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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

EEG.

In previous research on this data [55], an independent component analysis (ICA) was conducted to verify if all artifacts were excluded. To look for any effects of ICA component rejection, we compared the power spectra using two approaches: (1) after visual artifact rejection only (before ICA) and (2) after additional ICA component rejection (after ICA). To test for significant differences between the two approaches, a repeated measures ANOVA was performed, considering mean band power as the within-subject variables and groups (unilateral vs. bilateral tinnitus) as the between-subject variable. As the mean power in delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–45 Hz) did not show statistically significant differences between the two approaches, all results reported are ICA-corrected data.

2.3. Data analysis

2.3.1. Demographic and clinical variables

Description of the samples was carried out using the statistical package SPSS 20 with appropriate parametric tests (chi-square for categorical variables, analyses of variance for continuous variables) and nonparametric tests (Kruskal-Wallis) were performed. Post-hoc analyses were adjusted by means of Bonferroni corrections (analysis of variance) and Dunn test (Kruskal-Wallis) at a significance level of 0.05.

2.3.2. sLoreta

The standardized low-resolution brain electromagnetic tomography (sLoreta) software was used to compute the cortical three-dimensional distribution of current density. The sLoreta method is non-parametric; more specifically, it is a properly standardized discrete, three-dimensional (3D) distributed, linear, minimum norm inverse solution. The particular form of standardization used in sLoreta allows the exact localization of point sources, yielding images of standardized current density with zero localization errors, albeit with low spatial resolution but high temporal resolution. The sLoreta solution space consists of 6239 voxels (voxel size: 5 × 5 × 5 mm) and is restricted to cortical gray matter and hippocampi, as defined by the standard MNI brain template derived from the international 10/20 system [24].

The methodology (sLoreta) used is a non-parametric permutation test. It is based on estimating, via randomization, the empirical probability distribution for the max-statistic, under the null hypothesis comparisons [4]. This methodology corrects for multiple testing (i.e. for the collection of tests performed for all voxels, and for all frequency bands). Due to the non-parametric nature of this method, its validity does not rely on any assumption of Gaussianity [4]. The significance threshold for all tests was based on a permutation test with 5000 permutations. Comparisons were made between the healthy controls versus tinnitus group with PD, healthy controls versus tinnitus without PD, and between the tinnitus groups with PD and tinnitus with no PD. These comparisons were performed on a whole brain by sLORETA statistical contrast maps through multiple voxel-by-voxel comparisons in a logarithm of *t*-ratio.

2.3.3. Influence of co-variables

A within-group regression analysis was performed to assess the influence of tinnitus severity on the previous sLoreta analysis using the scores on the TQ as dependent variable. Similar regression analyses were conducted for the influence of anxiety severity using the HADS scores as dependent variables and for age and gender as dependent variables.

2.3.4. Lagged phase coherence: connectivity analysis

Coherence and phase synchronization between time series corresponding to different spatial locations are usually interpreted as indicators of the “connectivity”. However, any measure of dependence is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction [1]. However, Pascual-Marqui [49] introduced new measures of coherence and phase synchronization taking into accounts only non-instantaneous (lagged) connectivity, effectively removing the confounding factor of volume conduction. Such “lagged phase coherence” between two sources can be interpreted as the amount of cross talk between the regions contributing to the source activity [3]. Since the two components oscillate coherently with a phase lag, the cross talk can be interpreted as information sharing by axonal transmission. More precisely, the discrete Fourier transform decomposes the signal in a finite series of cosine and sine waves at the Fourier frequencies (62). The lag of the cosine waves with respect to their sine counterparts is inversely proportional to their frequency and amounts to a quarter of the period; for example, the period of a sinusoidal wave at 10 Hz is 100 ms. The sine is shifted a quarter of a cycle (25 ms) with the respect to the cosine. Then the lagged phase coherence at 10 Hz indicates coherent oscillations with a 25 ms delay, while at 20 Hz the delay is 12.5 ms, etc. The threshold of significance for a given lagged phase coherence value according to asymptotic results can be found as described by Pascual-Marqui [49,50], where the definition of lagged phase coherence can be found as well. As such, this measure of dependence can be applied to any number of brain areas jointly, i.e., distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between the multivariate time series are defined. The measures are non-negative, and take the value zero only when there is independence and are defined in the frequency domain: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10-12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–44 Hz). Lagged phase synchronization/coherence or functional connectivity contrast maps were calculated and correlated with the mean hearing loss, the range of the hearing loss and the hearing loss at the tinnitus frequency for the different frequency bands. The significance threshold was based on a permutation test with 5000 permutations. This methodology corrects for multiple testing (i.e. for the collection of tests performed for all voxels, and for all frequency bands).

We selected a-priori ROIs from the literature on tinnitus and anxiety [32]: amygdala (BA 34 + 35), insula (BA 13), ACC (divided in two ROIs: BA 25 and BA 24 + 32). If one or more of these specific regions emerge from the primary analysis, they will be added to the connectivity analyses in a second phase. The reported connectivity models have an alpha-significance level below 0.05.

3. Results

3.1. Demographic and clinical characteristics

The groups showed no significant age or gender-related differences. The overall mean age was 47 years and the male/female ratio in all groups was 3 to 1. Tinnitus patients with PD scored higher on the TQ than those without PD (mean score 47.94 vs. 34.25; $p = 0.009$) as well as on the HADS (mean score 22.69 vs. 7.98; $p < 0.001$). 2 patients with tinnitus and PD also met the DSM-IV criteria for comorbid depressive disorder.

3.2. Frequency source localization

Between-group comparisons revealed a significant diminished activity in the precuneus (BA 7) in the theta frequency band (Fig. 1; $p = 0.015$) in the tinnitus patients with PD compared to their peers without PD. We also found a similarly diminished activity in the same region, the precuneus/cuneus (BA 31) extending into the retrosplenial part of the posterior cingulate cortex (Fig. 2; $p = 0.007$), for the comorbid patients but now compared to the healthy controls. No differences were found for the other frequencies or between the tinnitus patients without PD and the controls.

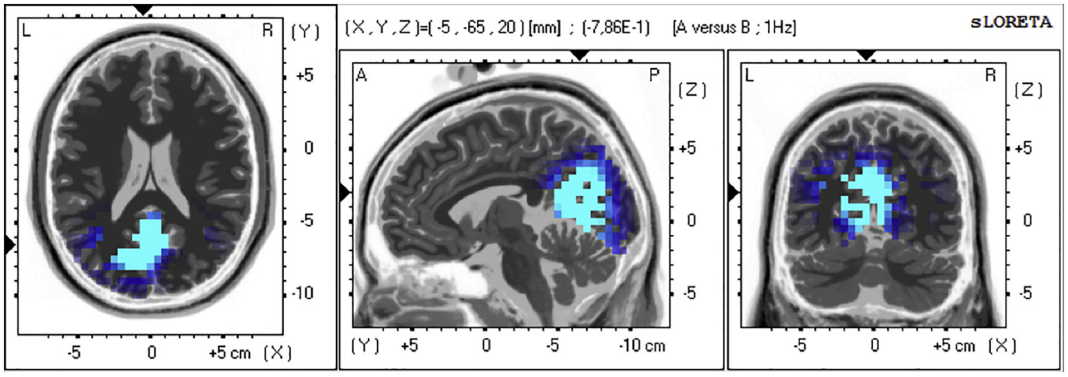

Fig. 1. Difference in activity between tinnitus patients with and without comorbid panic disorder. Blue = diminished activity; Threshold = 0.759; scale exponent was set at 20.09 for better visibility of the results. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Modulation of sLoreta by tinnitus severity or anxiety severity

Our regression analysis showed a unidirectional modulation of the HADS-D in the tinnitus without PD group ($p = 0.044$), although HADS-D scores were significantly lower in this group compared to the tinnitus with PD group (see Table 1). Age, gender, HADS-A, HADS total, and TQ did not show any significant modulations in both groups.

3.4. Connectivity analysis

In the first phase of the connectivity analysis, four ROIs were included: the insula (BA13), amygdala (BA34/35), the subgenual ACC (BA25), and the dorsal ACC (BA24/32). Tinnitus patients with PD showed diminished connectivity on the alpha1 frequency between the dACC (BA 24/32) and the three other regions compared to the controls (Fig. 3; $p = 0.001$). No other between-group differences were found.

In the second phase, two ROIs identified in the sLORETA analysis (BA 7 and BA 31) were added to the connectivity analysis. This second analysis did not change any of the results.

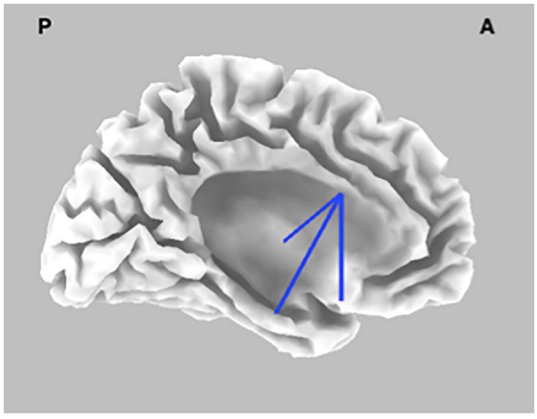

Fig. 3. Difference in functional connectivity between tinnitus patients with comorbid panic disorder and healthy controls. Blue = diminished connectivity between dorsal ACC and sgACC, amygdala and insula; the right hemisphere is not displayed for better visibility of the results. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

This study was a first attempt at exploring the impact of comorbid panic disorder on regional brain function in adults with chronic tinnitus. Although brain networks related to tinnitus overlap significantly with brain networks associated with anxiety, we did not observe any differential brain activity in our tinnitus sample without PD and the healthy controls. However, we did find differences in brain activity in terms of diminished theta activity in the precuneus/cuneus in the tinnitus group with PD, more specifically in BA 7 when compared to the tinnitus group without PD, and BA 31 when compared to the healthy controls. Our results accordingly did not bear out our hypothesis of a common (de)activation pattern for both disorders. Furthermore, our functional connectivity analysis showed diminished connectivity between the ACC and three other regions (i.e., the subgenual ACC, insula, and amygdala) in the tinnitus group with PD compared to the healthy controls. We hence consider the assumption of a strongly involved

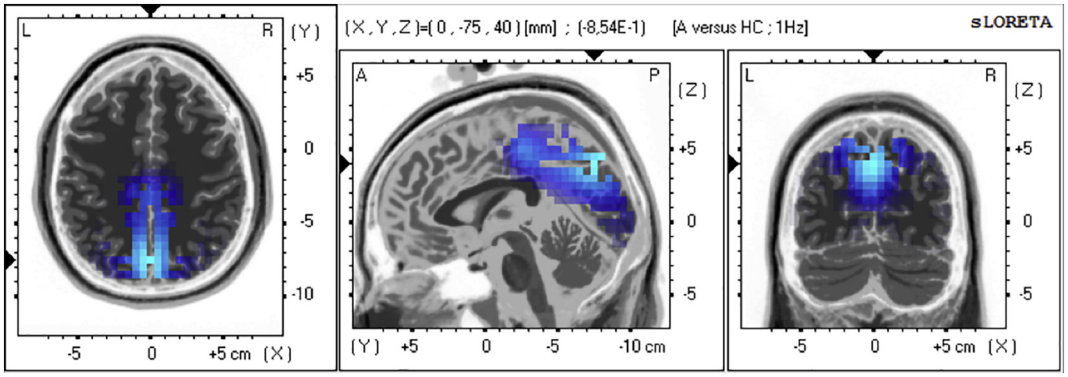

Fig. 2. Difference in activity between tinnitus patients with comorbid panic disorder and healthy controls. Blue = diminished activity; Threshold = 0.764; scale exponent was set at 20.09 for better visibility of the results. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

limbic system to be confirmed by these results but were unable to disentangle the effects of tinnitus and PD from each other. As to distress, higher scores on the HADS did have a quantitative effect on the brain activity of the tinnitus patients without PD.

4.1. Electrophysiological correlates of tinnitus and panic disorder

We found no differences comparing tinnitus patients without PD and healthy controls. This is both contrary to our hypothesis and a significant part of the literature on tinnitus and EEG that does report various changes in delta [2,12,43,44,56], theta [12,56], and alpha frequencies [35,43,44]. Still, several other studies, some from the same research groups, did not replicate these findings and also reported null findings [2,33,35,40–42,56,57,58,59,60,61]. These ambivalent findings may be explained by the complexity of the condition and imaging procedures, and the great heterogeneity in tinnitus populations. Alternatively or additionally, while some of the studies tested and corrected for general distress, to our knowledge, none had assessed their participants for concurrent psychiatric disorders as we did in this study.

The literature on resting EEGs in PD is sparser than it is for tinnitus. The diminished theta activity we observed in the precuneus is not reported by other studies. While Wise et al. [45] did find a reduction in overall power in participants with PD compared to healthy controls, the reduction was mainly due to diminished beta activity with trends for alpha1 and alpha2 but null findings for the theta frequency. Comparing the same groups, Gerez et al. [18] also observed diminished beta and delta activity but no differences in theta activity.

Neither the localization of brain activity nor the functional connectivity analyses yielded any significant differences in specific auditory regions of the brain. All the changes in brain connectivity obtained were related to brain regions more commonly involved in emotional distress (amygdala, ACC, and insula) and were also not influenced by the diminished activity of the precuneus. We accordingly assume that in our study it is the presence of PD that accounts for the findings more so than does the presence of tinnitus. However, as the study design does not allow any firm conclusions, we cannot rule out the possibility of a significant interaction between PD and tinnitus.

4.2. Distress in tinnitus patients does matter

The tinnitus group with PD scored significantly higher on the Tinnitus Questionnaire than the tinnitus group without PD did, confirming the concept that comorbidity is generally accompanied by higher levels of distress. Furthermore, the unidirectional modulation of the HADS-D we observed in the tinnitus patients indicates that distress influences brain activity in the absence of PD. We consider the HADS to measure general distress as it is designed to screen for psychological distress associated with somatic diseases. Our results then fit well with the assumed involvement of a general distress network in tinnitus [26,32,40,41] and other work showing correlations between (tinnitus-related) distress and changes in delta [5], theta [5], and beta frequencies [23]. In the presence of concurrent psychopathology such as PD, any effect of general distress might be too small to show up in analyses such as we conducted, explaining why it did show in the group of tinnitus patients without comorbidity.

4.3. Brain networks

The brain connectivity analysis revealed a diminished alpha1 connectivity between the dorsal ACC and the subgenual ACC, insula, and amygdala in the tinnitus group with PD compared to the healthy controls, which is in accordance with similar findings in chronic tinnitus patients [35].

The predefined brain regions (ACC, insula, amygdala) are part of the limbic system, an important brain network implicated in anxiety and affective behaviors [9]. There is an overlap in the neural networks of anxiety and tinnitus [32]. More precisely, the ACC, insula and amygdala make up the attention network, and consists of a dorsal and central attentional network of tinnitus (combined with the hippocampus) and the distress network (combined with the orbitofrontal cortex and the hippocampus) [26].

We added the precuneus to the connectivity analysis based on the results of the brain activity analysis. The precuneus is a structure strongly involved in self-consciousness [7,20,10] and thus frequently mentioned as an essential part of the resting-state network of the brain [38,46] Furthermore, the precuneus is part of the rich club network [5], which is proposed to integrate activity from different modules (eg auditory, salience, attention etc) [6]. Both tinnitus [27,36] and PD [8,14,29] are considered to be disorders characterized by a hypervigilance for internal or external sensations. This hypervigilant state might then alter resting-state activity, resulting in diminished theta activity in this key component of the resting-state network. However, we found no changes in connectivity with the other ROIs.

4.4. Limitations

A general limitation when studying tinnitus and PD is the significant amount of heterogeneity in individuals suffering from either or both disorders. To minimize heterogeneity as much as possible, we recruited participants with well-diagnosed non-pulsatile tinnitus who subsequently underwent a thorough psychiatric evaluation to exclude for psychopathology other than PD. Although a particular strength of our study, the downside of this approach is the resulting relatively small sample size and the accordingly large effect sizes. Smaller effect sizes for complex interactions between tinnitus and PD may have gone undetected as a result. Inclusion of patients suffering only from PD might have shed more light on these more subtle interactions. A recent and still understudied aspect in this field is the influence of hyperacusis. Recent literature [1] showed that hyperacusis had a 4.4 fold impact on PDSS while no influence was found for THI. However, at the time of designing and executing this study, the influence of hyperacusis on tinnitus and its mental consequences were not yet broadly investigated. As such, this study is limited regarding the influence of hyperacusis and future studies should include more information on this aspect. Another methodological limitation consist of not expanding our list of a-priori selected ROI's with other interesting brain areas involved in perception or emotion regulation (e.g. prefrontal cortex). To have included these regions would have had an impact on the required significance levels for the results, so was decided to primarily choose for stricter significance. Finally, the cross-sectional design of our study does not allow causality to be established.

4.5. General conclusion and recommendations for future research

We observed no differential brain activity between the tinnitus only sample and the control group. We did find theta activity and brain connectivity to be diminished in the tinnitus group with concurrent PD compared to the patterns observed in the healthy controls. In tinnitus patients both PD and general distress appears to result in changes in electrophysiological activity and brain connectivity.

Future research should also include a panic-only group to investigate potential interactions between PD and tinnitus and consider the limbic system, a network likely to be implicated in tinnitus even in the absence of psychopathology. Given that a significant proportion of tinnitus patients suffer from heightened levels of distress, a reliable assessment of general distress should be included in future research designs and in standard practice in clinical settings.

Conflict of interest

The authors report no financial or other relationships relevant to the subject of this article.

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