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Deafferentation-based pathophysiological differences in phantom sound: Tinnitus with and without hearing loss

Sven Vanneste [a,*], Dirk De Ridder [b]

[a] School of Behavioral and Brain Sciences, The University of Texas at Dallas, USA
[b] Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, New Zealand

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ABSTRACT

Tinnitus has been considered an auditory phantom percept. Recently a theoretical multiphase compensation mechanism at a cortical level has been hypothesized linking auditory deafferentation to tinnitus. This Bayesian brain model predicts that two very different kinds of tinnitus should exist, depending on the amount of hearing loss: an auditory cortex related form of tinnitus not associated with hearing loss, and a (para)hippocampal form associated with hearing loss, in which the auditory cortex might be of little relevance. In order to verify this model, resting state source analyzed EEG recordings were made in 129 tinnitus patients, and correlated to the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency. Results demonstrate that tinnitus can be linked to 2 very different mechanisms. In patients with little or no hearing loss, the tinnitus seems to be more related to auditory cortex activity, but not to (para)hippocampal memory related activity, whereas in tinnitus patients with more severe hearing loss, tinnitus seems to be related to (para)hippocampal mechanisms. Furthermore hearing loss seems to drive the communication between the auditory cortex and the parahippocampus, as measured by functional and effective connectivity.

Introduction

Non-pulsatile tinnitus is the perception of a sound in the absence of a corresponding external sound source, and is therefore considered as an auditory phantom percept (Eggermont and Roberts, 2004; Jastreboff, 1990). Typically this has been related to an auditory deafferentation such as in noise trauma, presbyacusis, or other causes of auditory deprivation. Recently, a theoretical multiphase compensation mechanism at a cortical level has been hypothesized linking auditory deafferentation to tinnitus (De Ridder et al., 2014a). The theoretical model is based on the concept of the Bayesian brain, which expresses the view that our brain's main function is to reduce uncertainty which is inherently present in a changing environment (Friston, 2010). It does so by updating of memory-based prior beliefs about the world through acquiring new information from the environment via the senses (Knill and Pouget, 2004). Humans and other animals operate in a changing environment, thus in a world of sensory uncertainty. Uncertainty is a state in which a given representation of the world cannot be used as a guide to subsequent behavior, cognition or emotional processing (Harris et al., 2008). However, the environment is not completely random and recurring patterns can be predicted based on stored experience and the brain must process the uncertainty to generate perceptual representations of the world and guide future actions (Knill and Pouget, 2004). Thus, the brain must represent and use information about uncertainty in its computations for perception and action. Von Helmholtz suggested that the real world was a hypothesis or prediction. Bayes adds to that that perception is to be seen as an updated prediction by actively sampling the environment, as Bayesian inference. The Bayesian coding hypothesis states that the brain represents sensory information probabilistically, in the form of probability distributions and that perception is a process of probabilistic inference (Knill and Pouget, 2004). In order to reduce uncertainty, the brain has a model of the world that it tries to optimize using sensory inputs (Friston, 2010). In this view, the brain is an inference machine that actively predicts and explains its sensations. In other words, the brain makes predictions about what it is likely to encounter next, so it can respond efficiently to changes in the environment. It updates the prediction in a Bayesian way by actively sampling the environment. Bayesian inference can thus be conceptualized as the use of sensory information from the environment to update memory-based prior beliefs about the state of the world (i.e. beliefs that are held before sensory inputs are acquired) to produce posterior beliefs (i.e. beliefs that emerge after inputs have been acquired). These posterior beliefs are what we perceive, and they become the new prediction against which the next sensory inputs will be compared.

Auditory deafferentation limits the amount of information the brain can acquire to make sense of the world. In other words, auditory

* Corresponding author at: Lab for Auditory & Integrative Neuroscience, School of Behavioral & Brain Science, University of Texas at Dallas, W 1966 Inwood Rd, Dallas, TX 75235, USA.
E-mail address: sven.vanneste@utdallas.edu (S. Vanneste).
URL: http://www.lab-audin.org (S. Vanneste).

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deafferentation increases the (auditory) uncertainty of the environment. In order to minimize uncertainty, the deafferented brain area will attempt to obtain the missing information or fill in the missing information (De Ridder et al., 2014a). The model hypothesizes that deprived auditory information depends on the amount (bandwidth) of deafferented auditory channels. In a very limited amount of receptor loss, a selective increase of cortical excitability, either via increased excitatory tone or via reduced inhibitory tone will suffice (Rajan, 1998), and the missing information can be obtained via access of overlapping tuning curves of the neighboring cortical cells. If the deafferentation is somewhat larger a widening of auditory receptive fields (Chen et al., 1996) will permit to pull the missing information from the auditory cortical neighborhood. If this is insufficient, due to a still larger deafferentation, dendritic and axonal rewiring can occur (Hsieh et al., 2007), and if that doesn't work the missing auditory information can be pulled from (para)hippocampal memory (De Ridder et al., 2014a). This model explains why not all forms of tinnitus are related to topographical map reorganization (Langers et al., 2012), and predicts that in hearing loss which is too large for filling in via auditory cortex mediated plasticity, the (para)hippocampus becomes involved. The parahippocampal area can be considered as the main node of entry for auditory information to the medial temporal lobe memory system, where salient information is encoded into long-term memory (Engelien et al., 2000). The parahippocampal area has been hypothesized to play a central role in memory recollection, sending information from the hippocampus to the association areas, which might explain it involvement in the generation of simple auditory phantom percepts such as tinnitus (De Ridder et al., 2011a). The parahippocampal area has been implicated in tinnitus, both in EEG (De Ridder et al., 2011c; Joos et al., 2012; Moazami-Goudarzi et al., 2010; Vanneste and De Ridder, 2011a, 2012; Vanneste et al., 2010a, c, 2011a), PET (Schecklmann et al., 2011; Song et al., 2012) and resting state fMRI (rsfMRI) (Maudoux et al., 2012a, 2012b; Schmidt et al., 2013) studies, and parahippocampal-auditory cortex functional connectivity is consistently present in functional imaging studies related to tinnitus, both in MEG (Schlee et al., 2009), EEG (Vanneste et al., 2011b) and rsfMRI (Maudoux et al., 2012a, 2012b; Schmidt et al., 2013).

The Bayesian brain model thus predicts that different tinnitus generating mechanisms should exist based on the amount of hearing loss. It can be hypothesized that the parahippocampal area becomes involved in tinnitus associated with audiometrically detectable hearing loss. That is, limited damage to auditory receptors (i.e. increase of auditory uncertainty) can be compensated, i.e. filled-in, within the auditory cortex by local hyperactivity and local map plasticity. However, in patients with severe hearing loss, when local auditory cortical map plasticity cannot recruit the missing information from the auditory cortical neighborhood, auditory memory related areas become more involved to fill in the missing information. Hence, the model predicts that in tinnitus associated with more severe hearing loss the parahippocampus becomes more involved as a tinnitus generating mechanism, whereas in tinnitus without hearing loss the auditory cortex should be more involved. The aim of this study is to verify whether there is scientific support for the theoretical Bayesian tinnitus model proposed (De Ridder et al., 2014a).

Methods and materials

Subjects

Selection was based on the availability of both audiometric and EEG data of a consecutive group of recently evaluated tinnitus patients, in order to prevent a selection bias. Individuals with pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache, neurological disorders such as brain tumors, traumatic brain injury or stroke and individuals being treated for mental disorders were not included in the study in order to increase the sample homogeneity. Data of 129 tinnitus patients ($M = 49.67$ years; $Sd = 14.68$; 91 males and 38 females) were included from a database of the TRI multidisciplinary tinnitus clinic in Antwerp, Belgium. See Table 1 for an overview of the tinnitus characteristics.

All patients were interviewed as to the perceived location of the tinnitus (the left ear, in both ears, the right ear) as well as the tinnitus sound characteristics (pure tone-like tinnitus or noise-like tinnitus). In addition, all patients were screened for the extent of hearing loss (dB HL) using a pure tone audiometry using the British Society of Audiology procedures at .125 kHz, .25 kHz, .5 kHz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz (Audiology, 2008). Based on this audiogram we calculated both the mean hearing loss by taking the average of the hearing loss over all frequencies measured. The tinnitus patients were subsequently separated on the amount of hearing loss. That is, we set the threshold for dividing patients into the little or no hearing loss group at ≤ 20 dB HL ($n = 48$) and more severe hearing loss at > 20 dB HL ($n = 81$) (Farrior, 1956). In addition, we also calculated the range/width of the hearing loss by counting the amount of audiometric frequencies with a hearing loss > 20 dB HL based on a routine clinical audiometry.

Tinnitus patients were further tested for the tinnitus pitch (frequency) by performing a tinnitus matching analysis. In unilateral tinnitus patients, tinnitus matching was performed contralateral to the tinnitus ear. In bilateral tinnitus patients, tinnitus matching was performed contralateral to the worst tinnitus ear. First, a 1 kHz pure tone was presented contralateral to the (worst) tinnitus ear at 10 dB above the patient's hearing threshold in that ear. The pitch was adjusted until the patient judged the sound to resemble his/her tinnitus most (Meeus et al., 2009, 2011). Based on the tinnitus frequency, we calculated the hearing loss at the tinnitus frequency as obtained by tinnitus matching. For unilateral tinnitus the hearing loss contralateral to where the patient perceived the tinnitus was considered, while for bilateral tinnitus patients we calculated the mean of hearing thresholds. A numeric rating scale for loudness ('How loud is your tinnitus?': 0 = no tinnitus and 10 = as loud as imaginable') was assessed as well as the Dutch translation of the Tinnitus Questionnaire (TQ) (Meeus et al., 2007). This scale is comprised of 52 items and is a well-established measure for the assessment of a broad spectrum of tinnitus-related psychological complaints. The TQ measures emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints. As previously mentioned, the global TQ score can be computed to measure the general level of psychological and psychosomatic distress. In several studies, this measure has been shown to be a reliable and valid instrument in different countries (Hiller and Goebel, 1992; McCombe et al., 2001). A 3-point scale is given for all items, ranging from 'true' (2 points) to 'partly true' (1 point) and 'not true' (0 points). The total score (from 0 to 84) was computed according to standard criteria published in previous work

Table 1
Tinnitus characteristics

Lateralization	
Left	19
Right	18
Bilateral	92
Tone	
Pure tone	59
Noise Like	70
Tinnitus loudness	
Mean	5.22
Sd	2.40
Tinnitus distress	
Mean	35.97
Sd	16.83
Mean Hearing loss	
Mean	27.91
Sd	17.08
Range of the hearing loss	
Mean	9.41
Sd	5.1
Hearing loss at the tinnitus frequency	
Mean	40.84
Sd	26.75