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Review

Auditory–limbic interactions in chronic tinnitus: Challenges for neuroimaging research

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ABSTRACT

Tinnitus is a widespread auditory disorder affecting approximately 10–15% of the population, often with debilitating consequences. Although tinnitus commonly begins with damage to the auditory system due to loud-noise exposure, aging, or other etiologies, the exact neurophysiological basis of chronic tinnitus remains unknown. Many researchers point to a central auditory origin of tinnitus; however, a growing body of evidence also implicates other brain regions, including the limbic system. Correspondingly, we and others have proposed models of tinnitus in which the limbic and auditory systems both play critical roles and interact with one another. Specifically, we argue that damage to the auditory system generates an initial tinnitus signal, consistent with previous research. In our model, this "transient" tinnitus is suppressed when a limbic frontostriatal network, comprised of ventromedial prefrontal cortex and ventral striatum, successfully modulates thalamocortical transmission in the auditory system. Thus, in chronic tinnitus, limbic-system damage and resulting inefficiency of auditory–limbic interactions prevents proper compensation of the tinnitus signal. Neuroimaging studies utilizing connectivity methods like resting-state fMRI and diffusion MRI continue to uncover tinnitus-related anomalies throughout auditory, limbic, and other brain systems. However, directly assessing interactions between these brain regions and networks has proved to be more challenging. Here, we review existing empirical support for models of tinnitus stressing a critical role for involvement of "non-auditory" structures in tinnitus pathophysiology, and discuss the possible impact of newly refined connectivity techniques from neuroimaging on tinnitus research.

Contents

Abbreviations: AC, auditory cortex; BOLD, blood oxygenation level dependent; CSF, cerebrospinal fluid; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GAD-7, generalized anxiety disorder questionnaire 7; IC, inferior colliculus; LAC, left auditory cortex; MDN, mediodorsal nucleus; MEG, magnetoencephalography; MGN, medial geniculate nucleus; MRI, magnetic resonance imaging; NAc, nucleus accumbens; PET, positron emission tomography; PHQ-9, patient health questionnaire 9; RAC, right auditory cortex; VC, visual cortex; vmPFC, ventromedial prefrontal cortex

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1. Introduction

Chronic subjective tinnitus is a common auditory disorder in which patients experience ringing or buzzing “in the ear” in the absence of an external source of that perceived sound. There is a wealth of evidence linking tinnitus to dysfunction throughout the auditory system (Eggermont and Roberts, 2004; Roberts et al., 2010). However, an ever-growing number of studies, typically utilizing neuroimaging in humans, have identified tinnitus-related differences in function and anatomy outside central auditory pathways, particularly in structures considered to be part of the limbic system. Even if one were to assume that these limbic changes are the consequence (not the cause) of tinnitus, it seems that understanding central auditory dysfunction alone may not be sufficient to understand chronic tinnitus. We have previously proposed that chronic tinnitus is, in fact, caused by compromised limbic fronto-striato-thalamic circuits, which result in disordered evaluation of the tinnitus sensation's perceptual relevance and, thus, disordered gain control of the tinnitus percept within thalamo-cortical auditory networks (Fig. 1; Leaver et al., 2011; Mühlau et al., 2006; Rauschecker et al., 2010). Although fronto-striatal circuits and other limbic structures may also regulate emotion and mood (Bar, 2009; Blood et al., 1999; Ressler and Mayberg, 2007), their involvement in tinnitus pathophysiology suggests they may be part of a more general “appraisal network,” determining which sensations are of value, and ultimately affecting how (or whether) those sensations are experienced (Breiter et al., 2001; Kable and Glimcher, 2009). Although details vary, several other prominent theories of tinnitus pathophysiology also propose network-level disturbances involving brain regions both within and outside of the central auditory system (De Ridder et al., 2011; Eggermont and Roberts, 2004; Jastreboff, 1990; Levine et al., 2003; Møller, 2003). Most of the underlying data, however, consist of (highly variable) localized activations, so, clearly, there is a need for research examining the potentially complex interactions between brain regions and networks.

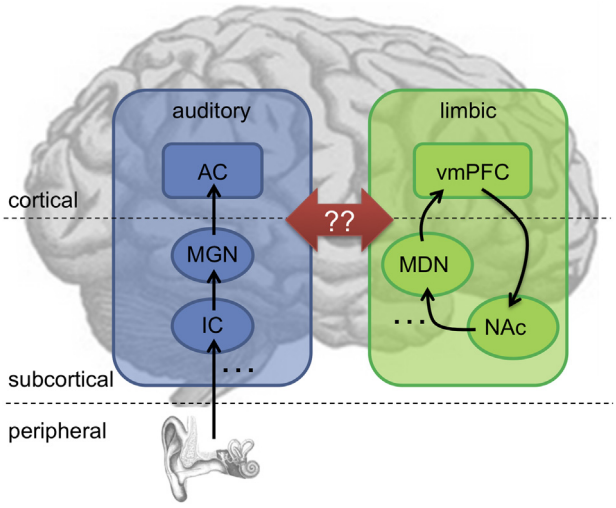

Fig. 1. A schematic model of auditory–limbic interactions in tinnitus. In our model of tinnitus, dysregulation of the auditory system by specific structures of the limbic system is what causes subjective tinnitus to become chronic (see Rauschecker et al., 2010; Leaver et al., 2011). Specifically, peripheral deafferentation of the central auditory pathway (shown in blue) causes increased activity leading to tinnitus via lesion-induced plasticity (Rauschecker, 1999). Typically, transient tinnitus can be assessed by limbic frontostriatal networks (green) as an unwanted and/or irrelevant stimulus (Leaver et al., 2011), and thus suppressed. In patients with chronic tinnitus, this regulatory mechanism does not function properly (Rauschecker et al., 2010): a volume loss is consistently found in the ventromedial prefrontal cortex (vmPFC; Mühlau et al., 2006; Leaver et al., 2011, 2012), and hyperactivity is found in the nucleus accumbens (NAc; Leaver et al., 2011). However, as indicated by the red arrows, exactly how and whether the auditory and limbic networks interact in the context of tinnitus remains to be determined. The initial tinnitus signal could enter limbic networks via projections from the auditory thalamus (MGN, medial geniculate nucleus) and/or auditory cortex (AC) to the amygdala and NAc, which is part of the ventral striatum (LeDoux et al., 1991), but may also enter through projections between AC and vmPFC (Romanski et al., 1999). Similarly, limbic structures could suppress auditory activity via projections between the vmPFC and MGN (via the thalamic reticular nucleus, Zikopoulos and Barbas, 2006); however, suppression may also occur via the medial dorsal nucleus (MDN; Pandya et al., 1994; Tanibuchi and Goldman-Rakic, 2003). Studies are sorely needed to test this and other models of tinnitus pathophysiology. Note that the placement of brain regions on this schematic is approximate and not intended to be anatomically accurate. Left hemisphere is shown; posterior is on the left; anterior on the right.

Connectivity analyses of human neuroimaging data will be critical for testing these current models of tinnitus, and for ultimately achieving a network-level understanding of tinnitus neuropathophysiology. Diffusion and functional resting-state connectivity magnetic resonance imaging (MRI) are relatively new techniques that allow inferences about anatomical (diffusion) and functional (resting-state) connections and relationships between brain structures (Fig. 2). Diffusion MRI measures water diffusion to infer direction and density of white matter tracts *in vivo* (Le Bihan, 2003; Pierpaoli et al., 1996); functional connectivity MRI measures temporal coherence in brain activity to infer functional connections between brain areas (Fox and Raichle, 2007). Similar functional connectivity analyses are also applied to EEG and MEG data, in which relationships are measured between brain regions, albeit with coarser spatial resolution. There has been an explosion in the use of both of these techniques in tinnitus research in recent years (Boyen et al., 2014; Crippa et al., 2010; Husain and Schmidt, 2014; Mahoney et al., 2011; Maudoux et al., 2012a, 2012b; Seydell-Greenwald et al., 2014b). However, although connectivity studies support existing evidence of anatomical and functional anomalies in specific isolated regions, using these techniques to verify the complex network dysfunction between regions proposed by current tinnitus models continues to present significant challenges. Therefore, it remains unclear what influence, if any, tinnitus-related anomalies in limbic and other non-auditory brain structures have on auditory-system dysfunction in chronic tinnitus. In this review, we first outline current evidence from human neuroimaging supporting the involvement of auditory and non-auditory structures in tinnitus pathophysiology, with emphasis placed on our own contributions, as supported by the Tinnitus Research Consortium for this Special Issue of *Hearing Research*. Then, we discuss the extent to which this and other evidence supports the idea that tinnitus pathophysiology involves disordered connections between auditory, limbic, and other brain systems, including a final discussion of the impact of ever-evolving techniques for connectivity neuroimaging and analysis.