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Review Article

Disturbed auditory perceptions: An Update

Introduction

The search for tinnitus mechanisms is a speculative endeavour; a broad number of mechanisms may cause the tinnitus symptom and numerous tinnitus models have been proposed in recent years. There is no objective methods for detecting or evaluating the severity of tinnitus and severe tinnitus is usually defined as a tinnitus that interferes with sleep, work and social life. Patients, who exhibit a strong emotional reaction to tinnitus, a high level of anxiety, and psychosomatic problems, indicate that the limbic and autonomic nervous systems are crucial in clinically relevant tinnitus cases. Tinnitus is only one of the possible clinical aspects concerning disturbed auditory perceptions. The objective of this review was to organize all described disturbed auditory perceptions, with particular reference to the definition and the pathogenesis of a chronic bothersome tinnitus.

Definitions and classification

Non-pulsatile tinnitus [1], is an auditory perception that occurs in the absence of any external stimulus [2], Namely it is the conscious perception of an unorganized acoustic impressions of various kinds [3], heard in the absence of external or internal physical sound sources [4]. From ecological point of view, we can consider tinnitus as the perception of an auditory object in the absence of an acoustic event: true sounds have an identifiable physical source, while tinnitus does not [5].

Sound perceived from physical sources internal to the body are "true sounds", such as blood flow, that could be a referred to stenosis in the carotid or vertebrobasilar arteries, and abnormal muscular contraction of the nasopharynx or middle ear, as can occur in palatal myoclonus. They are called "*objective tinnitus*"

because they are generated within the body, transmitted to the ear and generally they audible to the examiner [6]. *Somatic tinnitus or somatosound* instead not always is detectable by the examiner and in this sense differ from an objective tinnitus [7].

Pulsatile tinnitus is an example of somatosound generated by an acoustic source from the body described as having a rhythm synchronous with the heartbeat [8]. Known causes of pulsatile tinnitus are: high cardiac output states (anemia, hyperthyroidism); raised intracranial pressure (pseudotumor cerebri, brain tumor), vascular anomalies (dural arteriovenous malformations, dehiscent jugular bulb, sigmoid sinus diverticulum, emissary vein, persistent stapedial artery, carotid-cavernous fistula, aberrant internal carotid artery, carotid artery dissection, stenosis, or fibromuscular dysplasia); increased vascularity of the middle ear and temporal bone (e.g., glomus jugulare tumor, Paget's disease, otosclerosis); superior semicircular canal dehiscence; vascular compression of the auditory nerve. [8] Pulsatile tinnitus could also result from the blowing flow of the spiral capillary in the basilar membrane [9].

Somatic tinnitus may also have a modulation of its pitch and loudness by a somatic stimulation [10], such as voluntary or external manipulations of the jaw, movements of the eyes, or pressure applied to head and neck regions [11 12]. Somatic tinnitus is associated with upper cranio-cervical imbalances [13], and with mandibular disorders such as temporo-mandibular joint dysfunction [14,15].

The perception of sounds in organized form, such as music or speech in the absence of physical sound sources, is a phantom phenomenon called *acoustic hallucination* that particularly occurs in patients with schizophrenia or after consumption of hallucinogenic substances [3]. Acoustic hallucinations have been described also in conjunction with various diseases, injury, trauma, bereavement, sensory deprivation, religious experiences, near-death experiences, drugs and in people born profoundly deaf [16,17]. Musical hallucinations tend to occur in people with advanced age and with marked hearing loss without mental illnesses.

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Auditory imagery is a normal phenomenon that occurs for all people. It generally refers to perceptions of voices without understandable speech, music or other auditory perceptions in the absence of an appropriate stimulation [18]. It is a central type of tinnitus involving reverberator activity within neural loops at a high level of processing in the auditory cortex [19,20].

Summarizing, the origin of tinnitus can be within the auditory nervous system, in case of neurophysiologic or sensorineural tinnitus, or outside the auditory nervous system, in case of somatic tinnitus or somatosound [21]. However, the isolated term "tinnitus" conventionally refers to the neurophysiologic tinnitus.

Hyperacusis, in an unusual intolerance to ordinary environmental sounds [22]. It be conceived as a "pathology" of the loudness, the subjective perception of sound level [23]. Hyperacusis is an auditory disorder with or without hearing loss [24] where sounds of normal volume are perceived to be too loud or painful [25]. Hyperacusis arises in the auditory system, either peripheral (myasthenia gravis, Bell's palsy, Ramsay Hunt syndrome, Meniere syndrome, noise-induced hearing loss and other sensorineural auditory disorders) or central (migraine headaches, depression, head injury, William's syndrome, multiple sclerosis, transient ischaemic attack, Lyme disease, Addison's disease and stimulant drug dependency) [26,27].

Decreased sound tolerance (DST) consists not only of hyperacusis; it also consists of a fear of sound known as *phonophobia* or a strong dislike of sound called *misophonia* [26]. Patients with misophonia or phonophobia have abnormally strong reactions of the limbic and autonomic nervous systems, but do not have a significant activation of the auditory system, as observed in hyperacusis [26]. Patient's reactions are correlated with the spectrum and intensity of sounds in hyperacusis while patients with misophonia react only to the sound's meaning and to the context in which it occurs, whether or not it is loud for the individual. Furthermore, the subject may react to a given sound in a particular setting, but not in another one [28].

A Flow chart reporting the classification of various aspect of an altered auditory perception is showed in the figure 1.

ETHIOPATHOGENESIS

According to the earliest speculations about the site of tinnitus generation, one of the most common symptoms in ENT medicine [29], it was understood as an inner ear disease because it is typically associated with hearing loss [6,30,31]. However, not all tinnitus patients have a measurable hearing impairment. Recent animal studies have unraveled a type of permanent cochlear damage, without elevation of hearing thresholds, linked to a permanent and progressive degeneration of the auditory fibers that occurs in association with the damage of the inner hair cell synapse [32]. According to the theory of discordant damage [33], tinnitus is generated by the auditory periphery following partial damage to the organ of Corti, in which the outer hair cells (OHC) degenerate,
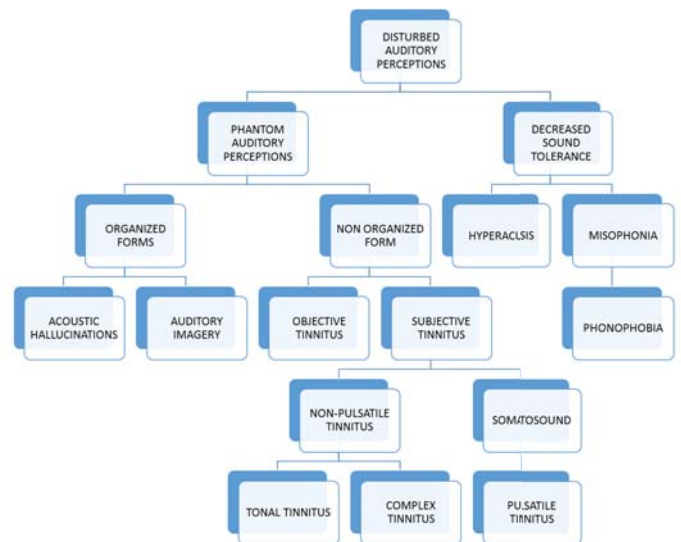
Figure 1: Schematic classification of all described symptoms concerning disturbed auditory perception.

whereas the corresponding inner hair cells (IHC) are spared. The death of the OHC is followed by an increase in the release of glutamate by the undamaged IHC, which is responsible for the onset of tinnitus [34]. The excitatory activity of glutamate is also favoured by the release of endogenous dinorphines from lateral efferences of the IHC at the level of type I nerves, during an emotional stress [35]. The discordant loss of ciliated cells, with the sequence of described phenomena, leads to an increase in the nervous activity of the cells of the dorsal cochlear nucleus (DCN) that is directly proportionate to the number of OHC that have been lost [36]. The significant correlation between the level of activity of the DCN and the presence of tinnitus gives this nucleus a highly relevant role as the cerebral centre responsible for modulating tinnitus. Its strategic position and nervous connections [cortical, from the locus coeruleus and the caudal pontine reticular nucleus, for auditory attention [37,38], states of anxiety and fear [39,40] and from the raphe nuclei for depressive states [19], also play a key role in the hierarchy of functional processes responsible for the perception of tinnitus [41]. Discordant theory explains why many individuals with tinnitus have normal hearing if there is only partial damage to OHCs, since up to 30% of OHCs can be damaged without inducing hearing loss [42]. Tinnitus have been identified as *tonal tinnitus*, that results from discordant dysfunction of OHCs and IHCs manifesting in a single area and *complex tinnitus*, that results from multiple areas of discordance [43]. The tinnitus spectrum typically mimics the region of the hearing loss, in case of low-frequency hearing loss the tinnitus is low pitched ("roaring"), whereas in high-frequency NIHL the tinnitus has a highpitched ringing or hissing sound [6].

Some patients clearly have a central type of tinnitus so that the OHC concept is not applicable and alternative mechanisms need to be considered [44]. This statement is supported by the fact that tinnitus persist in patients with vestibular schwannoma after auditory nerve section or destruction of the inner ear [45-47] or begins post-operatively in patients who did not experience tinnitus previously [48]. Indeed tinnitus can be caused by overstimulation or by deprivation of normal input.

In overstimulation the exposure to intense sounds first results in bending of the OHC stereocilia, effectively decoupling from tectorial membrane and preventing sound-induced excitation of OHC [33]. Overstimulation can also cause changes in the function of the central auditory nervous system with signs of hyperactivity and altered temporal integration in the inferior colliculus [49].

Auditory perception is possible by deprivation of auditory input in people with normal hearing when placed in a soundproof room. [50]. "It appears that tinnitus is present constantly but is masked by the ambient noise which floods our environment. This ambient noise level for ordinary quiet living conditions usually exceeds 35 dB, and apparently is of sufficient intensity to mask physiological tinnitus, which remains subaudible" [50]. Permanent deprivation such as may occur in individuals with hearing loss can cause chronic tinnitus [51]. The central nervous system aims to restore its normal evoked neural activity levels by increasing the synaptic gain [52], all the way along the central auditory pathway in order to adapt neural sensitivity to the reduced sensory inputs [53]. This gain control over amplifies "neural noise" causing the perception of tinnitus [54], so as triggers changing the central nervous system activity result in phantom auditory perceptions [33], similarly to chronic phantom pain and phantom limbs perception [33,55,56].

Phantoms limb sensations are related to a temporal incongruence between what is stored in memory (the presence of the limb) and the deprivation of a sensory input (the absence of the limb). In tinnitus, as in a true phantom sensation, the brain "hears" the sound of the missing frequencies. Phantom perceptions arise in a Bayesian way: the brain works as a probability machine that updates its memory-based predictions through active sensory exploration of the environment [57,58]. Tinnitus is the result of a prediction error due to the deafferentation where the missed input is filled in by the brain [59]. Auditory deafferentation is accompanied by a deficient inhibitory top-down noise-cancelling mechanism [60,61], in combination with central sensitization that results in increases of central gain, amplifying spontaneous and stimulus-induced activity which lead to tinnitus and hyperacusis, respectively. Because tinnitus and hyperacusis stem from the same mechanism (i.e. increased gain), they are always associated to some extents [26,62–64].

In hyperacusis sound intensities that are considered comfortable by most people are perceived unbearably loud [65]. The complaint of increased sensitivity in hyperacusis is different from loudness recruitment [53,66]. In hyperacusis sounds are not simply a bit loud, but truly unbearable. The individual perceives sound of moderate intensity as uncommonly loud in loudness recruitment, and sound of low intensity as uncomfortably loud in hyperacusis. Loudness recruitment does not vary with mood [65]. As it happens in tinnitus, subjects with clinically normal auditory thresholds can have hyperacusis. [66,67] Hyperacusis is an abnormal sound sensitivity arising from the auditory system, either peripheral or central [26]. Fackrell et al. [68], state: "association between hypersensitivity to sound, tinnitus, and peripheral auditory system damage present in stapedectomy, Menieres's disease, and sensorineural hearing loss led to hypotheses assuming peripheral contribution to the generation of hypersensitivity to sound" [69]. However clinical observations show the universal dominance of bilateral, symmetrical hyperacusis [70], which suggests a central mechanism.

The central nervous system can respond in two different ways to auditory deprivation, depending on the degree of deafferentation. A larger extent of deafferentation with a failure to appropriately adapt the central response gain, appears to be correlated with tinnitus. A lower extent of deafferentation, with an increase in response gain (synaptic strength) that spreads from the brainstem toward ascending pathways maintaining the stable neuronal circuit, leads to hyperacusis [32]. Hyperacusis is the consequence of the homeostatic adjustments of synaptic activity [71]. Dynorphins released from lateral efferent axons into the synaptic region beneath the cochlear inner hair cells during stressful episodes, represent the biochemical mechanisms associated with hyperacusis. The released excitatory neurotransmitter glutamate by inner hair cells, in response to stimuli or in silence, is enhanced at NMDA receptors. The consequence is an altered neural excitability of high-threshold (modiolar-oriented) type I neurons [35]. A common factor to neurological conditions with hyperacusis is disturbance of serotonin function [72], probably causing the increased auditory sensitivity or modulating central gain, manifested as central hyperacusis [69].

Phonophobia is an extreme form of misophonia, both are abnormally strong reactions of the limbic and autonomic nervous systems that not involve the activation of the auditory system, as hyperacusis does [26]. Misophonia is a specific acoustic cue, produced by a human being, provoked an impulsive aversive physical reaction with irritability, disgust and anger [73]. The proposed diagnostic criteria for misophonia are:

The presence or anticipation of a specific sound, produced by a human being (e.g. eating sounds, breathing sounds), provokes an impulsive aversive physical reaction which starts with irritation or disgust that instantaneously becomes anger.

This anger initiates a profound sense of loss of self-control with rare but potentially aggressive outbursts.

The person recognizes that the anger or disgust is excessive, unreasonable, or out of proportion to the circumstances or the provoking stressor.

The individual tends to avoid the misophonic situation, or if he/she does not avoid it, endures encounters with the misophonic sound situation with intense discomfort, anger or disgust.

The individual's anger, disgust or avoidance causes significant distress (i.e. it bothers the person that he or she has the anger or disgust) or significant interference in the person's day-to-day life. For example, the anger or disgust may make it difficult for the person to perform important tasks at work, meet new friends, attend classes, or interact with others.

The person's anger, disgust, and avoidance are not better explained by another disorder, such as obsessive-compulsive disorder (e.g. disgust in someone with an obsession about contamination) or post-traumatic stress disorder (e.g. avoidance of stimuli associated with a trauma related to threatened death, serious injury or threat to the physical integrity of self or others)

Phonophobia is a specific category of misophonia that occurs when the patient's fear of sound is the dominant emotion [19,74,75].

Chronic bothersome tinnitus

The generation and maintenance of chronic and bothersome tinnitus depend on cochlear dysfunction associated with adaptive processes involving both auditory pathway and non-auditory areas [76]. The cochlear nuclei, the inferior colliculus, the primary and the secondary auditory cortex are involved in the central auditory system [77]. The involved non-auditory structures are the subcallosal region including the nucleus accumbens [78]. Increased connectivity between auditory and emotional/autonomic areas is described in tinnitus patients [79]. Namely, the sensation of tinnitus is associated with neuronal activity in sensory auditory areas (posterior thalamus) together with cortical regions sub serving emotional, mnemonic and attentional functions. The neurophysiological model suggests that negative emotional and cognitive reaction to the tinnitus percept, leads to a distress response of the autonomic nervous system. The tinnitus perception is reinforced by the negative autonomic reaction through the mechanisms of conditioned reflexes [26,33]. There is a tinnitus-specific brain network that respond to any acoustic stimuli by activating limbic areas involved in stress reactivity and emotional processing and by reducing activation of areas responsible for attention and acoustic filtering (i.e. thalamus, frontal regions), possibly reinforcing negative effects of tinnitus [80]. Emotive stimuli, processed by the subcortical centres of the brain (i.e. the amygdala in the limbic system, activated by the posterior nuclei of the thalamus through the thalamic or subcortical pathway, the so-called "low road"), generate initial autonomic and neuroendocrine reactions alerting the organism, altering the heart rate, regulating perspiration, accelerating the respiratory rate and regulating muscle tension [81]. This rapid and unconscious response represents a primitive defence mechanism. Emotive stimuli, transmitted simultaneously by the thalamus also to the associative cortices (the so-called "high road"), are processed in a slower but more sophisticated manner, producing a conscious response better suited to the situation [81]. Tinnitus is transformed from a simple acoustical phenomenon, and thus acquires clinical significance, when it monopolizes the patient's attention, interfering with his or her ability to concentrate and hindering normal everyday activities. Moreover, since the perception of tinnitus is associated with a feeling of persistent annoyance, frustration, rage, anxiety and depression, it negatively affects nightly rest and the quality of sleep. Consequently, it has a strong impact on perceived quality of life (tinnitus-related pathology) [82].

Patients with tinnitus do not present a general attentional deficit but rather a specific deficit for top-down executive control of attention [83] that can explain some of the cognitive difficulties reported by tinnitus sufferers [84]. Patients with decompensate tinnitus show automatic processing of acoustic stimuli, thereby indicating that these patients spend more cognitive resources in acoustic stimulus processing. Overall tinnitus drives some of the variability in cognitive performance: working memory, sustained attention, alerting attention, selective attention and executive attention [85]. Individuals with tinnitus report concentration problems [86], that seem to be closely related to emotional distress and tinnitus intrusiveness [87,88]. Annoyance does not depend on the strength of the tinnitus-related activity but on the strength of the connection between the cerebral cortex, the auditory system, and the limbic and autonomic nervous system. A high degree of tinnitus annoyance is associated with severity of depression and anxiety [89]. Anxiety is the main psychological problem in tinnitus sufferer [90]. Chronic tinnitus patients report that tinnitus prevents them from falling asleep, have sleeping difficulties, associated worries about sleep and disturbed sleep [91–94]. Moreover, tinnitus perception and annoyance depend on the quality of the sleep. Impaired sleep quality, with a higher amount of light sleep [95], is correlated with tinnitus distress and tinnitus severity [96]. Insomnia represents a major problem in chronic tinnitus [97]. Total sleep deprivation, selective sleep interruption, and awakening from rapid eye movement sleep influences pain tolerance [98,99]. The overlap of neurophysiological mechanisms of chronic pain and tinnitus [100], suggest that similar mechanisms could also hold for tinnitus.

Conclusions

Tinnitus should be regarded as a group of diverse diseases with multiple potential mechanisms. The analogy between tinnitus and phantom limb pain indicate related changes in the neuronal activity of central pathways associated with the involvement of the non-auditory brain areas.

Tinnitus Patients need an otoaudiological examination, a psychological evaluation, as well as counselling based on current knowledge. Establishing the correct diagnosis through a regular diagnostic protocol will help patients to be relieved from their tinnitus.

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