, 30 per group, to be able to detect a moderate effect size at a power of 0.8 and a *p* value of 0.05 for our primary outcome'	8 weeks	sig. (but groups not matched on baseline TRQ)
Heijneman et al. (2012)	Explanatory—randomised crossover trial	1-Phase shift sound therapy 2-Placebo	Tinnitus-related distress	Primary	25	Not reported	'To determine the sample size, the 1.5-decrease in tinnitus loudness (from 6.4 to 4.9, standard deviation 2.2) on a 10-point visual analog scale was used, which was described by Vermeire et al. While testing 2-sided with $a = 0.05$ and 80% power, it was found that 19 patients would be needed to obtain significance, in a crossover randomized control study design'	1 week after the end of each treatment	n.s.

(continued)

Table 9.3 (continued)

Reference	Clinical trial design	Type of intervention(s)	Author-defined outcome domain	Primary or secondary outcome?	Sample size	Minimal clinically important difference	Sample size calculation	End points	Group diff.
ISRCTN ID: ISRCTN17631678	Explanatory—randomised crossover trial	1-Phase out auditory stimulation 2-Pacebo	Not reported	Secondary	60	Not reported	Not reported	5 and 9 weeks	Protocol only
Hanley et al. (2008)	Not applicable—observational study	customised acoustic stimulation coupled with counselling (Neuromonics)	Tinnitus distress	Primary	470	A threshold for a clinically significant improvement was set at 40% of pretreatment TRQ, in line with prior clinical studies of this technique	Not reported	Approx. 37 weeks	N/A
ClinicalTrials. gov ID: NCT00730834	Not applicable—observational study	Customised acoustic stimulation coupled with counselling (Neuromonics)	Not reported	Primary	53	Not reported	Not reported	6, 12, 24, 36 months	Protocol only
Távora-Vieira et al. (2011)	Not applicable—retrospective data analysis	1-Neuromonics standard protocol 2-Neuromonics variation of standard protocol	Not reported	Primary	1–13 2–13	The success rate of the treatment is defined by Neuromonics protocols as a reduction of at least 40% in TRQ scores.	Not reported	2, 4 and 6 months	Sig (4 months only)
McNeill et al. (2012)	Not applicable—retrospective data analysis	Hearing aids	Tinnitus distress	Primary	70	Not reported	Not reported	3 months	N/A

Perceived stress scale									
Hesser et al. (2012)	Explanatory—randomised controlled trial	1-Internet ACT 2-Internet CBT 3-Monitored online discussion forum	Perceived stress	Secondary	1–35 2–32 3–32	Not reported	Not reported	3 and 8 weeks and 1 year	n.s
Perceived stress questionnaire									
Seydel et al. (2010)	Explanatory—randomised controlled trial	1-Modified TRT 2-Waiting list	Stress	Primary	1–192 2–45	Not reported	Not reported	3 months	n.s.
ISRCTN ID: ISRCTN38408464	Pragmatic—randomised controlled trial	1-TRT with *Ginkgo biloba* extract (tablet) 2-TRT alone	Not reported	Primary	300	Not reported	Not reported	6, 12 and 24 weeks	Protocol only
Olze et al. (2012)	Not applicable—semi-retrospective study	Cochlear implantation	Stress	Primary	40	Not reported	Not reported	After implantation (not defined)	N/A
Depression Anxiety and Stress Scale (DASS)									
Abbott et al. (2009)	Explanatory—cluster randomised trial	1-Internet-based CBT 2-Internet-based information only	Tinnitus distress	Secondary	1–32 2–24	Not reported	Not reported	6 weeks	n.s

The TRQ is the most popular and is available in English, French, German and Swedish. The PSS has been translated from English into other languages including German, Swedish, Japanese and Arabic; PSQ is available in (at least) English and German, while DASS is available in over 40 languages

primary measure of treatment efficacy. For example, with respect to 13 studies using the TRQ as an outcome measure, nine trials assessed cognitive behaviour therapy (CBT) or an equivalent counselling approach, and one was an evaluation of a self-help book. Comparison of findings across studies is limited by the different study designs, choice of controls (active or waiting list), small sample sizes and various study end points. But some general statements can be made. First, the questionnaire instruments were generally responsive to detecting a reduction in scores after treatment, compared to before treatment (Fig. 9.4). However, for controlled trials, the most important result is the comparison of treatment-related change between groups, and here, the ability of the questionnaire instruments to detect these more subtle effects appeared less successful. When you simply look at the findings as reported by the study investigators, the TRQ appears to be rather mixed in its ability to detect significant changes in patient-reported stress between groups. Only three studies reported significant differences between groups (Kaldo et al. 2007; Robinson et al. 2008; Távora-Vieira et al. 2011). Four studies used general

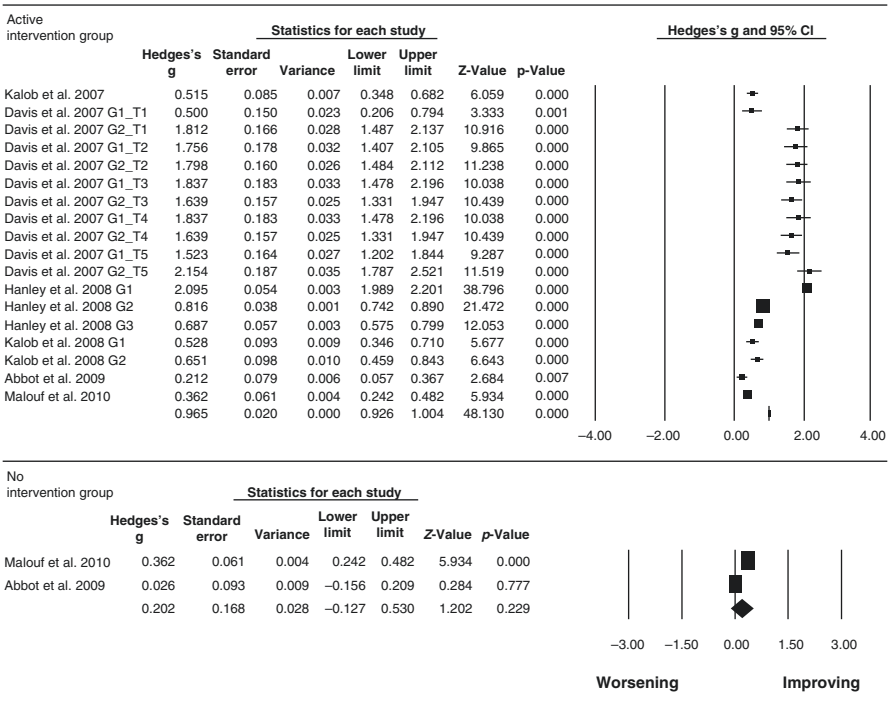

Fig. 9.4 Effect sizes for pre- versus post-intervention, within-group comparisons are shown for the Tinnitus Reaction Questionnaire. To be eligible for inclusion, group mean, standard deviation and sample size had to be reported. In some cases, this information was read from a graphical figure. Several studies report more than one active intervention group (G1–G3) and/or more than one end point (T1–T5). These details are reported in Table 9.3. The meta-analysis must be interpreted with caution due to the heterogeneity of the clinical trial design, but there seems to be a general responsiveness to active intervention over time

stress measures (PSS, PSQ and DASS) to assess the efficacy of CBT or an equivalent counselling approach, but none of these detected a significant between-group effect where findings were reported. The lack of statistical significance is likely to be another marker of underpowered clinical trial designs.

From the same systematic review of clinical trials assessing the treatment of adults with tinnitus, it can be seen that anxiety and depression questionnaires have also been used to determine treatment-related change in people with tinnitus. Table 9.2 illustrates their distribution. Just as was the case for diagnosis of mental health comorbidities with tinnitus (Pinto et al. 2014), the BDI, HADS and STAI were the preferred tools for assessing treatment-related changes in anxiety and depression in people with tinnitus. These questionnaire instruments have also been widely used outside the tinnitus field, in those clinical trials of interventions which are targeted at the treatment of anxiety and depression disorders (Churchill et al. 2013; Hunot et al. 2007, 2013; Joyce and Herbison 2015; Mayo-Wilson and Montgomery 2013; Ori et al. 2015). And the Beck Anxiety Inventory (BAI) (Beck 1988) has been used too.

Tutorial 9.3 Sample Size Calculation

It is never practical to study the whole population. Instead studies must select a subset of participants, which is smaller in size, but adequately represents the population from which it is drawn. This means that true inferences about the population can be made from the results obtained. This subset of participants is known as the **sample**, and the number of participants is known as the **sample size**.

The calculation of an adequate sample size is a crucial in the design of explanatory and pragmatic clinical trials. It is the process by which we calculate the optimum number of participants required to be able to arrive at ethically and scientifically valid results.

Generally, the sample size depends on:

- **Outcome instrument.** A single instrument should be predefined so that scores on this measure will be used to determine whether the treatment is beneficial or not. This is called the primary outcome.
- **Pooled standard deviation.** Standard deviation is a measure of variability in the scores measured by the primary outcome instrument within the population. It is usually estimated from previously reported studies, including pilot work.
- **Acceptable level of significance.** Statistical significance is denoted by the '*p*' value and convention is a *p* value of 5%. A $p = 0.05$ means that the investigators accept the erroneous detection of a difference 5 out of 100 times, when actually no difference exists. This is called the Type I error ('false positive').
- **Side of hypothesis testing.** For $p = 0.05$, a two-tailed test allocates 0.025 to testing the statistical significance in one direction (i.e. improving) and 0.025 to testing statistical significance in the other direction (i.e. worsening). In contrast, a one-tailed test allocates all 0.05 to one tail of the distri-

bution of the test statistic. Convention is for two-sided testing because there is rarely sufficient prior knowledge about the intervention effects at the end point of interest.

- **Power.** Statistical power relates to the probability of failing to detect a difference when actually there *is* a difference. Power is denoted as a percentage and convention is 80%. A power of 80% means that investigators accept that one in five times (i.e. 20%) a real difference will be missed. This is called the Type II error ('false negative').
- **Expected difference.** Just because a treatment-related change is statistically significant at $p < 0.05$, it does not necessarily mean that it is worth implementing in clinical practice. Any treatment-related benefit should also be meaningful to patients.

A challenge is thus to define the difference between the treatment and control groups in the scores measured by the primary outcome instrument that can be considered clinically meaningful. This is called the 'minimal clinically important difference'.

Additional factors can be taken into account when calculating the final sample size, and these include the expected drop-out rate, an unequal allocation ratio and the objective and design of the study.

9.8 Take-Home Messages

This chapter has defined and discussed perceived stress in the context of clinical research. The following key points have been discussed and are worth highlighting again in this concluding section.

Measuring Perceived Stress Associated with Tinnitus

- The Tinnitus Reaction Questionnaire (TRQ) is the *only* questionnaire that selectively measures perceived stress related to tinnitus for use in quantifying patient benefit from psychological interventions.
- The TRQ seems to be closely associated with patient-reported outcome measures for depression and anxiety. Indeed it can be argued that they are to some extent measuring the same underlying constructs.
- The TRQ holds promise as a responsive instrument for detecting improvements over time within a group of patients receiving a psychological intervention.

Measuring General Perceived Stress

- The Perceived Stress Scale (PSS), Perceived Stress Questionnaire (PSQ) and the Depression, Anxiety and Stress Scale (DASS) all measure general aspects of perceived stress.
- There is considerably less experience in using them for tinnitus research.

Stress measures are most likely to be suited for evaluating the effectiveness of psychological interventions, than non-pharmacological interventions such as sound therapy and electrophysiology. However, further research is needed to understand how well-suited these questionnaires are for use as an outcome measure in clinical trials for tinnitus. In particular, their responsiveness properties should be better characterised before any recommendations are made for clinical trial design. In the absence of such knowledge, informed decisions about sample size and what difference should be expected in order to interpret that the treatment can be noticed by patients. Until this point, there is a potential risk that null findings are not indicative of an ineffective intervention, but simply the wrong choice of outcome measure.

The relationship between certain personality traits, depressive mood, anxiety and tinnitus is highly relevant for understanding the degree to which tinnitus is amenable to intervention. Personality traits, such as emotional resilience and adaptive coping strategies, may enable one individual to be much less affected by stressors that would otherwise have negative health impacts. These modulatory factors are rarely taken into account when evaluating the impact of an intervention on perceived stress, yet they are of fundamental importance to understanding treatment efficacy and may explain some of the individual variability that is often seen in clinical practice and in clinical trials.

Disclaimer The views expressed in this publication are those of the author and not necessarily of the NHS, the National Institute for Health Research, or the Department of Health.

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