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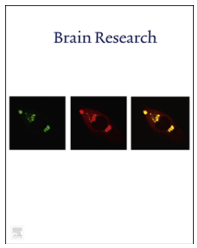

Review

Deep brain stimulation in tinnitus: Current and future perspectives

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ABSTRACT

Chronic tinnitus, also known as ringing in the ears, affects up to 15% of the adults and causes a serious socio-economic burden. At present, there is no treatment available which substantially reduces the perception of this phantom sound. In the past few years, preclinical and clinical studies have unraveled central mechanisms involved in the pathophysiology of tinnitus, replacing the classical periphery-based hypothesis. In subcortical auditory and non-auditory regions, increased spontaneous activity, neuronal bursting and synchrony were found. When reaching the auditory cortex, these neuronal alterations become perceptually relevant and consequently are perceived as phantom sound. A therapy with a potential to counteract deeply located pathological activity is deep brain stimulation, which has already been demonstrated to be effective in neurological diseases such as Parkinson's disease. In this review, several brain targets are discussed as possible targets for deep brain stimulation in tinnitus. The potential applicability of this treatment in tinnitus is discussed with examples from the preclinical field and clinical case studies.

Contents

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1. Introduction

Chronic subjective tinnitus currently affects up to 15% of the adult population (Heller, 2003; Møller, 2011), and its prevalence is increasing (Nondahl et al., 2012). The most severe degree of tinnitus is experienced in about 2.4% of the population (Axelsson and Ringdahl, 1989). Tinnitus is often associated with psychiatric disorders such as anxiety, insomnia and depression (Langguth et al., 2011; Zoger et al., 2006). In some cases, these behavioral symptoms lead to suicide (Coles, 1984; Lewis et al., 1994). Despite the severe impact tinnitus may have on the daily life of patients, no effective standard treatment is available to date that leads to a substantial remission of tinnitus.

It has been hypothesized that the substrate of tinnitus is located in the central nervous system (e.g. Eggermont, 2003; Jastreboff, 1990; Kaltenbach, 2000; Norena, 2011; Rauschecker, 1999) rather than in the periphery. Most of these hypotheses assume that initial damage to the peripheral receptor epithelium of the cochlea triggers maladaptive neuroplastic changes in the central auditory and limbic system that finally lead to the manifestation of chronic tinnitus. Based on these assumptions a number of neuromodulatory treatments, e.g. auditory cortex stimulation, direct electrical stimulation (De Ridder et al., 2007a) as well as transcranial magnetic stimulation (TMS) (Langguth et al., 2008) and stimulation of the auditory nerve (Holm et al., 2005) have been tested in search of an effective treatment against tinnitus. Some of these treatments have shown promising results. Yet, there is insufficient evidence that neuromodulation of the auditory nerve or auditory cortex causes long-term suppression of tinnitus (Bartels et al., 2007; Langguth et al., 2008). Stimulation with cochlear implants showed a substantial suppression of tinnitus in a group of patients (Arts et al., 2012). However, cochlear implants are currently solely applied in patients with bilateral severe sensorineural hearing loss, because of the risk of cochlear damage due to manipulation in the cochlea during surgery.

Recently, a more invasive neuromodulative technique, deep brain stimulation (DBS), has gained interest as a potential treatment for tinnitus (Cheung and Larson, 2010; Luo et al., 2012; Shi et al., 2009). DBS involves the delivery of electrical currents to a selected area in the subcortical central nervous system. At present, DBS is applied in patients with refractory movement such as Parkinson's disease and essential tremor (Janssen et al., 2014a; Krack et al., 2003). DBS might be a potential treatment for refractory tinnitus if a selective neurophysiological and/or anatomical substrate could be identified (De Ridder and Møller, 2011; Hariz et al., 2013; Soleymani et al., 2011).

Nonetheless, several researchers already initiated animal and human studies to treat tinnitus with DBS in different targets (Cheung and Larson, 2010; Luo et al., 2012). The most suitable brain structure for neuromodulatory treatment in tinnitus is still unclear. The goal of this review is to discuss possible targets for DBS therapy in tinnitus. To this aim we provide a comprehensive overview of studies that investigate tinnitus-related activity in auditory and non-auditory structures. First, we will briefly outline the pathophysiology of tinnitus, animal models in tinnitus and the rationale behind neuromodulative therapy for tinnitus.

2. The origin of tinnitus percepts

Since it has been proven that eighth-nerve sectioning does not improve tinnitus (Barrs and Brackmann, 1984; Gardner, 1984; House and Brackmann, 1981), it is no longer thought that tinnitus is a purely peripheral phenomenon. Rather, it is presumed that there is a prominent involvement of structures in the central nervous system in the pathophysiology of tinnitus. This view is supported by a Positron Emission Tomography (PET)-study (Lockwood et al., 1998) where unilateral external tone bursts resulted in bilateral auditory cortex activation, whereas alteration of the loudness of unilateral tinnitus with oro-facial movements only showed contralateral cortical effects. If tinnitus had a cochlear origin, these patients should have shown bilateral activity during modulation of tinnitus.