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Differential electrophysiological correlates of panic disorder in non-pulsatile tinnitus☆

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ABSTRACT

Aims: The prevalence of panic disorder (PD) reportedly is up to fivefold higher in people with tinnitus than it is in the general population. The brain networks in the two conditions overlap but the pathophysiological link remains unclear. In this study the electrophysiological brain activity is investigated in adults with non-pulsatile tinnitus with and without concurrent PD.

Methods: Resting-state EEGs of 16 participants with non-pulsatile tinnitus and PD were compared with those of 16 peers with non-pulsatile tinnitus without PD and as many healthy controls. The sLORETA technique was used to identify group-specific electrophysiological frequencies in the brain and to approximate the brain regions where differences occurred. The influence of distress was investigated and functional connectivity charted using the Region-of-Interest (ROI) approach (amygdala, anterior cingulate cortex (ACC), insula, precuneus).

Results: The comorbid group showed significantly diminished theta activity ($p < 0.05$) in the precuneus (BA7) compared to the tinnitus group without PD as well as in another region of the precuneus (BA31) as compared to the controls. Higher levels of distress influenced results in the tinnitus group without PD, while in those with PD a diminished connectivity was observed between the dorsal ACC and the other three ROIs as contrasted to the controls.

Conclusions: Adults with non-pulsatile tinnitus and concurrent PD show differential brain activity patterns to tinnitus only sufferers and healthy controls. Higher levels of distress may modulate brain activity in the absence of PD. Screening for distress is recommended in both clinical and research settings.

1. Introduction

Non-pulsatile tinnitus (further referred to as “tinnitus”) is most commonly referred to as a subjective auditory phantom phenomenon with patients perceiving an internal sound in the absence of a corresponding external sound source, which can be highly distressing [4,22].

Whereas most individuals who experience tinnitus apparently cope well with the condition, for every five patients there is one reporting to be emotionally affected by it [13], with 1.6% of the population experiencing major distress, and 0.5% feeling so severely impaired that they are unable to lead a normal life [11]. In these patients, tinnitus is frequently accompanied by subjective distress, concentration problems, depression, anxiety, irritability, sleep disturbances, and intense worrying [25]. Emotional factors, typical of depressive and anxiety disorders, are also reported to be strong predictors of a poor adjustment to tinnitus [48]. A recent review indicated the necessity of a personalized approach in the treatment of subjective tinnitus, including attention for those emotional factors [39].

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Table 1
Demographic and clinical characteristics.

	Tinnitus with panic disorder (n = 16)	Tinnitus without panic disorder (n = 16)	Healthy controls (n = 16)	Overall p value
Age, mean (SD), y	47.93 (11.34)	47.31 (11.29)	47.25 (11.22)	0.878
Female	25%	25%	25%	1
Right handedness	100%	100%	100%	1
HADS total score, mean (SD)	22.69 (4.35)	7.96 (3.70)	N/a	< 0.001
HADS-A subscale, mean (SD)	13.50 (1.79)	4.63 (1.93)	N/a	< 0.001
HADS-D subscale, mean (SD)	9.19 (3.76)	3.06 (2.08)	N/a	< 0.001
TQ, mean (SD)	47.94 (13.06)	34.25 (14.76)	N/a	0.009
Tinnitus type*	PT (11), NBN (10)	PT (12), NBN (5)	N/a	N/a
Psychiatric disorders				
Current comorbid MDD	2 (12.5%)	N/a	N/a	N/a
Past MDD	11 (68.75%)	N/a	N/a	N/a
Panic Disorder with Agorafobia	13 (81.25%)	N/a	N/a	N/a
Panic Disorder without Agorafobia	3 (18.75%)	N/a	N/a	N/a
Other comorbid anxiety disorders**	4 (25%)	N/a	N/a	N/a

HADS: Hamilton Anxiety and Depression Scale; SD: Standard deviation; TQ: Tinnitus questionnaire; PT: pure tinnitus; NBN: Narrow Band Noise; *PT could be combined with NBN; MDD: Major Depressive Disorder; ** other anxiety disorders include social phobia, specific phobias and obsessive compulsive disorders; N/a: not applicable.

Comorbidity with anxiety disorders is high, with panic disorder (PD) in particular being up to five times more prevalent in tinnitus populations than it is in the general population [32]. Tinnitus has also been added to the DSM 5 as a culture-specific symptom of PD, besides other symptoms like neck soreness, headache, and uncontrollable screaming and crying (63). While they are not yet part of the cardinal symptomatology of PD, the importance of these culturally relevant symptoms is increasingly being recognized.

Anxiety symptoms in tinnitus patients have traditionally been considered to be a learned reaction to tinnitus [22] but their exact relationship to the phenomenon still remains a matter of debate [25,32]. Theoretically, it is conceivable that these anxiety symptoms precede tinnitus onset and predispose for it. Alternatively, they may represent non-auditory symptoms resulting from the same pathophysiological changes that are involved in tinnitus generation [31]. Tinnitus brain networks overlap significantly with brain networks for anxiety, particularly the distress and attentional network and the limbic system [32]. It seems reasonable to suggest that anxiety disorders and tinnitus have more in common than originally presumed. Further research on this overlap and relationship between those phenomena could provide more insight into the neurophysiology of both phenomena.

The current study aims to examine the electrophysiological activity of comorbid PD in individuals suffering from tinnitus. A Low Resolution Electromagnetic Tomography (LORETA) approach will be used to localize cortical brain activity. As brain functions are the result of the complex interaction of brain networks, a connectivity analysis will also be performed. Our hypothesis is twofold in that we anticipate the presence of a common (de)activation and connectivity pattern in the tinnitus patients (with and without concurrent PD) relative to healthy controls as well as the presence of specific PD-related changes in activity and connectivity in the tinnitus sufferers with PD relative to those without PD mainly localized in the brain regions of the limbic system (ACC, insula, amygdala). We also assume that higher levels of distress will correlate with quantitative differences in activity/connectivity.

2. Material and methods

2.1. Participants and clinical assessment

Participants were recruited from a contemporaneous dataset from the multidisciplinary Tinnitus Research Initiative (TRI) Clinic of Antwerp University Hospital, Belgium where 624 tinnitus patients were screened between August 2011 and November 2012 using the Hospital Anxiety and Depression Scale (HADS, [47]). Exclusion criteria were the presence of pulsatile tinnitus, Ménière's disease, otosclerosis, chronic headache, and neurological disorders such as a brain tumor. A total of 164 patients with a HADS-A score above 11 were invited by phone and mail to participate in the study, of whom 29 were willing to participate and answered affirmatively on the SCID anxiety screening question: Have you ever had a panic attack, when you suddenly felt frightened or anxious or suddenly developed a lot of physical symptoms?. To assess the presence of psychiatric disorders other than PD the Dutch version of the SCID-I (version 2.0; [15]) was adopted, resulting in 16 of the 29 patients fulfilling the criteria for PD. PD severity was assessed using the Panic Disorder Severity Scale (PDSS; [28]), a widely used 7-item clinician-administered interview. Severity of tinnitus distress was obtained using the validated Dutch version [30,40,41] of the Tinnitus Questionnaire (TQ; [19]).

Three equally sized groups (n = 16) were formed, matched on group level on age, sex, handedness, and tinnitus type; a group of tinnitus patients with PD, a group of tinnitus patients without PD and a group of healthy controls. The control group was part of a large historical database of 256 subjects, collected from January 2011 until December 2013, screened by a psychiatrist and neurologist. None of these subjects are known to suffer from tinnitus. Exclusion criteria were known psychiatric or neurological illness, psychiatric history or drug/alcohol abuse, history of head injury (with loss of consciousness) or seizures, headache, or physical disability. For these healthy controls hearing assessment was not available. The demographic and clinical characteristics of the two patient groups are listed in Table 1. The study was approved by the ethics committee of Antwerp University Hospital and conducted in accordance with the declaration of Helsinki. Patients gave their written informed consent before participation.

2.2. EEG data acquisition

All EEGs were obtained as part of a standard diagnostic and neuromodulation treatment procedure. Mitsar Nova Tech EEG equipment was used in these procedures. Participants were seated upright in a comfortable chair in a fully lighted room. EEGs were recorded from 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) in the standard 10–20 international placement referenced to linked lobes and impedances were checked to remain below 5 kΩ. Data were collected for 100 2-s epochs eyes closed, sampling rate = 1024 Hz, and band passed 0.15–200 Hz. Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter applying a Hanning window) to 2–44 Hz. These data were transposed into Eureka! Software, plotted and carefully inspected manually for artifacts. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifacts were removed from the stream of the