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REVIEW

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Highlights

1. A 45% lifetime prevalence of comorbid anxiety disorder in tinnitus
2. Subcortical overlaps in and links between known tinnitus and anxiety networks
3. Direction of causality or possibility of a common vulnerability remains undefined
4. Ambiguous involvement of HPA axis; possible by different, acute/chronic, settings
5. To screen and treat anxiety could potentially improve perceived levels of tinnitus

Abstract

Background: The most common form of tinnitus is a subjective, auditory, and distressing phantom phenomenon. Comorbidity with depression is high but other important psychiatric disorders such as anxiety disorders have received less attention. The current paper reviews the literature on the associations between tinnitus and anxiety disorders and the underlying pathophysiology, and discusses the clinical implications. Methodology: PubMed and Web of Science were searched for all articles published up until October 2014 using combinations of the following search strings "Tinnitus", "Anxiety disorder", "Panic Disorder", "Generalized Anxiety Disorder", "Traumatic stress disorder", "PTSD" "Social Phobia", "Phobia Disorder", "Obsessive Compulsive Disorder", "Agoraphobia". Results: A total of 120 relevant papers were included. A 45% lifetime prevalence of anxiety disorders is reported in tinnitus populations, while an important overlap in associated (sub)cortical brain areas and cortico-subcortical networks involved in attention, distress, and memory functions is suggested. A disturbed hypothalamic-pituitary-adrenal axis function can be found in tinnitus and in anxiety disorders but, in comorbidity, the direction of the dysfunction is unclear. Conclusion: Comorbidity is high and screening for and treatment of anxiety disorders is recommended in moderate to severe tinnitus, as, given the overlap in the structural and functional brain circuitries involved, theoretically, their management could improve (subjective) levels of tinnitus although further empirical research on this topic is required.

Introduction

Most commonly, tinnitus is a subjective auditory phantom phenomenon with patients perceiving an internal sound in the absence of an external sound source, which can be highly distressing (Jastreboff, 1990;, Baguley et al, 2013)). Tinnitus can aetiologically be subdivided into a pulsatile and a non-pulsatile subtype. Pulsatile tinnitus may originate from vascular changes (a change in blood vessels near the ear, a change in awareness of that blood flow, etc.) or can be caused by muscular changes such as myoclonus of middle ear or palatal muscles (Baguley et al, 2013). Non-pulsatile tinnitus is currently viewed as the result of modified neural activity in the central auditory system consequential to peripheral damage in the auditory apparatus (Baguley et al, 2013). While multiple aetiologies of this modified neural activity are suggested, among which are sound trauma, peripheral hearing loss, and cochlear problems, the fact that in most cases non-pulsatile tinnitus persists after auditory nerve transection, suggests the critical involvement of more central mechanisms influencing the generation and maintenance of tinnitus (Langguth and Elgoyhen, 2012).

Whereas most individuals who experience tinnitus apparently cope well with the condition, 1 in 5 reports to be emotionally affected (Eggermont and Roberts, 2004), with 1.6% of the population experiencing major distress, and 0.5% feeling so severely impaired that they are unable to lead a normal life (Davis and El Rafaie, 2000). In these patients, tinnitus is frequently accompanied by subjective distress, concentration problems, depression, anxiety, irritability, sleep disturbances, and intense worrying (Langguth et al, 2011). Emotional factors typical of depressive and anxiety disorders are reported as strong predictors of a poor adjustment to tinnitus (Zöger et al, 2006). Even if

these symptoms have traditionally been considered a learned reaction to tinnitus (Jastreboff, 1990), their exact relationship to the phenomenon is still a matter of debate (Langguth et al, 2011). Theoretically, it is also conceivable that these symptoms precede tinnitus onset and predispose for it; alternatively, they may represent non-auditory symptoms resulting from the same pathophysiological changes that are involved in tinnitus generation (Möller, 2007). In our review of the literature we will focus on the comorbidity between tinnitus and anxiety disorders and the underlying pathophysiology.

People with anxiety disorders suffer unnecessary or have a disproportional apprehension or fear (Van Balkom et al, 2011). The third edition of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM III, APA, 1980) defined several specific anxiety disorders such as panic disorder, agoraphobia, social anxiety, posttraumatic stress syndrome (PTSD), obsessive-compulsive disorder, and generalized anxiety disorder . Their criteria have largely remained unchanged in subsequent editions (DSM IV, APA, 2000; DSM 5, APA, 2013) with the exception of the positions of obsessive-compulsive disorder, today classified in the "Obsessive Compulsive disorders" chapter, and PTSD, now included in the "Trauma and stress-related disorders" chapter (DSM 5, APA, 2013).

In our overview of the associations between tinnitus and anxiety disorders we will consider the following three main topics: 1. the comorbidity between the two disorders, 2. the neurobiological overlap between the disorders, and 3. the clinical implications of their associations.

Methodology

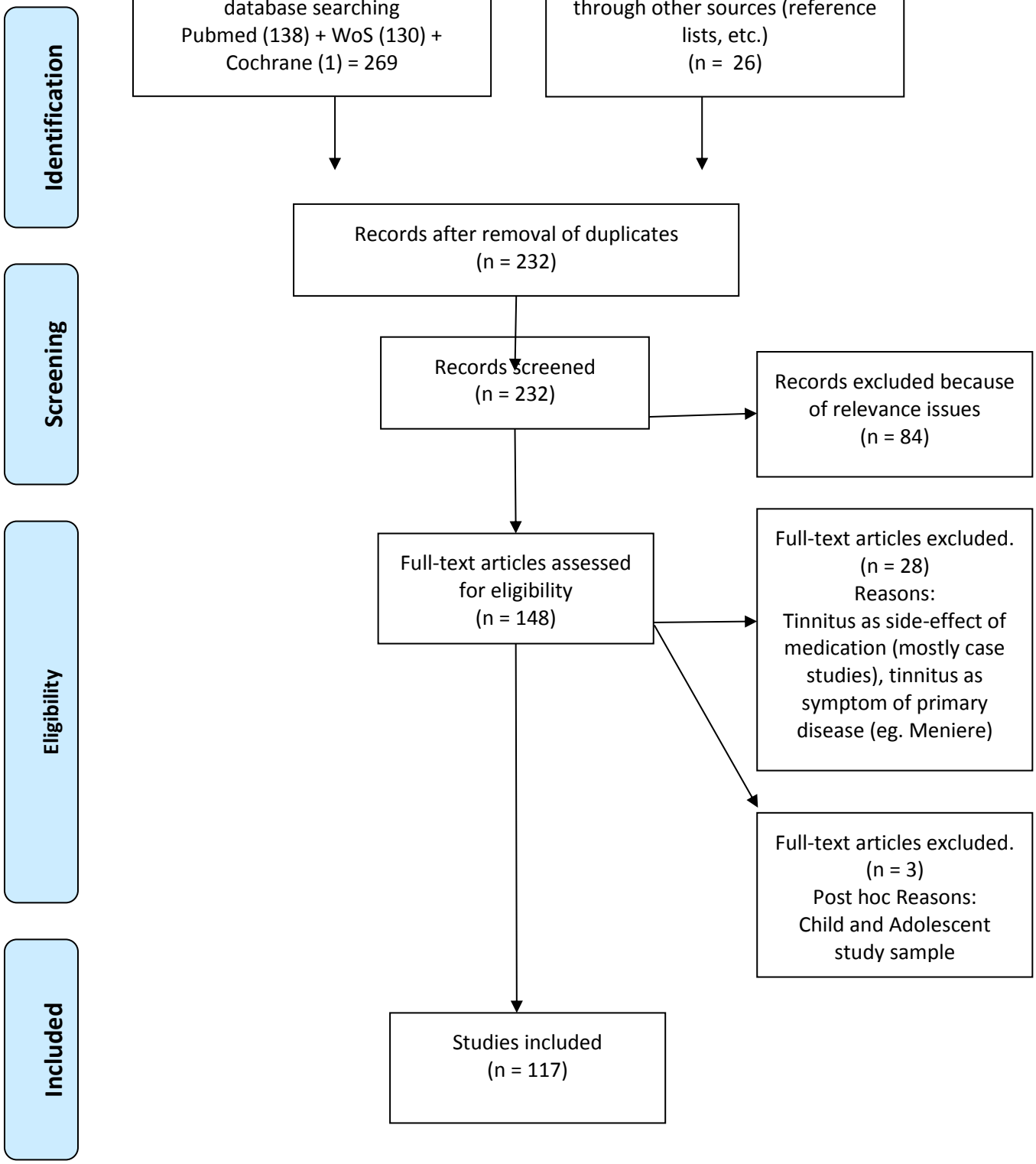
PubMed, Web of Science, and The Cochrane Library were searched for all articles published in English to date, including other (systematic) reviews. We used the following search strings for PubMed (("tinnitus"[MeSH Terms] OR "tinnitus"[All Fields]) AND ("anxiety disorders"[MeSH Terms] OR ("anxiety"[All Fields] AND "disorders"[All Fields]) OR "anxiety disorders"[All Fields] OR ("anxiety"[All Fields] AND "disorder"[All Fields]) OR "anxiety disorder"[All Fields]); for Web of Science we entered (Tinnitus AND (anxiety disorder OR panic disorder OR agoraphobia OR obsessive compulsive disorder OR phobic disorder OR traumatic stress disorder OR PTSD OR generalized anxiety disorder)), and in The Cochrane Library we searched titles, abstracts, and keywords ("anxiety disorder" AND "tinnitus"). The final search was conducted on 10 October 2014.

We examined reference lists from identified articles and reviews for other relevant articles and also included relevant book chapters from Neurobiology of Mental Illness (Charney et al, 2013) in our overview of neurobiological literature on anxiety disorders.

All abstracts were assessed for relevance and found eligible if a (potential) association between tinnitus and anxiety disorder was mentioned as the primary or secondary outcome of the study or the study's goals included epidemiology, aetiological models, neurobiological overlap between anxiety disorders and tinnitus, diagnostics, or treatment of anxiety disorders in tinnitus patients or vice versa (tinnitus in anxiety disorders). Next, full-text assessments, if accessible, were conducted on the basis of which the publication was either included or excluded. Epidemiological studies concerning prevalence of psychiatric disorders in tinnitus populations were only

included if these had been diagnosed using validated interviews such as the Structured Clinical Interview of DSM disorders (SCID, First et al, 2002), the Mini International Neuropsychiatric Interview (MINI, Sheehan et al, 1998), or the Composite International Diagnostic Interview (CIDI, Robins et al, 1989). Editorials, opinions, and commentaries were excluded, as well as papers in which tinnitus was only mentioned as a side effect of medication or as a symptom of any other primary disease (e.g. Ménière's disease). Taking into account that only three papers had children/adolescents as study population and the differences of clinical and neurodevelopment characteristics between children/adolescents and adults, we excluded those three papers. The search resulted in 117 relevant references, which were all included in the current review. A summary of the search strategy can be found in Figure 1.

!insert Figure 1: "Literature search flowchart" around here!


Identification
Screening
Eligibility
Included
Records identified through database searching Pubmed (138) + WoS (130) + Cochrane (1) = 269
Additional records identified through other sources (reference lists, etc.) (n = 26)
Records after removal of duplicates (n = 232)
Records screened (n = 232)
Records excluded because of relevance issues (n = 84)
Full-text articles assessed for eligibility (n = 148)
Full-text articles excluded. (n = 28) Reasons: Tinnitus as side-effect of medication (mostly case studies), tinnitus as symptom of primary disease (eg. Meniere)
Full-text articles excluded. (n = 3) Post hoc Reasons: Child and Adolescent study sample
Studies included (n = 117)

Results and discussion

Epidemiology of anxiety disorders in tinnitus populations

Lifetime and current prevalence

In many tinnitus populations, high rates of psychopathology and anxiety/depression are reported. Table 1 lists the studies that used a validated diagnostic interview to assess psychiatric disorders. Two of these, Zöger et al (2001) and Malakouti et al (2011), investigated the lifetime comorbidity of mental disorders using the Structured Clinical Interview for DSM Disorders (designed to determine psychopathology, e.g. depression, anxiety, or schizophrenia; DSM III-R) in 82 consecutive tinnitus patients and 400 chronic tinnitus patients, respectively, and both reported a lifetime anxiety disorder prevalence of 45%. The studies that investigated current anxiety disorders show greater variance while strict comparisons are hampered by the use of different diagnostic instruments (i.e. CIDI, SCID, and MINI) and sets of classification criteria (i.e. DSMIII-R, DSM IV, and ICD 10). However, differences between instruments and criteria are relatively small.

With the exception of the Shargorodsky et al study (2010) that also provides prevalence figures of generalized anxiety disorder in the general population (3.1%) and a tinnitus population (20.4%), no other tinnitus studies compared their results to the general population. However, the European Study of the Epidemiology of Mental Disorders study (Alfonso and Lepin, 2007) reports the prevalence of psychiatric disorders in a general population, which are here presented for comparison in table 2. Comparing these European prevalence data of general population with those reported for individuals with tinnitus, we found higher rates for all anxiety disorders in the tinnitus populations (Table 1).

194

195 !Insert Table 1 "Prevalence of anxiety disorders in tinnitus populations" around here!

Authors (Year)	Instrument	DSM version	n	Lifetime Anxiety Disorder (%)	Current Anxiety Disorder (%)	Anxiety disorders (%)
Holgers et al. (2005)	SCID	DSM III-R	82	45 (n=37)	45 (n=37)	GAD 9.7; Social 9; PD 11; OCD 7
Zoger et al. (2006)	SCID	DSM III-R	144	N/A	49 (n=71)	N/A
Belli et al. (2008)	SCID	DSM III-R	90	N/A	18.9 (n=17)	GAD 6.7; Social 6.7; OCD 1.1; PTSD 2.2; Specific 5.6
Shargorodsky et al. (2010)	CIDI	DSM IV	2265	N/A	N/A	GAD: 20.4
Malakouti et al. (2011)	SCID	DSM III-R	400	45.8 (n=183)	N/A	N/A
Marciano et al. (2003)	MINI	DSM IV	75	N/A	29.3 (n=22)	N/A
Juris et al. (2013)	MINI	DSM IV	62	N/A	47 (n=29)	GAD 16; Social 23; PD 6; OCD 10; PTSD 3; Agora; 15
Zirke et al. (2013)	CIDI	ICD 10	100	N/A	32 (n=32)	N/A

DSM: Diagnostic and Statistical Manual of DSM disorders; SCID: Structured Clinical Interview of DSM Disorders; MINI: Mini International Neuropsychiatric Interview; CIDI: Composite International

Diagnostic Interview; GAD: Generalized Anxiety disorder; PD: Panic disorder; PTSD: Posttraumatic Stress Disorder; Agora: Agoraphobia; OCD: Obsessive-compulsive Disorder; Social: Social Phobia; N/A: Not Applicable

!Insert Table 2 "ESEMED prevalences" around here!

Disorder	Lifetime (%)	12-month (%)
Generalized anxiety disorder	2.8	1.0
Social phobia	2.4	1.2
Specific phobia	7.7	3.5
Post Traumatic Stress Disorder	1.9	0.9
Agoraphobia	0.9	0.4
Panic disorder	2.1	0.8
Any anxiety disorder	13.6	6.4

Impact of tinnitus severity on anxiety disorder prevalence

Holgers et al (2005) used the data set of the group's earlier study (Zöger et al, 2001) for their 24-month follow-up study. Based on the presence of two criteria: 1) absence from work in excess of 30 consecutive days and 2) more than three visits to the therapist or audiologist, they created a severe tinnitus sufferers positive (STS+) and a severe tinnitus sufferers negative (STS-) subgroup. The difference between the STS+ and STS- group with respect to the prevalence of any lifetime mental disorder (90% versus 73%) was significant. It remained significant and even more pronounced for anxiety disorders (26% versus 10%). Depression-anxiety comorbidity also showed significant group differences, with more comorbid anxiety disorders in the STS+ group (71% versus 44%). The higher prevalence of mental disorders and, more specifically, anxiety disorders, in the more severely functionally affected tinnitus sufferers suggests that a comorbid anxiety disorder influences the perceived severity of tinnitus and quality of

life. In Holgers et al (2005) view, screening for anxiety disorders and their treatment are thus of great importance in the rehabilitation of severe tinnitus.

In 2006, Zöger et al performed an additional follow-up study to investigate the relationship between tinnitus severity and psychiatric disorders. Besides the first sample of 82 consecutive tinnitus patients, an additional 144 tinnitus patients were recruited and identified as being at high risk of developing chronic and debilitating tinnitus using the Nottingham Health Profile, a generic health questionnaire gauging lack of energy, pain, emotional disturbances, sleep disturbances, social isolation, and physical mobility. While the first group (82 consecutive patients) showed a 45% prevalence for any current anxiety disorder and a 13% prevalence for multiple anxiety disorders, the corresponding percentages for the second high-risk group were 49% and 19%, highlighting the relevance of anxiety disorders in tinnitus populations with a high risk of chronicity (Zöger et al, 2006).

These results were partly reproduced by Zirke et al (2013) who reported a 32% prevalence rate for anxiety disorder, with patients with decompensated tinnitus suffering significantly more frequently and more severely from anxiety disorders than the patients with compensated tinnitus. Patients with comorbid depression or anxiety disorder also reported significantly higher tinnitus-related distress levels than peers free of any psychological disorder.

The impact of hyperacusis, a common comorbidity in tinnitus, on certain tinnitus characteristics is well studied (Anari et al, 1999; Nelson and Chen, 2004; Gilles et al, 2014), but its effect on psychiatric comorbidity is not. Investigating psychiatric

comorbidity in hyperacusis patients, Juris et al (2013) found that 79% (n=49) of the total sample reported tinnitus and 47% (n=29) an anxiety disorder. Although the anxiety disorders in the tinnitus subpopulation were not further specified, it is reasonable to assume some overlap. Furthermore, Goebel and Floetzinger (2008) found the patients with hyperacusis and tinnitus to have more psychiatric morbidity than those with tinnitus alone, indicating that psychiatric comorbidity is more linked to tinnitus than it is to hyperacusis.

Holgers et al (2005) reported more psychiatric comorbidity in patients with more severe tinnitus and suggested the inclusion of psychiatric symptoms and disorders as severity indicators of tinnitus. Another study, by Cho et al (2013), investigated the effect of anxiety and depressive symptoms, as assessed with the Beck Anxiety Inventory and the Beck Depression Inventory, respectively, on the subjective level of tinnitus using the Tinnitus Handicap Index. They found a significant correlation in the patients with a Tinnitus Handicap Index above 38 (moderate) and recommended systematic evaluation of anxiety and/or depressive symptoms if tinnitus severity scores are moderate or higher.

Causality between tinnitus and anxiety disorders

While the prevalence of anxiety disorders in tinnitus populations is high, we found no studies on the prevalence of tinnitus in populations with anxiety disorders. As only one direction of the relationship is known, this precludes any conclusion as to the opposite direction. We also found no longitudinal studies on this subject and hence have cross-sectional, correlation-only results. However, two cross-sectional studies did try to assess

the first manifestation of symptoms of the two disorders with careful history taking. Salviati et al (2014) reported that half of the patients they interviewed had an anxiety disorder prior to the onset of tinnitus. Also, four out of 10 patients affected by chronic tinnitus reported a family history of psychiatric disorders. In the second study, the relationship between tinnitus onset and stressful events or mental disorders was explored with open questions and careful history taking (Zöger et al, 2006): only six of 63 patients with depressive and/or an anxiety disorder had tinnitus prior to their mental complaints. Surprisingly, when the patients were asked about the cause of their mental problems, a majority indicated that these were secondary to their tinnitus, contradicting their earlier assertions that the mental disorder preceded the tinnitus. While these results do not imply causality, it does appear that mental disorders frequently precede tinnitus, suggesting that a pre-existing mental vulnerability could predispose an individual to more (severe) tinnitus complaints. Arguably, psychological symptoms and tinnitus may be linked by a common vulnerability such as a dysfunctional neurobiological circuit, explaining why anxiety symptoms and tinnitus often emerge at or around the same time.

Neurobiological links between tinnitus and anxiety disorders

As reported in the previous section, comorbidity of tinnitus and anxiety disorders is relatively high. In this section we will discuss the neurobiological overlap between the conditions.

Neurocircuitry

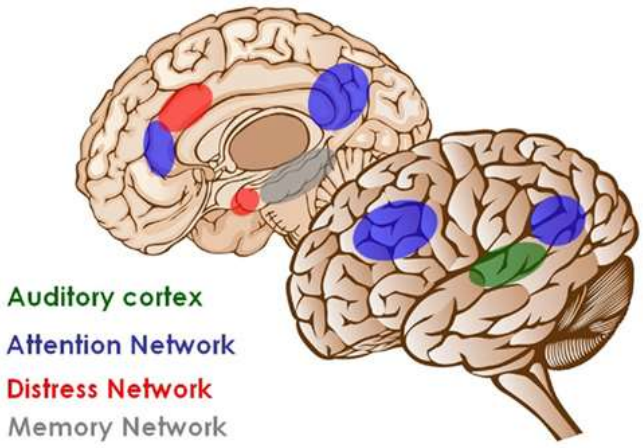
The auditory cortex is a central structure in tinnitus but not commonly implicated in anxiety disorders. However, activity changes in central auditory pathways are mediated by alterations in GABAergic, glycinergic, and glutamatergic neurotransmission (Yang et al, 2011; Richardson et al, 2012; Brozoski et al, 2012). It is also well known that GABA, the major inhibitory neurotransmitter in the brain, is also critically involved in anxiety networks; thus, an acute reduction in GABA transmission causes anxiety in patients and healthy controls (Horowski and Dorow, 2002), while the anxiolytic action of benzodiazepines, used in the pharmacological treatment of anxiety, is exerted through GABAergic pathways (Möller, 2011).

Langguth et al (2012) recently proposed the existence of three functional tinnitus networks: a distress network, a salience network, and a memory network (Figure 2). The distress network can be triggered by pain, real or phantom auditory stimuli, or other sensations (Langguth et al 2012; Leaveret al, 2012) and includes several limbic structures such as the amygdala, anterior cingulate cortex, hippocampus, orbitofrontal cortex, and anterior insular cortex. The attention network, which makes the patient "conscious" of the phantom auditory stimuli, involves the anterior cingulate cortex, anterior insular cortex, amygdala, and the hippocampus (Jastreboff, 1990; Moller, 2003;

Lockwood et al, 1998; Shulman, 1995), while the memory network, although mostly comprising the hippocampus and the amygdala, is considered essential to learning and conditioning of threat behaviour. The involvement of these networks is insufficient to explain the development of the initial phantom auditory perception in itself but they are considered to be essential for the development of conscious and chronic tinnitus and, possibly, its complications (e.g. anxiety disorders).

!Insert Figure 2: "brain networks" around here!

!Image from: Langguth B, Schecklmann M, Lehner A, Landgrebe M, Poeppl TB, Kreuzer PM, Schlee W, Weisz N, Vanneste S and De Ridder D. Neuroimaging and neuromodulation: complementary approaches for identifying the neuronal correlates of tinnitus. Front. Syst. Neurosci., 09 April 2012 | doi: 10.3389/fnsys.2012.00015!



Most of the structures mentioned in these different networks related to tinnitus are indeed also involved in anxiety disorders and some are part of the limbic system, a critical functional network in anxiety disorders, where the amygdala plays an important role in emotional processing and threat detection (Cain and Ledoux, 2008; Sullivan et al,

2003; Ledoux et al, 2012). It is often associated with aversive reactions in general and has been mentioned as a possible "final common pathway" for the expression of tinnitus (Mirz et al, 2000; Vanneste et al, 2010). The hippocampus has not been extensively studied in anxiety disorders or tinnitus but has an important role in declarative memory. The anterior hippocampus is strongly connected to the amygdala and the prefrontal cortex (PFC), and critical in fear memory and extinction while the posterior hippocampus is more linked to anxiety-related behaviour and responses (Kraus and Canlon, 2012). Another structure heavily connected to the amygdala is the insula. It receives projections from the amygdala and transmits these to the anterior cingulate cortex. The function of the insula is frequently associated with interoceptive awareness and monitoring of the autonomic nervous systems (Craig 2009). Most particularly in panic disorder, interoceptive awareness is an important factor in the catastrophic misinterpretation of slight variations in body functions such as an elevated heart or respiratory rate triggering a panic attack. The shared activation of the same structures in tinnitus and anxiety suggests that the two conditions are more intertwined than previously thought.

There is strong evidence of hyperresponsiveness of the limbic system in both tinnitus (Shulman et al, 1995; Lockwood et al 1998) and anxiety disorders (Martin et al, 2009; Etkin and Wager, 2007; Charney et al, 2013). The locus ceuruleus and the raphe nucleus are thought to be the two subcortical areas driving this hyperreactivity. The locus ceuruleus is strongly implicated in anxiety reactions and mediates arousal and attentional targeting (Redmond and Huang, 1979; Pohl et al, 1987; Tanaka et al, 2000). Electrical or drug stimulation of the locus ceuruleus induces anxiety while drugs inhibiting locus ceuruleus activity reduce anxiety (Nashold et al, 1977; Tanaka, 2000).

Research has shown that the dorsal cochlear nucleus may be a site that is involved in the generation of tinnitus (Kaltenbach et al, 2006) and since fusiform cells in the dorsal cochlear nucleus are among the targets of locus ceuruleus-efferent projections, locus ceuruleus hyperactivity could result in facilitory effects on fusiform cells in the dorsal cochlear nucleus, contributing to the aggravation or even the induction of tinnitus. This locus ceuruleus to dorsal cochlear nucleus pathway supports the involvement of limbic structures in the onset and modulation of tinnitus.

This link could also work the other way, with neurons in the dorsal cochlear nucleus sending projections to two subdivisions of the reticular formation, including the caudal pontine reticular nucleus and the lateral paragigantocellular nucleus (Lingenhohl and Friauf, 1994; Kandler and Herbert, 1991; Bellintani-Guardia et al, 1996). While both receive input from cochlear root neurons, the lateral paragigantocellular nucleus is one of the main sources of excitatory input to the locus ceuruleus (Lopez et al, 1999; Sinex et al, 2001; Aston-Jones et al, 1986). This pathway indicates how hyperactivity in the dorsal cochlear nucleus can contribute through stimulation of the locus ceuruleus to anxious responses to tinnitus. These processes are probably not sufficient in and of themselves, but are still necessary for the conscious perception of tinnitus and therefore their involvement in several networks of higher-order brain structures, such as the abovementioned distress, salience, and memory networks is needed.

Thus, interactions between the limbic and the auditory systems occur in both directions (Amaral and Price, 1984; Pitkanen et al, 2000; Marsh et al, 2002; Sah et al; 2003, Kraus et Canlon, 2012) and have been related to different brain functions and behaviours, from

auditory fear conditioning (Phelps and Ledoux, 2005) to plasticity in auditory cortical responses to sounds (Bjordahl et al, 1998; Kilgard and Merzenich, 1998), and to emotional responses to vocal stimuli (Sander et al, 2005; Fecteau et al, 2007; Wiethoff et al, 2009; Leitman et al, 2010; Gadziola et al, 2012; Peterson et al 2008). Accordingly, while a mood or anxiety disorder may not be a prerequisite for the development of tinnitus, stress and negative affect could modulate those brain networks that are involved.

Impact of distress and anxiety on tinnitus

There is ample evidence from both animal and human studies suggesting that emotional states influence the perception of tinnitus. Using m-chlorophenylpiperazine , a serotonin 5-Hydroxytrytophan 2c receptor agonist, Guitton (2005) induced an anxiety-like state in rats affected by salicylate-induced tinnitus, which exacerbated the tinnitus-related effects. These results are in line with the notion that interference of the auditory filtering systems influences the perception of tinnitus. While this animal model has been well studied, providing evidence that salicylate damages the cochlea and that application of an N-methyl-D-aspartate antagonist directly into the cochlea blocks the induction of tinnitus, the incidence of salicylate-induced tinnitus in humans is rather low, implying that other neurophysiological mechanisms underlie tinnitus.

In humans, serotonergic axons projections may modulate tinnitus-related activity in auditory pathways via the thalamic reticular nucleus (Rauschecker et al, 2010) or their mechanisms (Simpson and Davies, 2000; Caperton and Thompson, 2010), while somatosensory-afferent input from the neck and face regions has also been shown to

influence activity in the central auditory system (Roberts et al, 2010), possibly explaining the role of jaw movements in the generation and perception of tinnitus (Vielsmeier et al, 2012). Additionally, neuroimaging studies, further discussed below (voxel-based morphometry: Leaver et al, 2012; fMRI Fiorette, 2011; MEG: Schlee et al, 2009), show that emotional symptoms of depression and/or anxiety are correlated with tinnitus severity, perceived intensity, and volumetric changes in the brain. It is clear that tinnitus-related activity is modulated by mechanisms and/or structures not exclusively used in auditory functions and that other non-auditory brain areas are most likely involved in the pathophysiology of tinnitus.

Comparing grey matter in tinnitus sufferers and controls, Leaver et al (2012) found significantly less gray matter volume in the ventromedial PFC (vmPFC), dorsomedial PFC (dmPFC), and left supramarginal gyrus adjacent to the posterior auditory cortex in the patients. The volumes of other subcortical structures such as the thalamus, caudate, putamen, globus pallidus, nucleus accumbens, amygdala, and hippocampus did not differ between the two groups. The magnitude of importance of these results should be viewed in the context of rather small sample sizes (tinnitus n=23; controls=21) and the general complexity of interpreting anatomical differences in many neuroimaging studies. However, the authors reported some correlations between anatomical differences and certain tinnitus characteristics: a significant positive correlation between dmPFC volume and the percentage of time participants were aware of their tinnitus, a significant negative correlation between vmPFC volume and tinnitus loudness in that tinnitus was perceived to be louder with lower gray matter volumes, while cortical thickness in the anterior insula correlated with tinnitus distress and combined depression-anxiety scores, which ratings also showed a negative correlation with the

change of volume in the subgenual anterior cingulate cortex. Together, these results indicate that the neural systems implicated in tinnitus perception are distinct from those affected by tinnitus distress, mood disorders, or noise sensitivity. It is also in line with the notion that midline frontal brain areas are involved in regulating interoceptive perceptions (Kucinad et al, 2007; Drevets et al, 1997; Mayberg, 1997; Floresco et al, 2009), thereby suggesting that an intact vmPFC is necessary to suppress unwanted cortical activity as seen in tinnitus patients. This assumption would likewise hold for anxiety disorders where the vmPFC has been shown to be essential for the top-down control (suppression) of a threat response (Cain and Ledoux, 2008; Sullivan et al, 2003; Ledoux et al, 2012), which inference is also supported by Rauschecker et al (2010) who reported hyperreactivity in the nucleus accumbens and reduced cortical thickness in the vmPFC. Other researchers suggest the critical involvement of a larger network including several forebrain circuits, the limbic system, and the auditory cortex (De Ridder et al, 2011; Langguth et al 2012).

A neuroendocrine perspective

Does tinnitus lead to stress or does stress induce, maintain, or exacerbate tinnitus symptoms? Although a clear association exists between tinnitus and different kinds of stressors such as occupational stress, physical illness, poor sleep quality (Hasson et al, 2011), inferences on causality are problematic since longitudinal studies are lacking. The hypothalamic-pituitary-adrenal (HPA) axis, a major component of the acute stress response in humans, is influenced by noise as well as stress exposure through amygdalar and subsequent hypothalamic activation (Knipper et al, 2013). Short-term exposure to noise with an intensity well below the safety norm can already induce higher cortisol levels in both tinnitus patients and healthy controls (Hébert and Lupien,

2009). In turn, elevated cortisol levels can affect inner hair cell and spiral ganglionic synapses in the cochlea as well as hippocampal and amygdalar functioning, increasing the risk of maladaptive auditive central circuitry responses (and tinnitus), and emotional and memory processing, respectively. Stress-induced elevation of cortisol could lead to changes in the cochlear mineralocorticoid receptor function (and subsequent disturbances of potassium concentrations, resulting in tinnitus) or in auditory system neuronal plasticity (Mazurek et al., 2012).

Not surprisingly, several studies have shown important dysfunctions of the HPA in tinnitus including chronically elevated baseline salivary cortisol concentrations in patients with high tinnitus-related distress (Hébert, Paiement, and Lupien, 2004), a blunted cortisol reactivity to psychosocial stress (Hébert and Lupien, 2007), as well as aggravated and prolonged cortisol suppression after dexamethasone challenge (Simoens and Hébert, 2012). Earlier in the HPA cascade, levels of adrenocorticotropic hormone in tinnitus patients were inversely related to psychological test scores (Savastano et al, 2007). These findings have prompted the hypothesis that in tinnitus patients the negative feedback systems of the HPA axis are more sensitive (Simoens and Hébert, 2012).

The relevance of the HPA axis in anxiety disorders is well established but is better known for its hyperactivity than for its blunted response seen in tinnitus research. Since dysregulation of the HPA axis is commonly viewed as a consequence rather than the origin of anxiety, it could explain the comorbidity of tinnitus and anxiety disorders in the absence of a shared cause, with the HPA axis serving as the common pathway. Further research into the mechanisms and extent of HPA axis dysregulation in tinnitus as

compared to anxiety is necessary and should include a dexamethasone/corticopropin releasing factor test (Simoens and Hébert, 2012).

Clinical implications

Phenomenology

From a phenomenological perspective, the various links between tinnitus and anxiety disorders can be understood when considering their neurobiological interactions. First, interoceptive awareness is associated with the insula and amygdala, both involved in tinnitus and anxiety disorders, with both conditions being associated with interoceptive awareness. More precisely, the typically heightened interoceptive sensitivity in tinnitus patients (such as blood flow changes near the ear in pulsatile tinnitus or the common comorbidity of hyperacusis in non-pulsatile tinnitus) and the heightened interoceptive perceptions observed in patients with panic disorder (rising heart rate, breathing difficulties, etc.) may be caused by the same mechanism.

Secondly, the display of a strong preoccupation with their disease in the more severely affected tinnitus sufferers is comparable to obsessive thinking, part of the obsessive-compulsive disorder spectrum. As obsessive thoughts are mostly correlated to the orbitofrontal cortex, anterior cingulate cortex, and the striatum (Pittenger et al, 2011), the anterior cingulate cortex, part of the salience network, may then be the common structure for the tinnitus preoccupation and the obsessive thoughts. Also, chronic tinnitus may elicit conditioned responses such as avoidance of public spaces and noisy social surroundings as observed in agoraphobia and social anxiety.

Thirdly, while no life-threatening trauma, auditory trauma, a possible cause of tinnitus, might even give rise to PTSD. This relationship was briefly explored by Hinton et al (2006) in a population of Cambodian refugees, showing that tinnitus can trigger trauma-

related memories (being struck to the head) resulting in PTSD. This study adds to the evidence that a negative bi-directional relationship between tinnitus and anxiety disorders exists. A chart-review study by Fagelson (2007) on 300 veterans also confirmed these findings and includes a review of neurobiological literature on PTSD and tinnitus.

Considering that tinnitus is an arousal-reactive symptom that is aggravated by anxiety arousal, tinnitus will in turn worsen the anxiety response, thus possibly inducing a vicious circle. This commonality may be seen as a logical phenomenological consequence of the neurobiological overlap between the two disorders and be a starting point for novel neurophysiological research and therapeutic developments in this field.

Screening and diagnosis of mental disorders

Long-term treatment outcomes for psychiatric disorders are commonly more favourable if treatment is started early. Unfortunately, patients do not always seek timely help for their mental problems. Moreover, the predominance of tinnitus symptoms should not obscure the likely involvement of other psychopathological processes in this patient population (Belli et al, 2008). In a follow-up study, Malakouti et al (2012) showed that three months of medical treatment of the comorbid mental disorders in chronic tinnitus patients reduced tinnitus intensity and associated disability. Irrespective of the mechanisms of psychotropics and their link with buzz sound, the agents were found to be effective in reducing the subjective intensity of the tinnitus, decreasing disability and improving quality of life. In the Zöger et al study (2001) of 55 tinnitus patients with a lifetime mental disorder, only 28 had visited a healthcare provider for psychological

distress during their lifetime, while a mere five patients had been in contact with health services during the last three years in relation to their psychological symptoms.

In view of the significant comorbidity of tinnitus with anxiety disorders and their neurobiological overlap, we support the recent recommendation to screen all patients with tinnitus for psychological distress using a standardized procedure (Baguley, 2013, Tunkel et al; 2014). The Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) is a widely used 14-item (7 anxiety, 7 depression) self-report questionnaire originally designed to screen for and discriminate between anxiety and depression. While a thorough 10-year review and meta-analysis have shown that the Hospital Anxiety and Depression Scale is an effective measure of emotional distress, its discriminatory power is rather low (Cosco et al, 2012; Norton et al, 2013). Nevertheless, this concise scale may be used as a preliminary screening instrument that can be followed up by more validated diagnostic interviews such as the SCID, MINI, or CIDI. With a standard protocol in place, the diagnosis and treatment of tinnitus patients could be improved and referrals to a psychiatric unit speeded up to prevent chronicity and reduce complications while improving overall quality of life.

Psychotherapeutic interventions

Together with education, counselling, and hearing-aid evaluation, cognitive-behavioural therapy (CBT) received the strongest recommendation for persistent and vexing tinnitus (Tunkel et al, 2014) but is only indicated in cases of tinnitus with psychological distress (Baguley, 2013). Being extensively evidence-based, CBT combines behavioural and cognitive interventions, with the first being directed at reducing maladaptive behaviours and replacing these with more adaptive practices by moderating their triggers and

consequences and by offering behavioural stimuli that elicit new learning. The cognitive interventions target maladaptive cognitions, self-statements, or beliefs. CBT typically applies problem-focused intervention strategies derived from learning theory and cognitive theory principles (Craske, 2009) and generally includes components such as psychoeducation (on the nature of the anxiety), symptom self-monitoring, somatic exercises, cognitive restructuring, fictional and in vivo exposure to feared stimuli while phasing out safety-seeking signals, and relapse prevention (Otte, 2011).

Recent reviews and meta-analyses concluded that CBT is highly effective in anxiety disorders (Olatunji et al, 2010; Butler et al, 2006; Deacon and Abramowitz, 2004). Several systematic reviews also showed positive effects on tinnitus and quality-of-life indices (Martinez-Devesa et al; 2010), on tinnitus-specific outcomes, and, albeit to a lesser extent, mood outcomes (Hesser et al, 2010), and was superior to other behavioural treatments (Andersson and Lyttkens, 1999). However the superiority of CBT over other psychotherapeutic treatment for tinnitus patients remains questionable due to few large-scale, well-controlled trials (Hesser et al, 2011) or by more general methodological limitations as discussed by McFerran and Baguley (2008). As the availability of CBT can be limited and related costs high, internet-delivered CBT was introduced, improving access and lowering costs. Comparing a waiting-list control group and a tinnitus group, the efficacy of internet-based CBT was shown immediately following treatment conclusion and at a 1-year follow up (Kaldo et al, 2007; Andersson et al, 2002). An initial randomized control trial compared internet-delivered CBT (n=32) to internet-delivered acceptance and commitment therapy (n=35) by Hesser et al (2012) and found no significant differences between treatments at posttreatment up until 1 year follow up. In contrast, evidence for the beneficial effects of Tinnitus

Retraining Therapy, one of the most widely used interventions for the condition, is lacking and the latest Cochrane review (Phillips and McFerran, 2010) only identified a single randomized control trial, rated as "poor quality", that showed TRT to be more effective than tinnitus masking (without including other (psychotherapeutic) treatments). While available evidence indicates that CBT is effective in patients groups with tinnitus distress (Martinez et al, 2010; Hesser et al, 2012), no studies were included comparing CBT directly to another psychotherapeutic program but only comparing CBT to waiting list control or another active intervention (yoga, education and minimal contact-education) (McFerran and Baguley, 2009).

Pharmacological treatment

The latest tinnitus guidelines discourage the routine use of any medication while no agent has currently been approved by the US FDA for the treatment of tinnitus (Tunkel et al, 2014). However, this negative recommendation does not apply when tinnitus co-occurs with an anxiety disorder, depression, or a seizure disorder (Tunkel et al, 2014). Any standard treatment for these disorders should be initiated or maintained as if no tinnitus was present. However, it does raise some concerns that tinnitus is reported as a rare side-effect of antidepressants, mostly occurring at the start of the regimen, but much of the literature on the topic consists of case studies. The latest Cochrane review (Baldo et al, 2012) on the use of antidepressants for tinnitus found a slight positive effect on tinnitus variables, mainly for high doses of tricyclic antidepressants or selective serotonine reuptake inhibitors, but also stressed the generally poor quality of the research included. As for the use of benzodiazepines, the available evidence of their efficacy in tinnitus management is insufficient and the benefit-harm ratio questionable

due to the risk of dependency with chronic use (Tunkel et al, 2014). Given the neurobiological overlap in comorbid patients, the agents' potential beneficial effects on tinnitus should not be disregarded as improvement of the anxiety disorder may also positively affect the mentioned tinnitus brain networks, most particularly the distress network.

Non-invasive brain stimulation

Transcranial magnetic stimulation (TMS) is a technique whereby focalized cortical areas of the brain are stimulated using an electromagnetic induction. In the comprehensive guidelines on the indications for TMS (Lefaucheur et al, 2014), low-frequency (1Hz) rTMS unilaterally applied to temporal or temporoparietal cortical areas for tinnitus received a level-C recommendation (possible therapeutic efficacy). Its efficacy was found to be superior to placebo for subjective tinnitus but effects were partial and transient. Main limitations of the studies included consisted of small sample sizes, an exploratory study design and unclearly defined primary outcome measures. Due to the lack of research, no recommendation for other TMS approaches in tinnitus could be made. High-frequency rTMS applied to the right dorsolateral PFC (DLPFC) in the treatment of PTSD received a level-C recommendation but there were too few studies for other anxiety disorders to warrant any recommendations. As mentioned, TMS is mostly used for focalized stimulation of cortical areas and more elaborate knowledge of other cortical areas that may be involved is required to expand the use of TMS, particularly when it tends not to affect subcortical areas. However, promising new developments such as a double-cone coil may allow the direct or indirect stimulation of

deeper brain areas (Vanneste et al, 2012), while an H-coil may cover larger cortical areas when no specific area is yet known to be primarily involved.

In transcranial direct current stimulation (tDCS) a polarity-dependent, subthreshold current is delivered directly to the relevant brain area. tDCS has shown short-term effectiveness in tinnitus when the left temporoparietal (Fregni et al, 2006; Garin et al, 2011) and the DLPFC (Vanneste and De Ridder, 2012) are targeted but long-term effects have not yet been charted. Hardly any research has investigated tDCS for the treatment of anxiety disorders, which is rather surprising considering the impact of tDCS on functional cortico-subcortical networks and even more so considering that the involvement of the DLPFC in anxiety disorders has already been established (Charney et al, 2013) and targeted in TMS treatments (Lefaucheur et al, 2014).

Further research

Several topics have to date received little or no systematic attention, leaving many questions unanswered.

While the prevalence of anxiety disorders is high in tinnitus populations, the impact of screening for these comorbid disorders and their subsequent treatment on the outcome of (subjective) tinnitus and quality-of-life features is still unclear. Nevertheless, the possibility that treatment of the comorbid disorder may yield a significant reduction in tinnitus-related stress should not be disregarded in clinical practice.

The direction and magnitude of their causal relationship also remains largely unknown. Does one disorder cause the other or do they merely influence each other's course? Might there be an underlying common vulnerability, possibly genetic or physiological in nature that causes both disorders independently from each other while both are similarly affected by contextual factors such as traumatic life events? Longitudinal studies investigating the onset of the two disorders and the impact of one on the other could shed some light on this issue. Problematic is the absence of consensus on the (validity of the) scales/questionnaires to use in these studies. Hence, clear diagnostic research criteria (Baguley, 2013; Landgrebe 2012) and validated diagnostic instruments for both tinnitus and anxiety disorders are required to avoid ambiguous results and should be a research priority in this field. Several interesting results have not been replicated due to these varying methodologies, making reviews and meta-analysis difficult. Moving forward without addressing these issues will substantially stall new insights and evaluation of treatment options.

Another relevant issue is the effect of tinnitus severity and duration on the occurrence of anxiety disorders. In tinnitus, symptom severity has been found to be more closely related to neuropsychiatric factors or general health status than to auditory factors such as the degree of hearing loss and the frequency or intensity modulations (Zöger, 2006, Henry and Maike, 2000). Taking into account that most people with tinnitus do not seek help and that studies primarily include help-seekers who traditionally suffer more severely than non-help-seekers (Scott et al, 2000), the prevalence of anxiety disorders in general tinnitus populations could be overestimated in these studies. This does not preclude the possibility that help-seekers may also be more affected because of pre-existing vulnerabilities and are therefore predisposed to suffer from more (severe) symptoms.

Research into the neurobiological correlates of anxiety disorders in tinnitus may also yield more in-depth insight. Few studies have gathered functional data with functional neuroimaging, electrophysiological assessments (e.g. EEG), or cortisol assays (stress-response) to differentiate tinnitus and anxiety disorders. Such data could help identify and provide more information on the involvement of each structure or network in relation to specific characteristics of the two disorders. Additionally, knowledge of these neurobiological correlates may yield new potential treatment targets, specifically for non-invasive brain stimulation.

In the treatment of certain brain disorders TMS and tDCS have already shown great promise, which bodes well for the treatment of tinnitus and (comorbid) anxiety disorders. In the past few years TMS for tinnitus mainly targeted temporoparietal areas

683 of the brain, with the primary outcomes focusing on sound intensity. However, based on
684 our current knowledge, we propose that the impact of anxiety and distress is very likely
685 to also exert a substantial effect on (self-reported levels of) tinnitus and quality of life.
686 Since the DLPFC currently is the cortical area targeted most in the treatment of anxiety
687 disorders, future clinical TMS and tDCS studies should therefore consider the effects on
688 (self-reported) symptoms of both comorbid disorders and include the DLPFC and other
689 focal regions implicated in anxiety syndromes.
690
691 Recent findings pertaining to the stress-response systems in tinnitus and anxiety
692 disorders were remarkable and deserve closer scrutiny. While anxiety disorders are, by
693 and large, associated with HPA-axis hyperactivity, tinnitus studies reported
694 hypoactivity. Here, a flawed definition of stress, i.e. the failure to differentiate between
695 acute and chronic stress, could explain some of the contradicting findings. Additionally,
696 research on typical HPA modulations in the development of tinnitus could provide more
697 insight into possible changes in the HPA function during the transition from acute onset
698 to more chronic variants.

Conclusions

Although still modest, there is a growing awareness of psychological issues in tinnitus patients. A significant increase in the lifetime and current prevalence of anxiety disorders in tinnitus populations is consistently reported but to date little is known about its co-occurrence with specific anxiety disorders.

Tinnitus literature is converging on several brain networks that are also involved in anxiety disorders, which in light of the disorders' high comorbidity is a logical finding: their common cognitive and behavioural aspects may be presumed to be a consequence of the involvement of these networks.

As to the clinical implications of our growing insight into these disorders, there is increasing support for screening tinnitus patients for psychological distress and psychiatric disorders. There also is renewed attention for the potential benefits of psychopharmacology, CBT, and non-invasive brain stimulation in the treatment of tinnitus patients with a comorbid anxiety disorder. Yet, as much is still unknown about their onset, causality, and neurobiology, further research into the various co-occurring disorders and their associations is indispensable to help improve treatment.

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