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Reduced sound-evoked and resting-state BOLD fMRI connectivity in tinnitus

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ABSTRACT

The exact neurophysiological basis of chronic tinnitus, which affects 10-15% of the population, remains unknown and is controversial at many levels. It is an open question whether phantom sound perception results from increased central neural gain or not, a crucial question for any future therapeutic intervention strategies for tinnitus.

We performed a comprehensive study of mild hearing-impaired participants with and without tinnitus, excluding participants with co-occurrences of hyperacusis. A right-hemisphere correlation between tinnitus loudness and auditory perceptual difficulty was observed in the tinnitus group, independent of differences in hearing thresholds. This correlation was linked to reduced and delayed sound-induced suprathreshold auditory brain responses (ABR wave V) in the tinnitus group, suggesting subsided rather than exaggerated central neural responsiveness. When anatomically predefined auditory regions of interest were analysed for altered sound-evoked BOLD fMRI activity, it became evident that subcortical and cortical auditory regions and regions involved in sound detection (posterior insula, hippocampus), responded with reduced BOLD activity in the tinnitus group, emphasizing reduced, rather than increased, central neural gain. Regarding previous findings of evoked BOLD activity being linked to positive connectivities at rest, we additionally analysed r-fcMRI responses in anatomically predefined auditory regions and regions associated with sound detection. A profound reduction in positive interhemispheric connections of homologous auditory brain regions and a decline in the positive connectivities between lower auditory brainstem regions and regions involved in sound detection (hippocampus, posterior insula) were observed in the tinnitus group. The finding went hand-in-hand with the emotional (amygdala, anterior insula) and temporofrontal/stress-regulating regions (prefrontal cortex, inferior frontal gyrus) that were no longer positively connected with auditory cortex regions in the tinnitus group but were instead positively connected to lower-level auditory brainstem regions. Delayed sound processing, reduced sound-evoked BOLD fMRI activity and altered r-fcMRI in the auditory midbrain correlated in the tinnitus group and showed right hemisphere dominance as did tinnitus loudness and perceptual difficulty. The findings suggest

Abbreviations: ABR, auditory brainstem response; BA, Brodmann area; BA13P, posterior insula; BA13A, anterior insula; BA28, entorhinal cortex; BB-chirp, broadband chirp; BERA, brainstem-evoked response audiometry; CN, cochlear nucleus; CSF, cerebrospinal fluid; DL, dorsolateral; EFR, envelope-followed responses; ENT, ear, nose and throat; FA, flip angle; FDR, false discovery rate; FOV, field of view; FWHM, full width at half maximum; G-H-S, Goebel-Hiller-Score; HF-chirp, high-frequency chirp; High-SR AF, high-spontaneous firing rates auditory fibers; HPA, hypothalamic-pituitary-adrenal; IC, inferior colliculus; L, left; LF-chirp, low-frequency chirp; Low-SR AF, low-spontaneous firing rates auditory fibers; M, medial; MGB, medial geniculate body; MNI, Montreal Neurological Institute; PFC, prefrontal cortex; PTA, pure tone audiogram; R, right; rCBF, resting-state cerebral blood flow; rCBV, resting-state cerebral blood volume; ROI, region of interest; SD, standard deviation; SOC, superior olivary complex; SPL, sound pressure level; SPM, Statistical Parametric Mapping; TA, acquisition time; TE, echo time; TR, repetition time; VBM, voxel-based morphometry; zFC, z-values functional connectivity

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that reduced central neural gain in the auditory stream may lead to phantom perception through a failure to energize attentional/stress-regulating networks for contextualization of auditory-specific information. Reduced auditory-specific information flow in tinnitus has until now escaped detection in humans, as low-level auditory brain regions were previously omitted from neuroimaging studies.

Trial registration: German Clinical Trials Register DRKS0006332.

1. Introduction

Tinnitus, a phantom auditory sensation, affects approximately 10-15 % of the general population.

It is generally accepted that tinnitus is linked to increased spontaneous firing rates following deafferentation of auditory nerves (Brozoski et al., 2002; Chen and Jastreboff, 1995; Eggermont, 2012; Eggermont, 2015; Eggermont and Roberts, 2015; Kalappa et al., 2014; Kaltenbach et al., 2004; Kwon et al., 1999; Norena and Eggermont, 2003; Schaette and Kempter, 2012a; Shore et al., 2016; Weisz et al., 2005; Weisz et al., 2007; Yang and Bao, 2013). However, the tinnitus literature features various proposed neural correlates of how elevated spontaneous activity is connected to tinnitus. Almost all of the literature currently assumes that the generation of the elevated spontaneous activity is correlated with the percept of tinnitus through increased central neural gain in lower or higher brain levels (Marks et al., 2018; Noreña, 2015; Schaette and Kempter, 2012a; Schaette and McAlpine, 2011a; Sedley et al., 2016; Yang and Bao, 2013; Yang et al., 2011). Within this view deafferented regions may generate increases in the discharge rate in the brainstem to compensate for deprived auditory input (Noreña, 2015; Schaette and Kempter, 2012a; Schaette and McAlpine, 2011a). This is suggested to lead to elevated cortical activity essential for perception of tinnitus following disinhibition along the auditory path and auditory cortex (Roberts et al., 2010) accompanied by increased correlations with the SFR (Eggermont and Roberts, 2012).

Other studies, although not yet widely or independently supported, have instead suggested that the elevated spontaneous activity in tinnitus rather leads to failure to increase central neural gain, which is associated with a reduced signal-to-noise ratio and elevated noise levels (Knipper et al., 2013; Rüttiger et al., 2013a; Singer et al., 2013a; Zeng, 2013). A failure to increase central neural gain is hypothesized to be related to a critical loss of high-SR, low-threshold fibers, based on a high degree of IHC ribbon loss in animals with behavioral tinnitus (Rüttiger et al., 2013b; Singer et al., 2013b) and based on a mice mutant with a loss of specific auditory fiber characteristics and reduced tonic inhibitory strength in the ascending pathways (Chumak et al., 2016). As a consequence of the more severe damage to the IHC synapse in animals with tinnitus, the amplitudes of central ABR waves do not restore and molecular markers for plasticity of synaptic strength are not mobilized (Rüttiger et al., 2013b; Singer et al., 2013b), a feature that may be linked to elevated noise levels through reduced tonic inhibitory strength (Chumak et al., 2016).

This question is fundamental for a therapeutic intervention strategy for tinnitus that aims to influence the central imbalances in excitability present within the auditory pathway.

To shed more light on this existing inconsistency, we performed a multimodal dataset analysis of participants with tinnitus and volunteers without tinnitus. Aiming to maximize information about auditory-specific changes in tinnitus, the study design aligned with several *a priori* assumptions (i) we focused on mild hearing-impaired volunteers and participants with tinnitus with hearing thresholds < 40 dB in order to obtain homogenous groups (Knipper et al., 2013; Shore et al., 2016); (ii) we excluded participants with co-occurrences of tinnitus and hyperacusis which may disturb interference through dissimilar central neural responses (Gu et al., 2010; Song et al., 2014); (iii) as hearing-impaired matched rats with and without tinnitus have been shown to differ in terms of the size of suprathreshold central auditory brainstem response (ABR) waves independent of hearing thresholds (Rüttiger et al., 2013a), we included detection of suprathreshold ABR waves; (iv) As the sound-induced (ABR) wave size (wave amplitude) reflects synchronized neural activity (Johnson and Kiang, 1976; Ruttiger et al., 2017), we included BOLD fMRI activity, which is known to change in response to a task requiring elevated local metabolism (Logothetis et al., 2001); (v) as an increased level of evoked BOLD fMRI activity has been previously linked to more synchronous fMRI correlations at rest (Haag et al., 2015), we hoped to strengthen the obtained findings through additional analyses of resting-state functional connectivity MRI (r-fcMRI) in anatomically predefined auditory pathway and connected regions; and (vi) finally, the accepted influence of corticosterone levels on early and late ABR waves after tinnitus-inducing trauma (Singer et al., 2018; Singer et al., 2013a) and the positive association between glucocorticoid resistance and tinnitus (Hébert et al., 2012; Mazurek et al., 2012), motivated us to analyze the cortisol levels of each participant.

Alternatively, regarding higher-level central neural gain as a neural correlate for tinnitus generation, our findings rather support reduced auditory response gain as a neural correlate of tinnitus. This response change has previously escaped attention in tinnitus patients, as lower auditory brainstem regions were not routinely imaged. The findings provide candidate neural correlates for predicted tinnitus precursors in previous tinnitus models (Jastreboff, 1999b; Sedley et al., 2016) that are discussed in the context of current tinnitus therapies.

2. Materials and methods

2.1. Participants

From 58 participants 34 were included in the study based on hearing thresholds not > 40 dB per single frequency in the pure tone audiogram (PTA) and hyperacusis questionnaire outcome (see including and exclusion criteria Supplementary Table S2).

2.2. Tinnitus questionnaire

The Goebel-Hiller-Score (G-H-S) tinnitus questionnaire was used to assess different aspects concerning tinnitus severity, laterality, emotional distress, cognitive distress, self-experienced intrusiveness, and auditory perceptual difficulty scores (Hiller et al., 1994) as described under methods (see for detail Supplementary material). In order to assess the presence of hyperacusis, a Hyperacusis Questionnaire (Fischer, 2013) was administered to all participants.

2.3. Audiological evaluation

Ear examination, tympanometry, acoustic reflex measurements, pure tone audiometry and speech audiometry were determined as described in Supplementary material. The auditory evoked brainstem response (ABR) testing was done by using a brainstem evoked response audiometry (BERA) system as described in detail in Supplementary material.

2.4. Calculation of supra-threshold ABR wave fine structure

From the averaged ABR of a single ear and stimulus SPL, the absolute latencies and amplitudes of distinct components within the waveform of the ABR were extracted and attributed as described in detail