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Review

Neural networks of tinnitus in humans: Elucidating severity and habituation

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ABSTRACT

The article reviews current data about the neural correlates of an individual's reaction to tinnitus, primarily from studies that employ magnetic resonance imaging (MRI). Human studies employing brain imaging remain the most commonly used method to understand neural biomarkers of the reaction to tinnitus, a subjective hearing disorder. Evidence from anatomical and functional MRI studies is reviewed to better understand the large-scale neural networks implicated in tinnitus habituation and severity. These networks are concerned with attention, audition, and emotion, both during tasks and at 'rest' when no goal-directed activity is expected. I place the data in the context of published literature and current theories about tinnitus severity, while explaining the challenges and limitations of human MRI studies. A possible model of habituation to tinnitus is described, that of the attention system (via the frontal cortex) suppressing the response from the amygdala and the use of alternate nodes of the limbic system such as the insula and the parahippocampal gyrus when mediating emotion.
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1. Introduction

The present article is a narrow review, focused on neural networks implicated in tinnitus perception and the reaction of an individual to that percept. The studies reviewed are primarily based on magnetic resonance imaging (MRI), functional MRI (fMRI) and diffusion tensor imaging (DTI) studies, although other brain imaging techniques have done much to elucidate these networks. Because this review is focused on an individual's reaction to the percept, primarily elucidating tinnitus-related severity or habituation, it describes human studies.

Tinnitus severity is a composite of several behavioral measures or aspects of tinnitus perception. It typically ranges from slight or

Abbreviations: MRI, magnetic resonance imaging

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mild to severe or profound. For instance, the Tinnitus Handicap Inventory (THI) (Newman et al., 1996) classifies patients into 5 grades on a 100-point scale using a 25-item questionnaire, from slight (0–16), mild (18–36), moderate (38–56), severe (58–76) to catastrophic (78–100). Both the THI and other questionnaires, such as the Tinnitus Primary Function Questionnaire (TPFQ) (Kuk et al., 1990; Tyler et al., 2014) and the Tinnitus Functional Index (TFI) (Meikle et al., 2012), provide a means to unpack the term tinnitus severity along a number of dimensions. The TFI metric uses eight subscales (intrusive, sense of control, cognitive, sleep, auditory, relaxation, quality of life, and emotional), whereas the TPFQ employs four subscales (hearing, attention, emotion and sleep) and the THI uses three subscales (functional related to mental, physical, and social functioning; emotional; and catastrophic views of tinnitus). The questions typically measure a person's reaction to the presence of tinnitus, except for perhaps questions related to hearing that may capture information about the percept itself or its accompanying hearing loss. Thus, severity is assumed to be a composite of measures along several dimensions, and the dimensions that are measured in the various questionnaires may differ, although they overlap considerably. A further point to note is that while THI classifies patients into defined categories of severity, TPFQ does not, and categories based on the TFI are recent. Whereas Meikle et al. (2012) did not provide information about patient classification, recently, Henry et al. (2015) have published preliminary data to support categorization of patients completing the TFI into three categories of mild tinnitus, significant problems with tinnitus, and severe problems that necessitate aggressive interventions. Regardless of the precise metric, on one end of the severity spectrum are the successful copers who have managed to habituate to their chronic tinnitus and score low on these indices. At the other end are those who score at the highest end of the indices, are extremely bothered by tinnitus, and often have a confluence of related comorbidities of mood disorders.

It is not the purpose of this review to compare efficacy of different self-report instruments of assessing tinnitus, but rather to relate behavioral measures of tinnitus severity to neural correlates. The subscales of these questionnaires appear to assess an individual's reaction along several orthogonal dimensions, when in reality these questions may be used to assess the same concept (e.g. emotional outlook of a person in TFI can be accessed via at least three subscales, such as quality of life, emotional, and relaxation.). For the purposes of this review, I have chosen to concentrate on three overarching dimensions of a person's reaction to tinnitus, namely, attention, emotion, and audition. Brain imaging, specifically MRI, is an excellent tool to study the structural and functional properties of the neural networks involved in processing these sensory and cognitive functions.

The body of work created by my lab under the aegis of the Tinnitus Research Consortium explores the neural networks of tinnitus using the brain imaging tools described below. I use these studies as a starting point to discuss the current state of knowledge regarding the neural networks implicated in tinnitus severity. Because we conducted a series of imaging studies on the same groups of participants and replicated parts of certain studies, one can combine the results to make stronger claims about these neural bases. In this review, I focus on specific alterations of the functioning of different neural networks based on data from various paradigms and tools used in our research. I place our results in the context of published literature and current theories about tinnitus-related severity. I end the review with a proposed model of neural networks underlying tinnitus severity. Please note that recent reviews have established more comprehensive and diverse models of tinnitus generation and persistence (e.g., Roberts et al., 2013; De Ridder et al., 2014; Eggermont, 2015); this review is primarily concerned with using MRI studies to better understand the neural networks implicated in tinnitus-related severity.

1.1. Brain imaging tools and neural networks

Before I review the necessary data sets, it is helpful to briefly describe the typical neural networks associated with audition, emotion processing and in mediating attention that likely exhibiting effects of tinnitus severity. The auditory network includes the primary auditory cortex located in the Heschl's gyrus and the secondary cortex located in the superior temporal gyrus (Damoiseaux et al., 2006; Mantini et al., 2007; Smith et al., 2009). Subcortical auditory processing regions, part of the central auditory pathways, from the auditory nerve to the medial geniculate body in the thalamus, complete the network (Hackett, 2011). In this review, I focus primarily on the primary and secondary auditory cortices. The limbic network, related to processing emotion, includes the parahippocampus, the insula, and the amygdala (Stein et al., 2007; Robinson et al., 2010). There are several different networks relevant to attention, including the dorsal (comprising the bilateral frontal eye fields and intraparietal sulci) and ventral (including the ventral frontal cortex and temporoparietal junction) attention systems (Fox et al., 2005, 2006; Lee et al., 2013). The dorsal and ventral attention networks have been shown to be functionally distinct, with the former used for top-down voluntary attention and the latter used to attend to unexpected stimuli (Corbetta and Shulman, 2002; Fritz et al., 2007; Vossel et al., 2014). Key regions in the networks we will discuss in this paper are shown in the table in Fig. 1.

The most common way to examine the function of any such neural network is to have participants perform goal-directed tasks that evoke their use. However, these networks can also be examined during a resting state, without performing a task to activate them. Resting state studies examine correlations in spontaneous fluctuations in the brain when a task is not being performed. Such correlations have revealed highly replicable networks which correspond to evoked task-based networks including those discussed above, as well as visual and salience networks, among others. The networks consistently appear during the analysis of fMRI data and have also been shown to have specific electrophysiological signatures (Mantini et al., 2007). One resting state network, the default mode network, is unique in that it is active at rest and becomes less active when a task is being performed, and it has been implicated in episodic memory and self-referential processing (Fox et al., 2009). Regions of this network include the posterior cingulate cortex/precuneus, the medial prefrontal cortex (bilateral), and the superior frontal gyrus (Mantini et al., 2007). The default mode network has been shown to be anti-correlated with what is referred to as the task-positive network, in particular the dorsal-attention system (Fox et al., 2009), making it an interesting network to study in the context of tinnitus. Indeed, the study of the resting state is pertinent to tinnitus patients, as tinnitus is often most bothersome while a person is at rest, without a task to divert attention from the tinnitus percept, and may be useful in differentiating tinnitus patients from control groups.

Functional measures using fMRI focus on the blood oxygenation level dependent (BOLD) response, exploiting the fact that the level of oxygen in the blood is higher in brain regions that are active (Buxton, 2013). Task-based fMRI studies compare the BOLD level during a task to the level during a baseline state, and results are presented as a subtraction between the two. Such task-based studies are relevant when relating behavioral measures of attention or emotion processing, for instance, to tinnitus severity measures and to their neural correlates (Carpenter-Thompson et al., 2015b). Region of interest (ROI) analysis can also be used to look at changes in the response in target areas based on *a priori*

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