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Neural correlates of tinnitus related distress: An fMRI-study

Dennis Golm [a,*], Carsten Schmidt-Samoa [b], Peter Dechent [b], Birgit Kröner-Herwig [a]

[a] Georg-August-University, Georg-Elias-Mueller-Institute of Psychology, Department of Clinical Psychology and Psychotherapy, Gosslerstrasse 14, 37073 Goettingen, Germany
[b] Georg-August-University, UMG, MR-Research in Neurology and Psychiatry, Robert-Koch-Str. 40, 37075 Goettingen, Germany

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ABSTRACT

Chronic tinnitus affects approximately 5% of the population. Severe distress due to the phantom noise is experienced by 20% of the tinnitus patients. This distress cannot be predicted by psychoacoustic features of the tinnitus. It is commonly assumed that negative cognitive emotional evaluation of the tinnitus and its expected consequences is a major factor that determines the impact of tinnitus-related distress. Models of tinnitus distress and recently conducted research propose differences in limbic, frontal and parietal processing between highly and low distressed tinnitus patients. An experimental paradigm using verbal material to stimulate cognitive emotional processing of tinnitus-related information was conducted. Age and sex matched highly ($n = 16$) and low ($n = 16$) distressed tinnitus patients and healthy controls ($n = 16$) underwent functional magnetic resonance imaging (fMRI) while sentences with neutral, negative or tinnitus-related content were presented. A random effects group analysis was performed on the basis of the general linear model. Tinnitus patients showed stronger activations to tinnitus-related sentences in comparison to neutral sentences than healthy controls in various limbic/emotion processing areas, such as the anterior cingulate cortex, midcingulate cortex, posterior cingulate cortex, retrosplenial cortex and insula and also in frontal areas. Highly and low distressed tinnitus patients differed in terms of activation of the left middle frontal gyrus. A connectivity analysis and correlational analysis between the predictors of the general linear model of relevant contrasts and tinnitus-related distress further supported the idea of a fronto-parietal-cingulate network, which seems to be more active in highly distressed tinnitus patients. This network may present an aspecific distress network. Based on the findings the left middle frontal gyrus and the right medial frontal gyrus are suggested as target regions for neuromodulatory approaches in the treatment of tinnitus. For future studies we recommend the use of idiosyncratic stimulus material.

1. Introduction

Tinnitus is the perception of sound in the absence of external noise (Møller, 2011). Approximately 5% of the population is affected by chronic tinnitus (Fabijanska et al., 1999; Palmer et al., 2002). However, only 20% of the afflicted individuals experience severe distress related to the phantom noise (tinnitus) (Davis and Rafaie, 2000; Andersson and Kaldo, 2004). Common problems related to tinnitus are sleeping difficulties, concentration problems, mood disturbances and hearing problems (Andersson and Kaldo, 2004). The amount of perceived distress cannot be predicted by the psychometrically measured qualities of the sound of the tinnitus

Abbreviation: ACC, anterior cingulate cortex; aMCC, anterior midcingulate cortex; ATQ, Automatic Thoughts Questionnaire; BA, Brodmann Area; BOLD, blood oxygen level dependent; DLPFC, dorsolateral prefrontal cortex; dPCC, dorsal posterior cingulate cortex; DSM-IV, diagnostic and statistical manual of mental disorders (fourth edition); fMRI, functional magnetic resonance imaging; Gdys, generally negative sentences; GÜF, Geräuschüberempfindlichkeitsfragebogen (Questionnaire on Hypersensitivity to Sound); HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; HDT, highly distressed tinnitus patients; LDL, loudness discomfort level; LDT, low distressed tinnitus patients; LORETA, Low Resolution Brain Electromagnetic Tomography; LSD, least significant difference; MCC, midcingulate cortex; MML, minimal masking level; MR, magnetic resonance; MRI, magnetic resonance imaging; Neu, neutral sentences; pACC, posterior anterior cingulate cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; PHQ-D, German version of the Patient Health Questionnaire; RI, residual inhibition; RSC, retrosplenial cortex; rTMS, repetitive transcranial magnetic stimulation; sACC, subgenual anterior cingulate cortex; SAM, Self-Assessment Manikin; scACC, subcallosal anterior cingulate cortex; STI, Structured Tinnitus Interview; tDCS, transcranial direct current stimulation; Tdys, tinnitus-related sentences; TE, echo time; TMS, transcranial magnetic stimulation; TQ, Tinnitus Questionnaire; TR, repetition time; VLPFC, ventrolateral prefrontal cortex.

* Corresponding author. Tel.: +49 551 39 5325; fax: +49 551 39 3544.
E-mail addresses: dgolm@psych.uni-goettingen.de (D. Golm), carsten.schmidt-samoa@med.uni-goettingen.de (C. Schmidt-Samoa), pdechen@gwdg.de (P. Dechent), bkroene@uni-goettingen.de (B. Kröner-Herwig).

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(Henry and Meikle, 2000; Hiller and Goebel, 2007). It is commonly assumed that negative cognitive emotional evaluation of tinnitus and its expected consequences is a major factor determing the impact of tinnitus-related distress. The Neurophysiological Model by Jastreboff (Jastreboff et al., 1996) proposes that distress emerges if the initial perception of the tinnitus is associated with negative evaluation (*e.g.* "*I am going deaf*"). This process activates the limbic and concordantly the autonomic nervous system. In chronic tinnitus, the tinnitus sound is supposed to activate these systems without conscious evaluation through conditioning processes. According to the model, habituation will be impeded due to the emotional significance of the perception, resulting in the experience of distress and the development of psychological symptoms.

Recently, an important extension of the Neurophysiological Model, termed the Global Brain Model, has been proposed (Schlee et al., 2011). According to the model, reduced sensory input due to damage in the hearing system decreases inhibitory mechanisms in the central auditory system and finally enhances excitability of the auditory cortices. The model further states that activity in the auditory cortex is modulated by a fronto-parietal-cingulate network, which is supposed to be more active in highly distressed tinnitus patients. Key structures in this network are: the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex, the anterior cingulate cortex (ACC) and the precuneus/posterior cingulate cortex (PCC).

De Ridder (2011) assumes an aspecific network consisting of the amygdala, the ACC and the anterior insula as being responsible for tinnitus-related distress. This assumption has been tested on resting-state EEG data of highly and low distressed tinnitus patients as well as healthy controls (De Ridder et al., 2011). The data was analyzed with a group blind source separation analysis, a method similar to the independent component analysis in fMRI (see Schmithorst and Holland, 2004 for details). One component was identified in which the brain activity in two frequency bands (14–18 Hz, 22–26 Hz) differed between highly and low distressed tinnitus patients. That component consisted of the medial frontal gyrus, rectal gyrus and the ACC (Brodmann Area (BA) 11, 25), the middle frontal gyrus (BA 11), inferior frontal gyrus (BA 47), parahippocampal gyrus (BA 28/34) and the insula (BA 13). Furthermore a positive correlation in the alpha and beta range of these regions with tinnitus-related distress was found (De Ridder et al., 2011). Distress in relation to pain has also been associated with activity of the prefrontal cortex, the insula and the ACC (Moisset and Bouhassira, 2007), thus supporting the assumption of an aspecific distress network (De Ridder et al., 2004).

There is only one more recent resting-state EEG-study that compared highly and low distressed tinnitus patients. Anatomic locations were analyzed using Low Resolution Brain Electromagnetic Tomography (LORETA). Various emotion-related areas showed more synchronized activity in highly distressed tinnitus patients, including the subcallosal ACC (scACC), the anterior insula cortex, the parahippocampal area and the amygdala. Less synchronized activity was shown in the precuneus, PCC and DLPFC and ventrolateral prefrontal cortex (VLPFC). A stepwise backward regression analysis showed that the scACC, the parahippocampal area, the PCC and the DLPFC contributed significantly to tinnitus-related distress (Vanneste et al., 2010b). Thus, Vanneste et al. (2010b) did not confirm the role of the precuneus in the distress network as suggested by the Global Brain Model. However, disadvantages of LORETA-analyses in comparison to fMRI are a lower spatial resolution and a restriction to cortical gray matter and the hippocampus (Mulert et al., 2004). A correlation between the strength of inflow to the temporal cortices and tinnitus-related distress was found in a resting-state study that used Magnetoencephalography. The temporal cortices received input from the prefrontal cortex (PFC), cuneus, precuneus and the PCC (Schlee et al., 2009). Further evidence for the importance of the proposed brain regions in the tinnitus distress network comes from studies using transcranial magnetic stimulation (TMS). It has been found that a good response to repetitive TMS (rTMS) as measured by the Tinnitus Questionnaire (TQ) (Hallam, 1996; Goebel and Hiller, 1998) correlates with tinnitus associated activity in the ACC (Plewnia et al., 2007). In another study, a group of tinnitus patients was treated either with low-frequency temporal rTMS or a combination of low-frequency temporal and high-frequency prefrontal rTMS. Directly after therapy both groups improved regarding their level of tinnitus-related distress as measured by the TQ. After three month follow-up, an advantage of the combined treatment was shown (Kleinjung et al., 2008). This study indicates a potential role of the PFC in the distress network of tinnitus patients. Judging from these studies, regions of interest in a fronto-parietal-limbic network seem to be the ACC, PCC, insula, amygdala, parahippocampal gyrus (limbic), the PFC and the precuneus (parietal cortex). Complementary to the existing resting-state studies, we wanted to activate distress-related brain regions by tinnitus-related stimulus material to determine how highly and low distressed tinnitus patients differ in their activation of the network. An understanding of the distress network and its mechanisms could help to identify targets for neuromodulatory approaches like TMS in the therapy of tinnitus.

The Neurophysiological Model states a negative initial evaluation of the tinnitus as a crucial condition for the development of tinnitus annoyance (Jastreboff et al., 1996). Negative evaluations are also a maintaining factor of tinnitus-related distress as part of a vicious circle, which should lead to stress, heightened tinnitus perception and attention focus on the phantom sound (Mertin and Kröner-Herwig, 1997). A study conducted on 81 tinnitus sufferers, who among others filled in the Tinnitus Cognitions Questionnaire (Wilson and Henry, unpublished) and the Automatic Thoughts Questionnaire (ATQ) (Hollon and Kendall, 1980), found that highly distressed tinnitus patients had a greater tendency to engage in tinnitus-specific negative cognitions than low distressed individuals, while there were no differences in the ATQ as a measure of general dysfunctional cognitions (Henry and Wilson, 1995). Thus only the amount of negative tinnitus-related cognitions differentiated between highly and low distressed tinnitus afflicted individuals. Hence, tinnitus-related negative sentences are expected to represent an adequate stimulus material to activate the brain areas involved in tinnitus annoyance. Positive results regarding the adequacy of verbal stimuli to induce emotional processing were obtained from studies examining healthy subjects and psychopathology. Healthy subjects showed higher activations as measured by blood oxygen level dependent (BOLD) fMRI in the left precuneus and left ACC when reading emotional compared to neutral sentences (Medford et al., 2005). Another experiment showed that negative sentences activated the hippocampus and the middle frontal gyrus to a higher extent when participants were instructed to identify the emotion compared to the gender in visually presented sentences (Bleich-Cohen et al., 2006). Furthermore, it has been shown that audiological presented worry-sentences compared to neutral sentences elicit greater brain activation in various brain regions including the insula, parahippocampal gyrus, ACC, PCC, frontal gyrus and precuneus in patients with generalized anxiety disorder before an anxiety reducing treatment with citalopram (Hoehn-Saric et al., 2004). Thus, emotional sentences seem to be adequate stimuli for the examination of regions of interest in tinnitus patients. The aim of this study was to determine neural correlates of tinnitus-related distress using fMRI.

We hypothesized that highly distressed tinnitus patients (HDT) evaluate tinnitus-related sentences (Tdys) as being more negative, arousing and relevant than neutral (Neu) sentences and also more